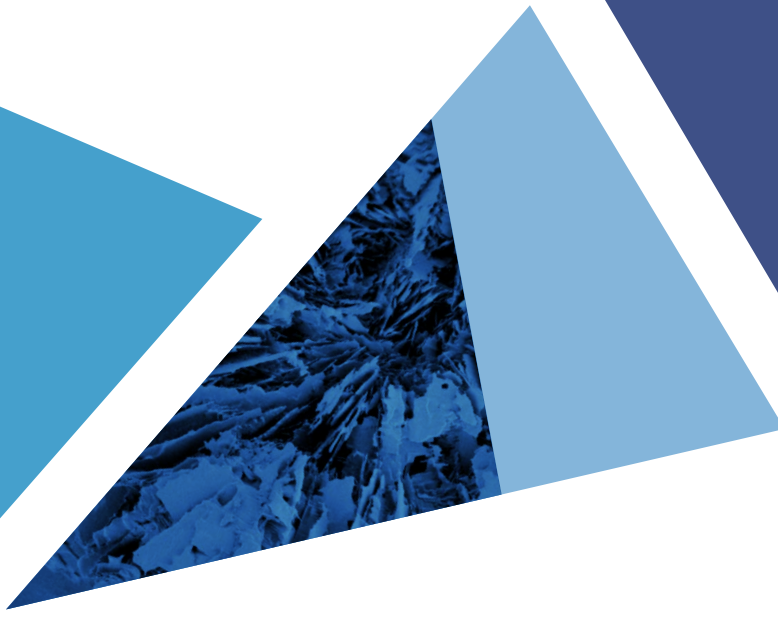
CMAC

FUTURE MANUFACTURING RESEARCH HUB

Annual Review

2017



EPSRC

Engineering and Physical Sciences Research Council

Contents

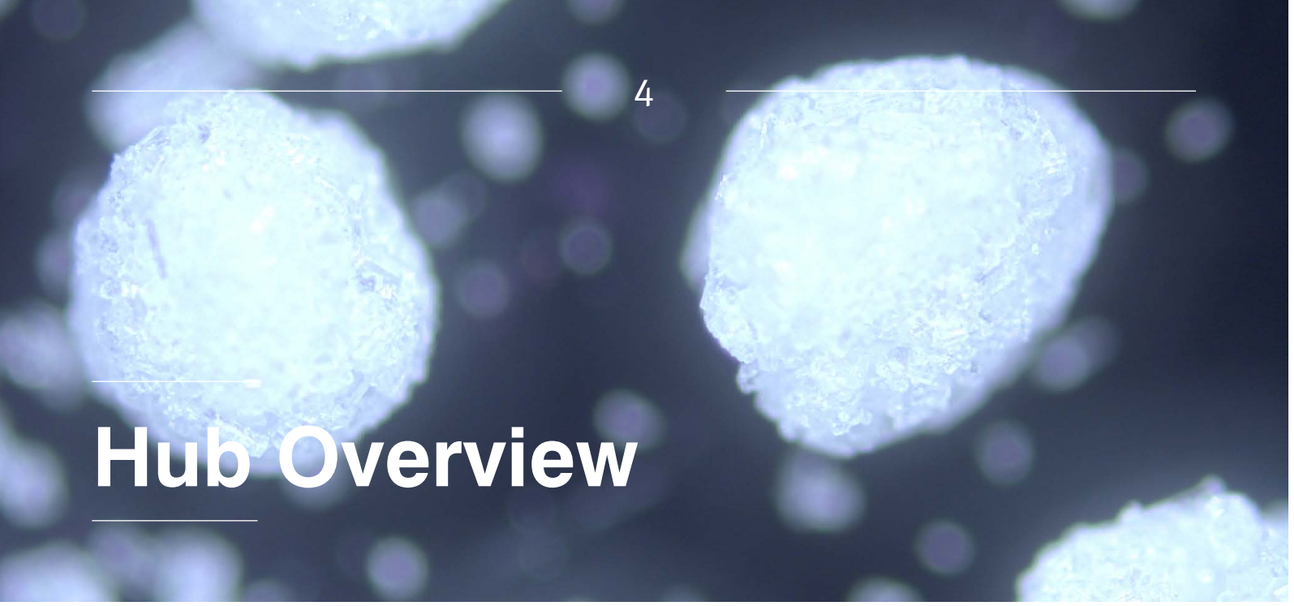
Opening Remarks

Welcome to the 1st Annual Review for the new EPSRC Future Continuous Manufacturing and Advanced Crystallisation Research Hub (CMAC). The Hub represents a major investment in UK manufacturing research by EPSRC and provides support for 7 years from January 2017 through to the end of 2023. This award has enabled us to bring together an excellent collaborative team to address the manufacturing research challenges identified by our industry partners. Our shared goals of improving the science and technology underpinning advanced pharmaceutical manufacture will lead to more efficient process development and advanced integrated continuous processing capabilities employing innovative digital design and digital manufacturing methods. The academic team involves expert groups from Strathclyde, Cambridge, Bath, Loughborough, Imperial College, Leeds and Sheffield who are carrying out exciting projects looking to understand and predict the properties of pharmaceutical materials, detail the mechanisms involved in transformations during processing, create new models that accurately describe advanced continuous processes, improve process analysis and advanced characterisation and integrate these tools in the design of novel predictive design tools and flexible microfactory platforms.

Key to the successes to date has been the support from our industry partners including GSK, AZ, Novartis, Bayer, Lilly, Takeda, Roche and Pfizer who continue to work closely with the academic community to identify areas where research can lead to new capabilities and impacts. Our technology and SME partners also are key partners in the collaborative network, generously providing time and support to access, test and develop novel technological solutions for continuous manufacturing and enable CMAC researchers to benefit from the latest advances in these areas. We also welcome the support from our Innovation spokes that include MMIP, CPI Ltd, NPL, KTN and MHRA for example. I look forward to working closely with them and all of the CMAC Hub partners to ensure that our research is translated to industry to transform the way that medicines are made and ultimately, improve the lives of patients through reliable access to safe, effective, high quality and increasingly personalised medicines.

In addition to our ambitious manufacturing research programme and translational activities, the review also introduces our ongoing training initiatives and the latest developments in CMAC's facilities. I look forward to working with existing and new colleagues over the coming years and would encourage any researcher, group or organisation interested in finding out how to engage to get in touch with us: we would be delighted to hear from you.

Professor Alastair Florence
Director



Hub Overview

The Future CMAC Hub is a world-class international hub for manufacturing research and training in continuous manufacturing and advanced crystallisation. Working in partnership with industry, its purpose is to transform current manufacturing processes into the medicine supply chain of the future.

Figure 1. CMAC vision and core areas of focus: research, facilities, skills and translation

CMAC's vision has been developed through close collaboration with industry and the support of its Tier 1 partners, GlaxoSmithKline, AstraZeneca, Novartis, Bayer, Takeda, Lilly, Pfizer and Roche and a wide range of technology companies. CMAC has already leveraged a £150m funding portfolio and currently comprises more than 130 staff and researchers, including academics, post docs, 50 PhD students and an experienced support team. In 2017, the EPSRC Future Manufacturing Research Hub was launched. This 7 year program, led from the University of Strathclyde, comprises academic investigators and research staff across 7 leading universities. It will deliver predictive design tools and novel integrated continuous processing platforms for the supply of next generation high performance personalised products.

CMAC

- Develops new solutions to company specific problems
- Delivers measurable successes that are of real benefit to society
- 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
- Understands and integrates with the broader supply chain context
- Collaborates with world class business and academia on an international basis

Research

CMAC's leading manufacturing research programme is funded by the EPSRC Manufacturing Research Hub programme. The University of Strathclyde is the hub with delivery achieved by a multidisciplinary and collaborative academic team at the UK universities of Bath, Cambridge, Imperial, Leeds, Loughborough and Sheffield. Research with impact, has grown through new projects supported by EPSRC, InnovateUK, EU and industry. CMAC is a founding member of International Institute of Advanced Pharmaceutical Manufacturing (I2APM, www.i2apm.org) with partners C-SOPS (US) and RCPE (Austria). As part of the critical regulatory agenda CMAC and MIT organise a biennial conference with the FDA.

Training & Skills Development

CMAC has a unique Doctoral Training Centre, which operates across the partner universities. Training the next generation of scientists and engineers is vital to accelerating the adoption of continuous manufacturing. Additionally, a Master's programme in Advanced Pharmaceutical Manufacturing is delivered at Strathclyde. A key deliverable is the CMAC talent pipeline - see pages 22-23.

World Class Facilities

The £34M UK-RPIF scheme partnership established a world-class facility equipped with a comprehensive suite of continuous processing, process analysis, and characterisation equipment. The physical hub is within the new £89m Technology and Innovation Centre at Strathclyde opened by HM the Queen in July 2015. This provides open access approach across the established and evolving broad industry and academic community. In 2016, CMAC was the first ever academic winner of the Global International Society for Pharmaceutical Engineering (ISPE) Facility of the Year award.

Translation and Industry Engagement

CMAC has always benefited from strong industry engagement and leadership. An industry led membership organisation was created in 2011 and this has grown and developed over the years. The membership organisation operates under a pre-competitive, collaborative research and development model with senior level company support. The main industry partners (AstraZeneca, GSK, Novartis, Bayer, Lilly, Takeda, Roche and Pfizer) get an individual seat on the CMAC Board and an opportunity to influence the direction of future research and Hub activity. Integral to the CMAC ecosystem are the Tier 2 technology companies. These range from large companies, Siemens and PwC, to micro SMEs. This supportive environment helps translate research into equipment and products. In addition to CMAC members the Hub organises many open events for the broader industry landscape and collaborates with a wide range of additional companies locally, nationally and globally.

Hub Overview

Continuous Manufacturing and Advanced Crystallisation

Vision

To deliver predictive design tools and novel integrated continuous processing platforms for the supply of next generation high performance personalised products.

The Future CMAC Hub will address the urgent need to translate new molecules into high-value products through rapid predictive development pathways and integrated continuous manufacturing systems, enabling more personalised, responsive and flexible product provision through digitalised supply chains. Building on the significant success of the EPSRC Centre for Innovative Manufacturing (CIM), and informed by extensive engagement with national and global industry, end-users, technology providers, international academic programmes and regulatory agencies, the industry-academic team has co-created an ambitious Future CMAC Hub Vision. The Hub will deliver new predictive tools and design approaches for products, processes and supply chains to enable the potential of Quality-by-Design (QbD) and Industry 4.0 initiatives to be fully realised by our partners. Whilst these regulatory and industry-driven initiatives have set out ambitious visions, the enabling tools do not yet exist: the Future CMAC Hub will deliver the tools and technologies for process industries to translate them into tangible benefit and enable a step-change in industry practice.

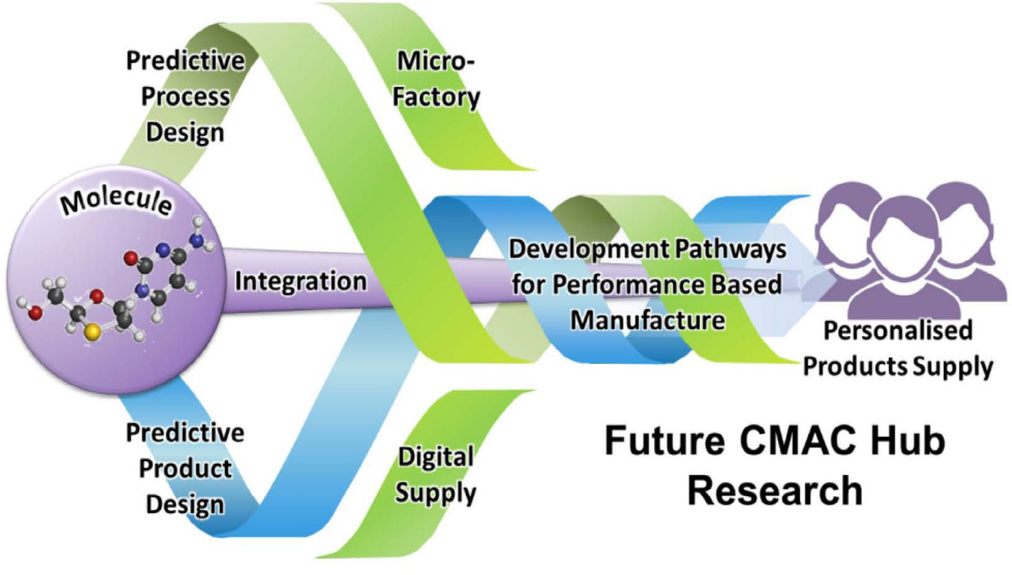


Figure 2: The Future CMAC Hub Vision

Academic Partners

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

Tier 1 Supporters / End Users

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

Tier 2 Technology Companies

Siemens · pwc · Mettler Toledo · PSE · Perceptive Engineering Ltd · Britest · Sirius analytical · Clairet Scientific Limited · NiTech Solutions · Technobis crystallization systems · Alconbury Weston Ltd · Booth Welsh Integrated Engineering Services · EDEM · Buchi · Snapdragon Chemistry · Black Trace · Syrris · dolomite · glass solutions · particle works · dolomite bio

Innovation Spokes

cpi · Cancer Research UK · NPL National Physical Laboratory · diamond · MMIP · Chemistry Growth Partnership · ReMediES RE-configuring MEDicines End-to-end Supply · ADDOPT Advanced Digital Design of Pharmaceutical Therapeutics · KTN the Knowledge Transfer Network · Knowledge Centre Materials Chemistry · MHRA Regulating Medicines and Medical Devices · Scottish Enterprise

CMAC also works with a broad range of collaborators.

Hub Overview

Research Goals

CMAC's research focus will be to deliver novel manufacturing technology that will enable industry to deliver better products, quickly, economically and sustainably. This will meet the demand for reduced development time and costs and to exploit emerging opportunities driven by the urgent needs of patients and consumers for more personalised product performance.

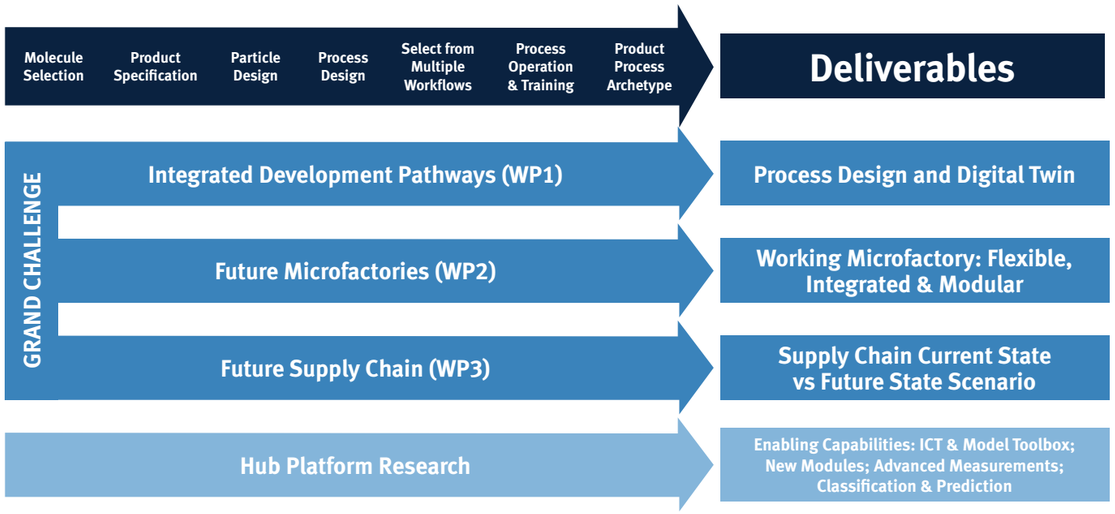
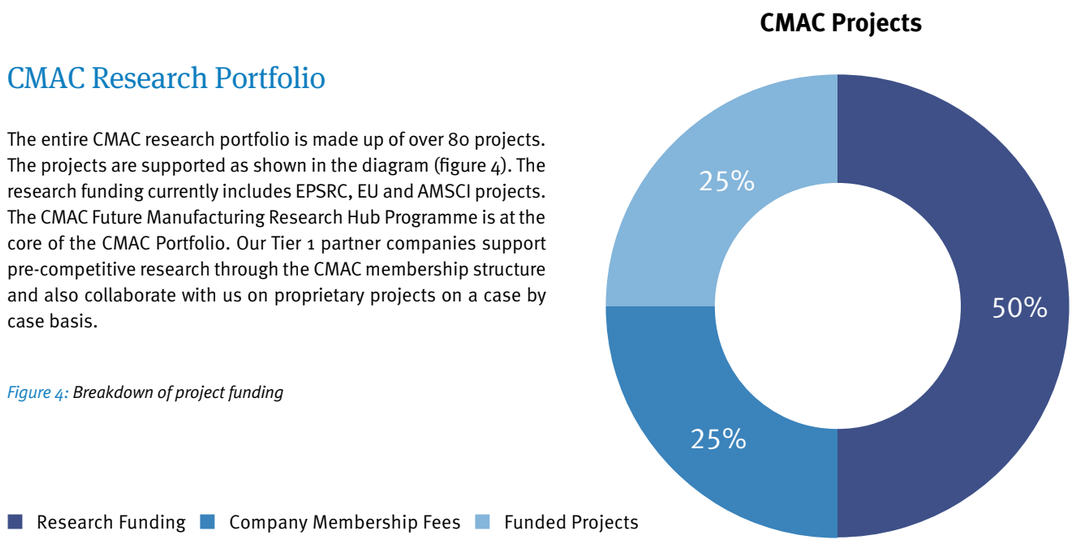


Figure 3: Rapid Performance Based Design and Continuous Manufacture of Particle Based Products

CMAC Research Portfolio

The entire CMAC research portfolio is made up of over 80 projects. The projects are supported as shown in the diagram (figure 4). The research funding currently includes EPSRC, EU and AMSCI projects. The CMAC Future Manufacturing Research Hub Programme is at the core of the CMAC Portfolio. Our Tier 1 partner companies support pre-competitive research through the CMAC membership structure and also collaborate with us on proprietary projects on a case by case basis.

Figure 4: Breakdown of project funding

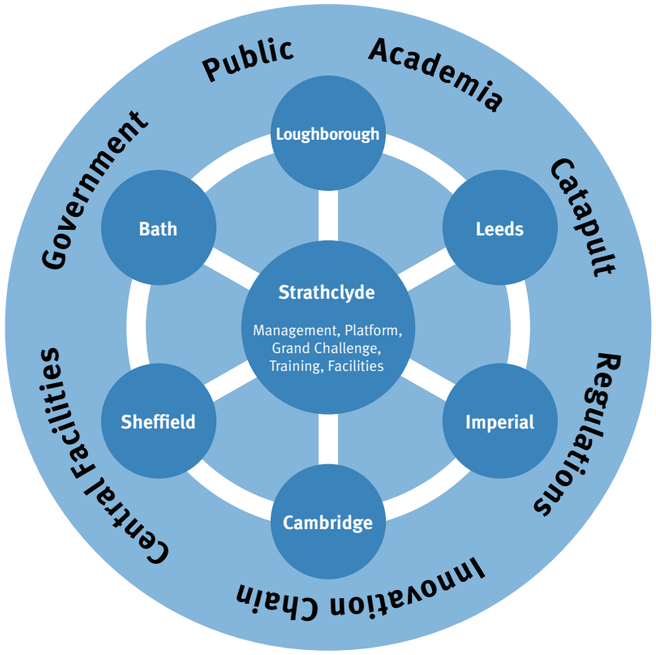


CMAC Partners

The Future CMAC Hub research programme is delivered by the seven partner universities with Strathclyde as the Hub and Bath, Cambridge, Imperial, Leeds, Loughborough and Sheffield as spokes. CMAC currently has over 130 people involved with over 70 researchers from the seven Future CMAC Hub partner universities and the 3 additional Universities (Edinburgh, Glasgow and Heriot Watt) that have DTC researchers with CMAC.

CMAC has substantial industry engagement and support through 11 pharmaceutical, 5 chemical, 2 food and 19 technology companies (15 SMEs) as well as 12 key Innovation partners. (see page 7).

Figure 5: Hub and Spoke model



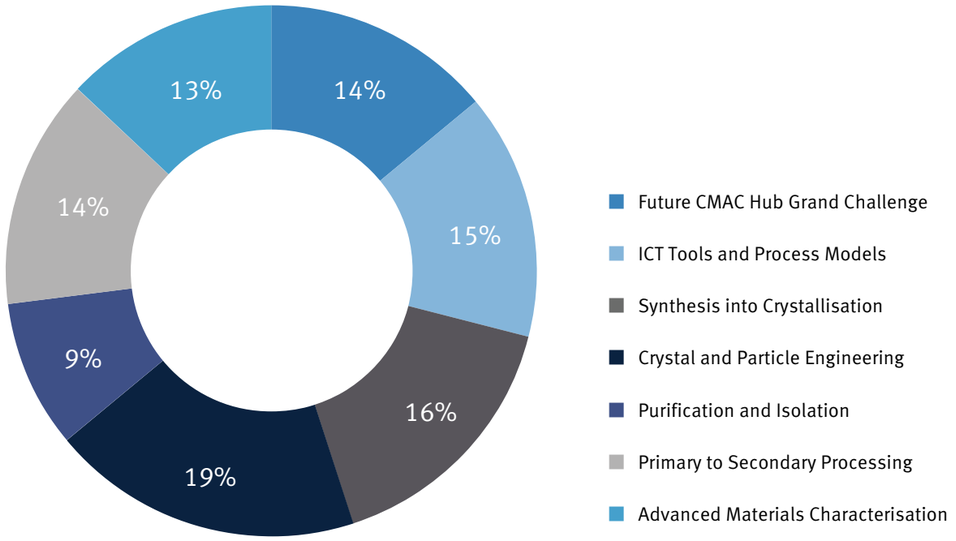


Figure 6: Breakdown of CMAC researchers by research area

Hub Overview

CMAC Manufacturing Innovation Roadmap

£100M funding portfolio 2011-2016	130 staff and student across network of 7 leading UK universities	8 Tier 1 partners GSK, AZ, Novartis, Bayer, Lilly, Pfizer, Roche, Takeda
7 years EPSRC funding secured	2016 IPSE Facility of Year Winner For Hub at University of Strathclyde	MMIC project front end study and Government support

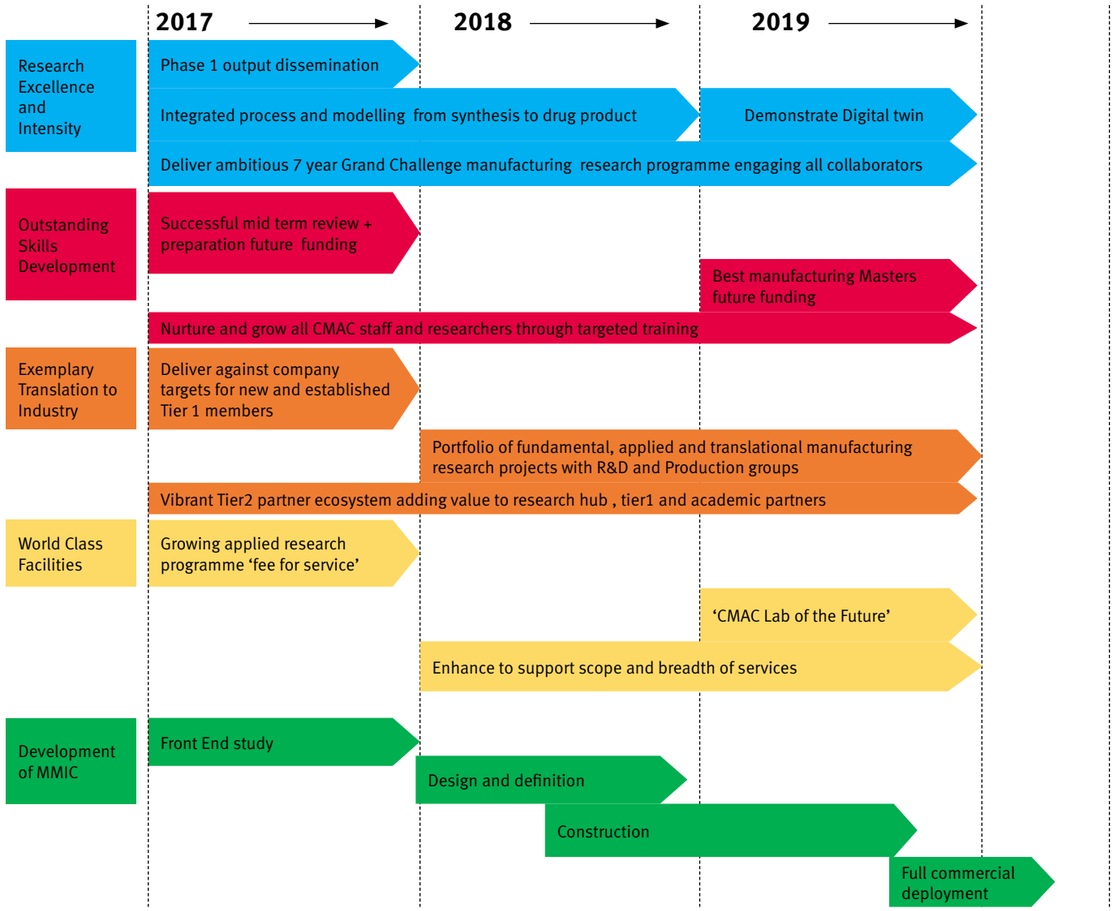


Figure 7: Innovation Roadmap

Why?

Optimised pharmaceutical and high-value chemical manufacturing operations across the value chain which

- Are economic, efficient, lean and world class
- Allows reduced time to market
- Are sustainable and wealth creating
- Deliver regulatory compliance

Benefits for patients

- Novel manufacturing technologies available
- Optimisation of processes that can be controlled or adapted

High value products resulting from

- Understanding of 'better and novel particles'
- Insight into particle formation
- Impact in formulation and quality attributes

High level impact of manufacturing research produced through

- Supportive governments
- Collaboration with companies
- Strong innovation network
- Strong UK Pharma base

Achieve in Future

- Leading Tier 1 and supply chain partners
- Peerless talent pool of PhD, MSc and post docs
- Impact of technology on new medicines and £1bn savings in manufacturing
- Process development with gram of material through modelling
- Grow world leading pre competitive £150m program
- Medicines Manufacturing Innovation Centre (MMIC) Operational

Benefits

- Improved manufacturing process and quality will benefit patients and producers driving CMAC sustainability
- Development of world class facilities will enable innovation across process and enhance to support manufacturing
- Focus on manufacturing translation will cement CMAC standing as leading International organisation influencing policy
- Production of microfactories will enable future pharmaceutical manufacturing and create jobs
- MMIC will save time, save capital and de risk investment for pharmaceutical companies.

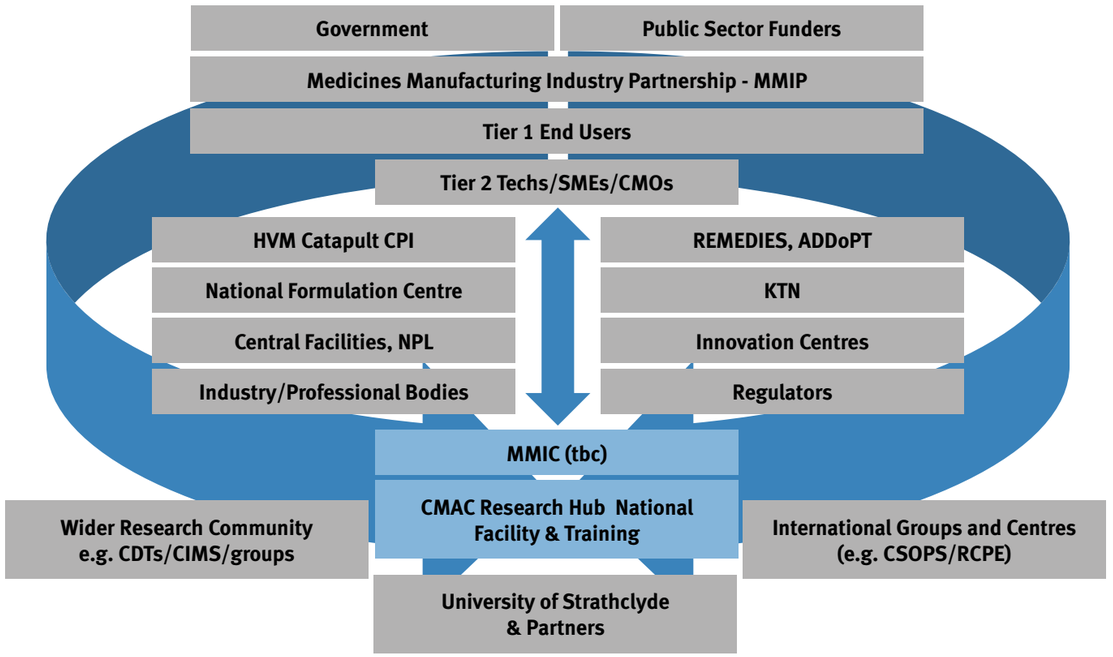


Figure 8: Innovation Landscape in UK

Hub Overview

Academic Engagement

- **Accelerating the adoption of continuous manufacturing**
- **Supporting UK collaboration in manufacturing research**
- **Maximising the impact of innovative manufacturing research**
- **Building the community through dissemination and outreach**

The Future CMAC Hub consists of seven academic partners, led from Strathclyde. Most of the researchers are based at those institutions. CMAC also has PhD researchers from Edinburgh, Glasgow and Heriot Watt who are part of the CMAC EPSRC DTC (EP/K503289/1) that was aligned with the EPSRC Centre for Innovative manufacturing in Continuous Manufacturing and Crystallisation that preceded the Future CMAC Hub (see page 47 for more details on the DTC).

CMAC acts as a focus for the wider research community in the area of continuous manufacturing and advanced crystallisation. Outreach, engagement activities and collaborations are key to CMAC's growth and success. Since 2011, CMAC has engaged with the wider community, acting to influence policy, facilitate and support events, develop national expertise and establish the CMAC National Facility. CMAC holds an important position in the collaborative research and innovation landscape in the UK. Our work has included policy influence and strategy development in the area of continuous manufacturing and advanced crystallisation.

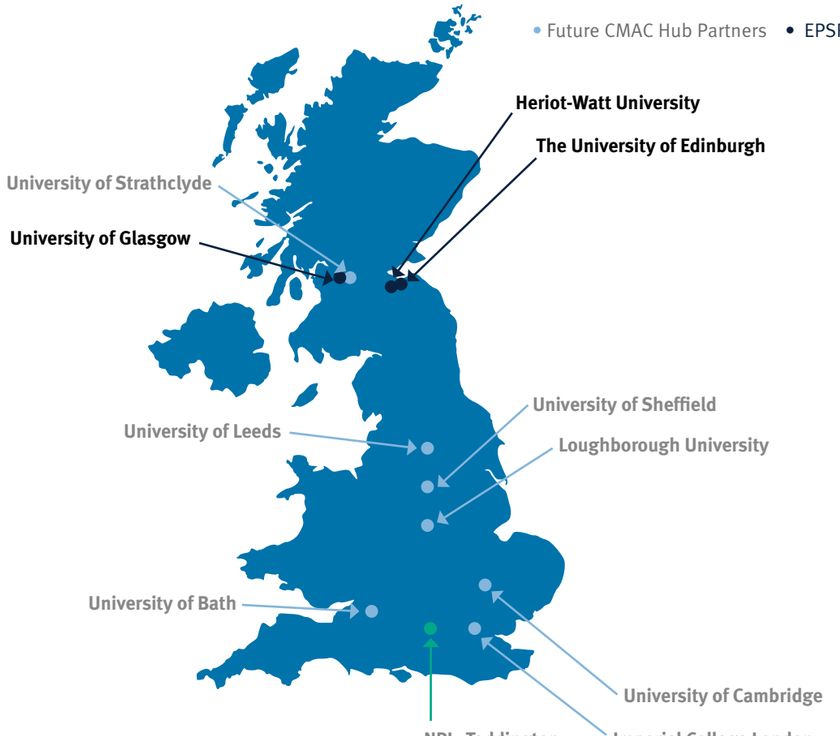


Figure 9: Map of UK institutions involved in hosting CMAC Researchers

The Hub has a number of projects that are part of the CMAC portfolio managed from Strathclyde, as well as being partners in aligned projects managed from other groups and Universities as shown in the figure 10. We have close links with the aligned projects summarised below. The CMAC Research Programme is explored on page 24.

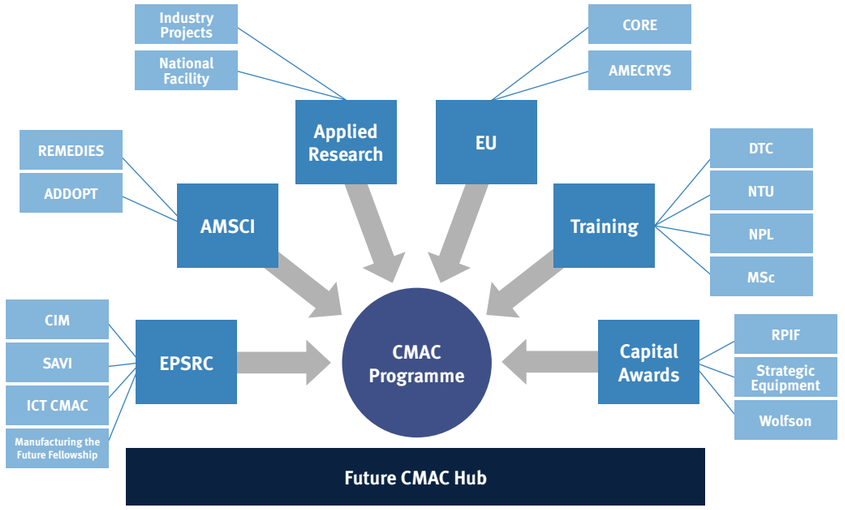


Figure 10: Map of funded projects

Aligned Projects

EPSRC
Dr Iain Oswald leads Pressure-Induced Nucleation for the Continuous Manufacture of supramolecular assemblies, with Prof Jan Sefcik and Prof Joop ter Horst as co-investigators. This project aligns with the Future CMAC Hub project, and seeks to develop a novel manufacturing methodology by which we are able to form new materials at high pressure and feed these into an industrial scale process. This project also has a post-doctoral and a PhD researcher based with CMAC at Strathclyde.

Prof Ivan Andonovic leads the Intelligent Decision Support and Control Technologies for Continuous Manufacturing of Pharmaceuticals and Fine Chemicals (ICT CMAC) project, with Prof Alastair Florence, Prof Jan Sefcik, Prof Chris Reilly, Dr Blair Johnston and Dr Alison Nordon of CMAC all being co-investigators. The project, which aligns with the CMAC programme, combines a range of disciplines in academia and the private sectors.

Prof Alastair Florence is a co-investigator on the Computationally Designed Templates for Exquisite Control of Polymorphic Form led from UCL by Prof Sally Price. There is a post-doctoral and a PhD researcher based with the CMAC team working on this project.

CMAC is a founding partner in I2APM. More details on this can be found on page 19.

EU
CMAC's Prof Joop ter Horst is part of the H2020 AMECRYS consortium (€335,500). AMECRYS aims at revolutionising the manufacture of biopharmaceuticals with innovative membrane crystallisation technology.

The field of chiral resolution & deracemization will become increasingly important in pharmaceutical industry and in CMAC. Prof Joop ter Horst leads a Marie Skłodowska-Curie Innovative Training Network on Continuous Resolution and Deracemization of Chiral Compounds by Crystallization (CORE). This European network brings together 15 PhD students, 8 academic and 7 industrial partners from 6 European countries to jointly construct an Industrial Toolbox on Continuous Resolution that provides next generation tools, approaches and methods to industry for the development of continuous resolution processes.

AMSCI
Refer to industry pages for AMSCI projects Remedies and ADDoPT on page 54-55.

Joint International PhD Programme with NTU
Refer to page 48.

NPL
CMAC hosts 3 PhD students as part of NPL Scotland. This UK joint research collaboration is focused on pharmaceutical metrology in pharmaceutical innovation and manufacturing.

Hub Overview

CMAC Open Day 2017

The CMAC Open Day 2017 launched the Future CMAC Hub as well as showcasing the significant growth and progress over the last five years of the CIM, highlighting key areas of manufacturing research which enable continuous manufacturing and future research directions. Through presentations, posters, exhibitions and tours of the world class facilities the attendees were informed of the latest research outputs from CMAC and the cutting edge technology. Keynote addresses were provided by Derek Bergland (Eli Lilly) and Sal Mascia (Continuus). There were 252 delegates from 71 organisations who attended the event.

Seminar Programme 2017

CMAC has an active programme of visiting academics who are invited to visit CMAC and to deliver a seminar to our researchers while they are here.

Year	Date	Name	Institution	Title
2017	8th February	Dr Charles D. Papageorgiou	Takeda	Overview of Continuous Crystallisation at Takeda
	28th March	Professor Matthias Kind	Karlsruhe Institute of Technology	Numerical Simulation of Technical Particle Formation Processes
	28th August	Dr Aniruddha Majumder	University of Aberdeen	Modelling and simulation studies of continuous crystallisation processes
	26th September	Dr Thomas Vetter	University of Manchester	Continuous particulate processes in the context of the pharmaceutical industry
	30th November	Dr Herman Kramer	TU Delft	Nucleation control in continuous crystallization processes

Visiting Researchers

CMAC hosted 5 visiting researchers during 2017.

Date range	CMAC Supervisor	Home Institution	Programme	Project
21 Aug-29 Sep	Prof Joop ter Horst	University of Rouen-France	CORE ITN	develop a screening methodology to quickly and reliably determine the crystallization-based resolution possibilities of a new chiral compounds, assessing the solid state and phase diagram in complex multicomponent systems of chiral compounds
21 Aug-29 Sep	Prof Joop ter Horst	Radboud University, Nijmegen	CORE ITN	Viedma Ripening-enabled Chiral Synthesis
21 Aug-29 Sep	Prof Joop ter Horst	Based at Syncom BV, Netherlands and at Strathclyde	CORE ITN	developing a flow method for the synthesis of a biological interesting fructosamine mimic: development of a continuous process for deracemizations
May-October	Prof Joop ter Horst	Radboud University in Nijmegen	Erasmus	Computational study of the co-crystals of Etiracetam and Leviracetam
Jan 2017	Dr Chris Price	University of Chemistry and Technology in Prague	Erasmus	Develop research on the effects of various solvents on tendency to form particle agglomerates during filtration, washing and drying of paracetamol.

Geldart Medal Winner

CMAC's Prof Jim Litster (Sheffield) has won the Geldart Medal from IChemE. The medal founded in 2014, is awarded biennially to one or more individuals who have made a significant recent contribution to research in particle technology. This is recognised through scientific advancements widely acknowledged within the community and high impact findings recognised outside the particle technology community.

Press

During 2017 CMAC was featured in:

26 January edition of Chemical Engineer Magazine "Continuous Collaboration".

03 April edition of Chemistry World. "The flow revolution".

24 May 2017, Pharmaceutical Online "Developing Mobile Continuous Process Technology: A Collaborative Innovation Case Study".

16 November, The Scotsman, "Fast-track medicine base in Scotland could be a game changer".

28th November, featured in the Herald, "Alastair Florence: 'The key to success is working pre-competitively with industry'".

Hub Overview

Conferences

The CMAC community has attended many conferences worldwide throughout 2017. Academics and senior technical staff have been invited to events including ESFRI, Brussels; BACG, Manchester; AIChE, Minneapolis; ISIC, Dublin; AAPS, San Diego and CPhI, Frankfurt, KTN Chemistry Showcase, York; RSC Continuous Flow Chemistry for Industrial Processes Symposium; ACCGE-21, New Mexico. Participation included acting as panel members, session chairs and invited speakers.

Visits

The CMAC Facilities at Strathclyde (see pages 38-41) have been visited by a wide range of visitors including Lord Duncan of Springbank, Parliamentary Undersecretary of State in the Scotland Office; RCPE directors Professor Johannes Khinast and Mr Massimo Bresciani; Prof Wei Shyy, Executive Vice-President & Provost Hong Kong University of Science & Technology (HKUST); Senior AZ team including Dr Dafni Bika (Global Head Pharmaceutical Technology and Development), Andy Evans (Site Manager Macclesfield Multi Format Facility) and Dr Andrew Jones (VP Manufacturing Science and Technology).

CMAC researchers have been very active during 2017 with major presence at BACG and ISIC, and 10th World Congress of Chemical Engineering, Barcelona. CMAC was represented by researchers at ISMIP IX, BIWIC, Bruker Micro CT, Biovia Forum, Allotrope Foundation, ChemSpec, and the RSC Symposium in Munich.

A full list of publications for 2017 can be found in the appendix on page 62.

Hub Overview

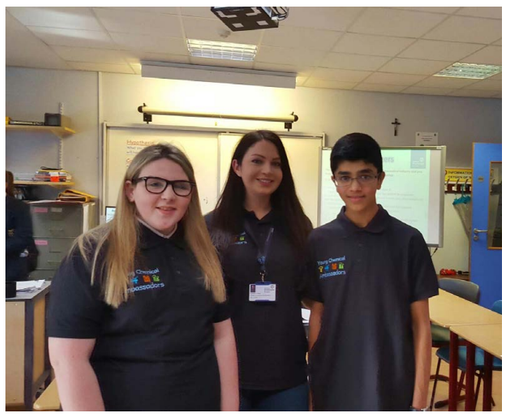
Public Outreach

Explorathon

CMAC researchers engaged with approximately 800 people at the Riverside Museum as part of Explorathon ‘17, a celebration of European Researchers’ Night across Scotland. The team exhibited a variety of demos at the Extravaganza event with the aim of promoting the research that is carried out in CMAC and how this is transforming the way that medicines are made.

Young Ambassador

As part of the Royal Society of Chemistry funded Young Chemical Ambassador Programme, CMAC DTC researcher Clarissa Forbes mentored two pupils to deliver a workshop to their chemistry class at St Andrews RC Secondary School in Glasgow on why crystals are important to chemical engineers working in the pharmaceutical industry.



Spectroscopy in a Suitcase

CMAC DTC researchers Alex Cousen, Ruth Lunt and Lois Wayment are part of the team at Bath who deliver the Royal Society of Chemistry’s Spectroscopy in a Suitcase scheme which provides portable NMR, IR and UV/Vis instruments to be taken in to schools.

Images of Research

CMAC's Monika Warzecha is the overall winner in this year's Images of Research at Strathclyde. Her image, in the 'Advanced Manufacturing and Materials' category, won via a public vote. The Images of Research were showcased on tour around Scotland and then, for the first time, to the European Parliament in Brussels for the European Innovation Summit. Twitter: @StrathImages

World of Work

CMAC DTC researcher Sarahjane Wood took part in a World of Work Career event in Wellshot Primary School, Tollcross, Glasgow. Sarahjane was invited along to tell them about what it is like being a scientist and working in a university lab. She reported back that the children seemed to enjoy themselves and were interested in finding out about what she does in CMAC.

Hub Overview

Internationalisation

I2APM

The International Institute for Advanced Pharmaceutical Manufacturing (I2APM) brings together world-leading academic expertise to deliver new end-to-end continuous manufacturing capabilities with the goal of advancing the science and technology of integrated primary and secondary continuous manufacturing of pharmaceutical products that will transform the global supply chain for medicines.

I2APM is a research and educational partnership between CMAC, the Center for Structured Organic Particulate Systems (C-SOPS) in the US and the Research Center Pharmaceutical Engineering (RCPE) in Austria. EPSRC SAVI funding has facilitated activities between CMAC and C-SOPS.

In addition to an executive and academic board, four working groups have been established which comprise members from each centre. These working groups, which meet monthly, advance activities in the following areas: events, regulatory/common language, research, and training.

Events Workgroup

First I2APM International Symposium

The first I2APM International Symposium and Training Day, hosted by CMAC, took place in the Technology and Innovation Centre at the University of Strathclyde in Glasgow on 30th November –1st December 2016. The event was opened on the 30th November with talks from Professor Johannes Khinast (RCPE), Professor Alberto Cuitino (C-SOPS), and CMAC Industrial Director Craig Johnston, who gave overviews of each centre, while CMAC Centre Manager Dr Andrea Johnston provided an I2APM update. Researchers and academics from RCPE, C-SOPS and CMAC participated with oral and poster presentations as well as discussions and social activities that aimed to initiate new collaborations.

Emerging Pharmaceutical Manufacturing Summit

The first Emerging Pharmaceutical Manufacturing Summit, hostedby C-SOPS in conjunction with I2APM, took place in Malta on 8th – 9th of May 2017. The summit brought together first and second wave technology adopters and academics, along with a diverse group of regulators, to stimulate further dialogue and adoption of continuous manufacturing of pharmaceuticals.

Regulatory / Common Language Workgroup

The regulatory working group have consolidated input from each centre's academic and industry partners into the following document: Draft Current Recommendations for Implementing and Developing Continuous Manufacturing of Solid Dosage Drug Products in Pharmaceutical Manufacturing. The document, which was initiated by C-SOPS in the US, will be shared with the FDA.

Research Workgroup Joint Research Project, CMAC – C-SOPS

A joint research project is currently underway between CMAC and C-SOPS, to investigate how modifications at the crystallisation stage of API production translate to behaviour in the secondary formulation stage. The outcome of this will be a joint research paper between CMAC and C-SOPS.

Flowsheet models were developed as part of the CMAC CIM phase II work to produce batches of API with different variables e.g. size, agglomeration, and the I2APM research theme will investigate if changing these variables has an effect on the properties of the drug product tablets.

Batches of paracetamol of different particle sizes have made at CMAC using continuous crystallisation and will be shipped to C-SOPS for secondary processing, using a continuous tabletting line. These batches will undergo characterisation testing at CMAC, and the same tests will be performed on the material at C-SOPS. Dissolution and physical tests will be performed on the tablets at C-SOPS.

Researcher	Host	Duration	Placement
John McGinty (CMAC)	C-SOPS, Purdue	March – April 2016	PAT based monitoring of the crystallisation kinetics
Heidi Gruber-Woefler (RCPE)	CMAC	September – December 2016	Develop a continuous synthesis of paracetamol with a directly coupled purification step via continuous crystallisation
Vaclav Svoboda (CMAC)	RCPE	February – March 2017	Developing phase diagrams of paracetamol/acetic acid/ impurities/solvent for integrated reaction, work-up and crystallization of paracetamol
Javier Cardona (CMAC)	RCPE	May 2017	Extracting crystal size and shape information from flow-through microscope videos
Sarahjane Wood (CMAC)	RCPE	July – September 2017	Effects of injection pressure on drug release and subsequent comparison of injection moulding equipment
Ravi Parekh (CMAC)	C-SOPS, Rutgers	August – September 2017	Breakage properties of wet granules by milling and to formulate and validate breakage models for use in predicting milling capabilities of caffeine granule formulation
Alice Turner & Sarahjane Wood (CMAC)	C-SOPS, Rutgers	September – October 2017	Analysis of innovative oral dosage forms using a range of PAT
Frederik Doerr (CMAC)	C-SOPS, Purdue	October 2017	Single particle compression measurements and mechanistic understanding of deformation on crystalline solids from droplet evaporation experiments

Hub Overview

Training Workgroup

The training workgroup are collating training material from all 3 centres, with the aim of producing a CPD training package of teaching material from CMAC, RCPE and C-SOPS. This package, which can be offered to industry, will cover different aspects of continuous manufacturing.

As part of the I2APM International Symposium, the training workgroup held a day of training on the 1st of December 2016 with sessions from C-SOPS, RCPE and CMAC. The training day involved sessions delivered by academics from each 3 centres and was concluded with a researcher network session to further discuss collaborative research projects.

3rd International Symposium on Continuous Manufacturing of Pharmaceuticals

CMAC and MIT co-hosted the 2nd International Symposium on Continuous Manufacturing of Pharmaceuticals (ISCMP) in Boston on 26-27 September 2016 with 300 attendees. After the 2014 event, eight significant white papers were produced http://iscmp2014.mit.edu/white-papers. One of the major outputs from the 2016 event is a regulatory white paper on continuous manufacturing of pharmaceuticals. Planning is in progress for the 3rd symposium which takes place in London, Autumn 2018.

CMAC FUTURE MANUFACTURING RESEARCH HUB

NANYANG TECHNOLOGICAL UNIVERSITY

NTU – Strathclyde Collaboration

The Collaboration between CMAC (Strathclyde) and SCBE (Nanyang Technological University - NTU) was initiated in 2012 and has 5 PhD researchers in place across the University of Strathclyde and NTU Singapore. A Symposium event was hosted at Strathclyde by Strathclyde Principle Sir Jim McDonald and NTU President Professor Bertil Andersson in late 2016. Workshop Outputs included updating future research funding plans and scoping projects for future researcher exchanges. A researcher placement scheme is now in operation between the two Universities and the first two placements have been completed with more planned for 2017/2018. Two new CMAC PhDs have just been recruited at Strathclyde as part of the continuing partnership between the two universities.

Hub Overview

Talent Pipeline

October 2011-October 2017

People are at the core of our success and developing a talent pool has been a key achievement.

INPUT

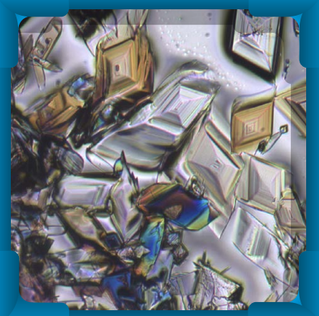
90 PhD Researchers

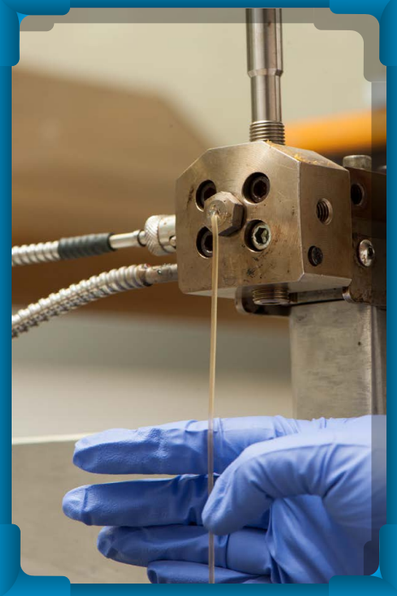
43 Research Associates

Future CMAC Hub (Cambridge, Imperial, Sheffield, Strathclyde)
CIM Phase I (Bath, Cambridge, Glasgow x2, Strathclyde x3)
CIM Phase II (Cambridge, Loughborough x3, Strathclyde x6)
ADDoPT (Strathclyde)
COST (Strathclyde x2)
CPOSS (Strathclyde x2)
ICT CMAC (Loughborough, Strathclyde x7)
Manufacturing With Light (Edinburgh)
MOPP (Strathclyde)
Proprietary Projects (Strathclyde x10)
Remedies (Strathclyde)

26 Management, Projects & Technical Support

Future CMAC Hub (Strathclyde x4)
CIM (Strathclyde x6)
Industry Team (Strathclyde x4)
National Facility & Technical Staff (Strathclyde x11)
ICT CMAC (Strathclyde)





The success of CMAC in developing researchers has resulted in a two-way exchange between Academia and Industry. This is coupled with researchers who have used their multidisciplinary skills learned through the CMAC programme to gain prestigious places in industry. This talent pipeline is a key performance indicator for CMAC and highly valued by industry.

OUTPUT

PhDs

DTC Bath ⇢ GSK, UK
DTC Bath ⇢ AZ, UK
PhD Bath ⇢Johnson Matthey, UK
PhD Cambridge ⇢Industry
DTC Edinburgh ⇢ Nalas Engineering, USA
PhD Edinburgh ⇢ MOD
PhD Edinburgh ⇢ University of Edinburgh
DTC Glasgow ⇢ University of Glasgow
PhD Glasgow ⇢ University of Glasgow
PhD Glasgow ⇢ University of Glasgow
PhD Heriot Watt ⇢ Solid Form Solutions, UK
PhD Heriot Watt ⇢ Solid Form Solutions, UK
DTC Loughborough ⇢ CMAC Strathclyde x2
DTC Loughborough ⇢ PSE
PhD Loughborough ⇢ CMAC Strathclyde
DTC Strathclyde ⇢ Johnson Matthey
DTC Strathclyde ⇢ CMAC Strathclyde x3
PhD Strathclyde ⇢ University of Strathclyde
PhD Strathclyde ⇢ CMAC Strathclyde
DTC Strathclyde ⇢ GSK, UK
PhD Strathclyde ⇢ Johnson Matthey
DTC Strathclyde ⇢ KTP Associate, University of Strathclyde
PhD Strathclyde ⇢ Mettler Toledo, Germany
PhD Strathclyde ⇢ MIT, US
PhD Strathclyde ⇢ science and engineering sector industry, Scotland

Research Associates

CIM Phase I RA Bath ⇢ University of Bath
CIM Phase I RA Cambridge ⇢ Ford
CIM Phase II RA Cambridge ⇢ Norwich Business School, Cambridge
CIM Phase I RA Glasgow ⇢ University of Nottingham, UK
CIM Phase I RA Loughborough ⇢ GSK, UK
CIM Phase II RA Loughborough ⇢ Loughborough
CIM Phase I RA Strathclyde ⇢ CPACT, UK
CIM Phase I RA Strathclyde ⇢, GSK, UK
CIM Phase I RA Strathclyde ⇢ MacFarlane Smith, UK
CIM Phase II RA Strathclyde ⇢ AstraZeneca, UK
CIM Phase II RA Strathclyde ⇢ National University of Ireland Galway
COST RA Strathclyde ⇢ University of Limerick
CPOSS RA Strathclyde ⇢ Eli Lilly, US
ICT CMAC RA Loughborough ⇢ Purdue, US
ICT CMAC RA Strathclyde ⇢ University of Strathclyde
Manufacturing With Light RA Edinburgh ⇢ University of Edinburgh
Proprietary Project RA Strathclyde ⇢ AZ, Macclesfield, UK
Proprietary Project RA Strathclyde ⇢ University of Bradford, UK
Proprietary Project RA Strathclyde ⇢ Imperial College London

Staff

Assistant Centre Manager ⇢ iBioIC, UK
DTC Administrator ⇢ University of Strathclyde, UK
Laboratory Manager ⇢ City University of New York, US
Management Accountant ⇢ Freelance Accountant
Senior Technician ⇢ Macquarie University, Australia
Technician ⇢ PhD at University of Glasgow, UK
Technician ⇢ Pharmaceutical Industry, Ireland

Research

EPSRC Future CMAC Hub Research Programme

Vision

To deliver predictive design tools and novel integrated continuous processing platforms for the supply of next generation high performance personalised products.

CMAC is developing cutting edge design and modelling tools alongside integrated production and supply chain systems to address the future needs of patients, consumers and industry. Health systems worldwide are facing challenges to deliver better medicines to more people with tightening budgets and this programme addresses these via use of continuous manufacturing.

The idea behind this research programme is to take a molecule and use as little material as possible to rapidly design an end-to-end continuous manufacturing process to deliver the product. The resulting process design will be used to deliver a microfactory that can manufacture the product. The business case to support this innovative way of producing pharmaceutical products will be developed in parallel.

A partnership of world class researchers, from seven universities whose expertise spans multiple disciplines, will deliver the research programme.

Scope

The CMAC Future Manufacturing Research Hub Programme will deliver a platform research capability that benefits collaborators and industry partners, and will address the grand challenge: 'Rapid performance-based design and continuous manufacture of structured particulate products'.

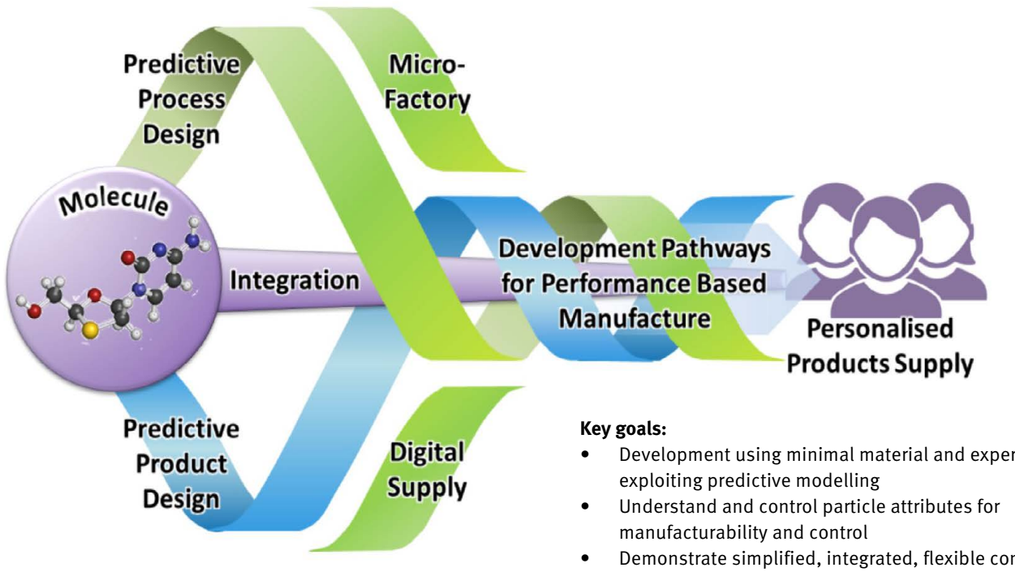


Figure 11: Future CMAC Hub Scope

Key goals:

- Development using minimal material and experiments exploiting predictive modelling
- Understand and control particle attributes for manufacturability and control
- Demonstrate simplified, integrated, flexible continuous process streams

Hub Platform Research

The Hub platform provides the underpinning operational framework, equipment capability and personnel to effectively support the targeted research activity in a flexible way over the course of the project. Specific activities include:

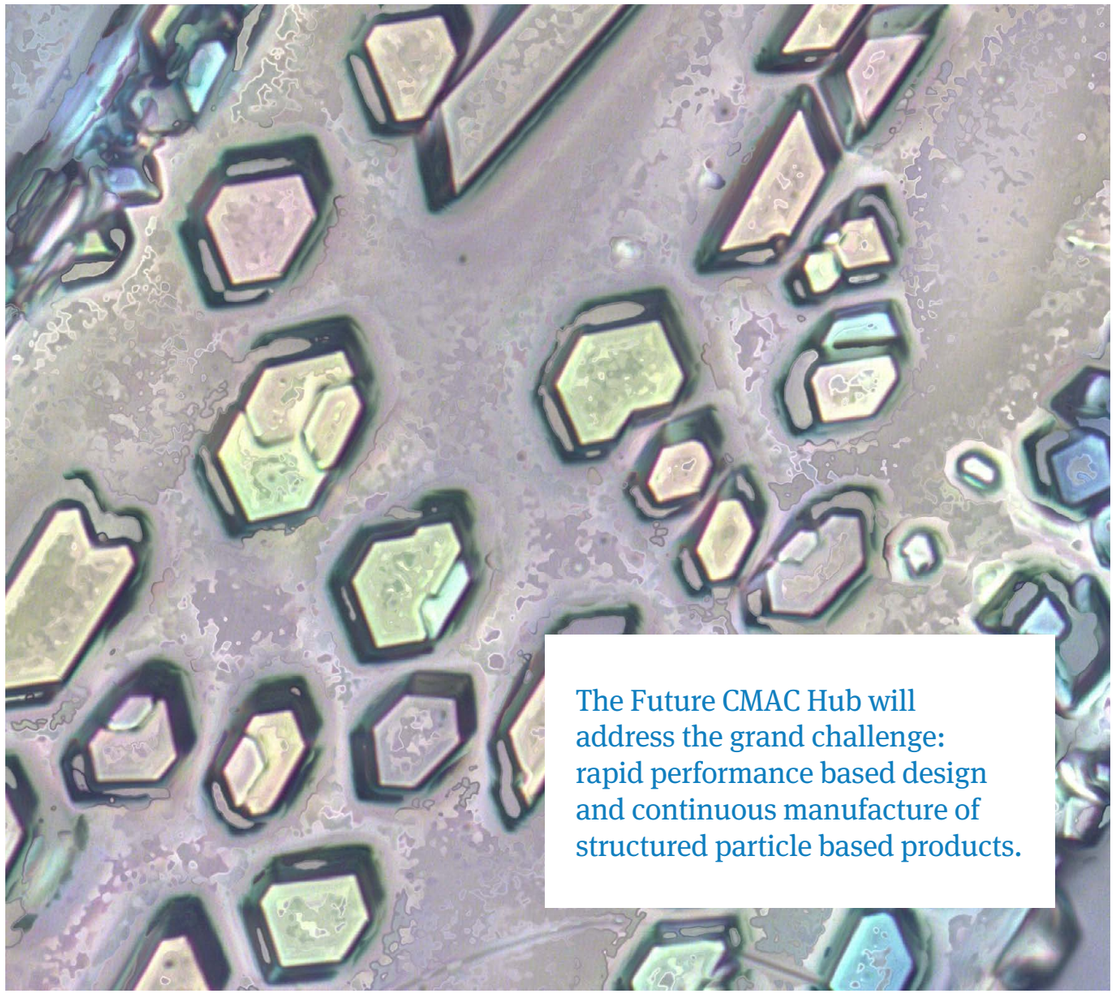
- Process technology development
- ICT tools for continuous manufacturing
- Developing the science base: characterisation, classification and prediction
- Informing programme evolution
- Enhancing skills development and training

Hub Grand Challenge Research

This project will deliver a step-change in capability to bring functional high-value solid products rapidly to market, with a focus on pharmaceutical products. Small molecule systems of interest to industry and academic partners will be investigated. The work will inform development of radically new approaches for advanced predictive design and integrated manufacturing.

Three main work packages will deliver the project:

- Integrated Development Pathways (WP1)
- Future Microfactories (WP2)
- Future Supply Chain (WP3)



The Future CMAC Hub will address the grand challenge: rapid performance based design and continuous manufacture of structured particle based products.

Research

Integrated Development Pathways (WP1)

This work will focus on rapid, predictive design of products and processes. It will develop a new capability by integrating theoretical, modelling, experimental and ICT approaches. Predictive design approaches that combine crystal engineering, particle engineering and structure generation to produce final dosage forms with consistent and predictable performance will be targeted.

Future MicroFactories (WP2)

Innovative flexible efficient production systems comprising integrated processing platforms are the goal of this work. At laboratory scale, prototype microfactories will be developed and operated based on the optimised process flowsheet identified using the integrated development pathways for each molecule of interest.

Future Supply Chain (WP3)

Future digital supply of personalised products and medicine is being investigated in parallel. We will develop new distributed manufacturing supply chain models that offer step changes in local volume flexibility and responsiveness, driving manufacturing closer to the point of need and personalisation. Supply network reconfiguration strategies will integrate technology capabilities emerging from integrated development pathways and future microfactories and explore supply chain digitalisation opportunities that connect the digital factory through to the end consumer/patient.

Digital Twin

For CMAC, digital twin refers to a virtual replica of experiments, equipment and/or measurements. Data from small scale experiments/measurements are used to parameterise their digital twins. These parameters are used to virtually design a full scale manufacturing process's digital twin, driving physical construction of that manufacturing process. When operational the manufacturing digital twin enables analysis of data, monitoring of systems and design of future implementations.

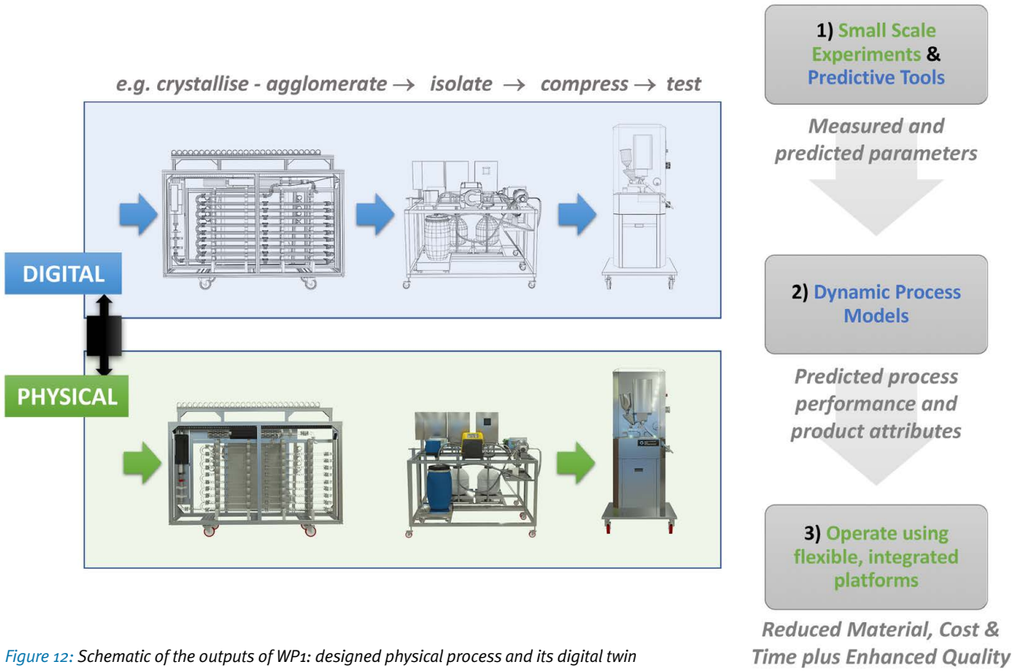


Figure 12: Schematic of the outputs of WP1: designed physical process and its digital twin

Product Process Archetypes and Microfactories

CMAC has identified three initial scenarios that combine addressing challenging physical properties with specific continuous manufacturing chain processes. We have termed these scenarios product process archetypes (PPAs). We will target PPAs where integrated continuous processing will deliver benefits. Underpinning this is the idea that there are types of particle that will likely have an ideal type of continuous manufacturing process that delivers desired product performance. For example "needle-like" crystals usually need to be processed in some way to give particles that are able to be handled easily and then formulated into products with desired performance.

CMAC has targeted three PPAs with a view to delivering three microfactories (MFs). PPA1 will deliver a microfactory that combines crystallisation, isolation, extrusion and 3D-printing or injection moulding of a drug/polymer suspension as a simplified process chain, reducing the number of steps in the process, as in figure 13.

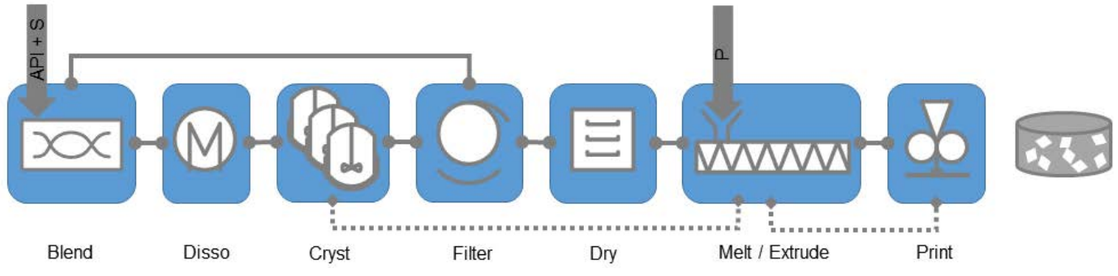


Figure 13: PPA1-----MF1 (example)

PPA2 is very similar to PPA1 but addresses API with poor molecular bioavailability as per figure 14.

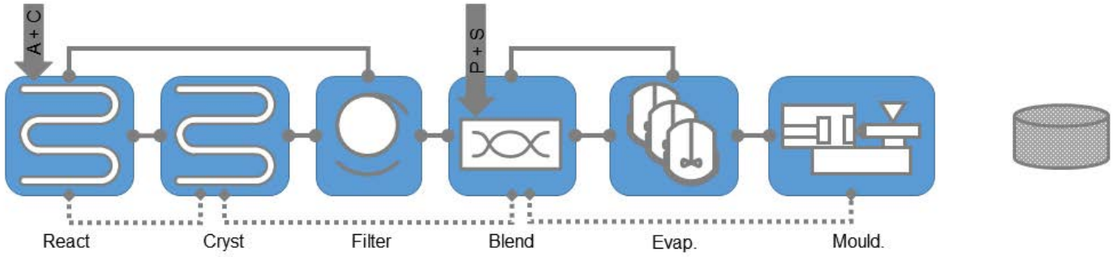


Figure 14: PPA2-----MF2 (example)

PPA3 will deliver microfactory 3 by combining continuous crystallisation, spherical agglomeration, and direct compression to produce the final dosage form and will address difficult morphology issues (e.g. needle like crystals) as per figure 15.

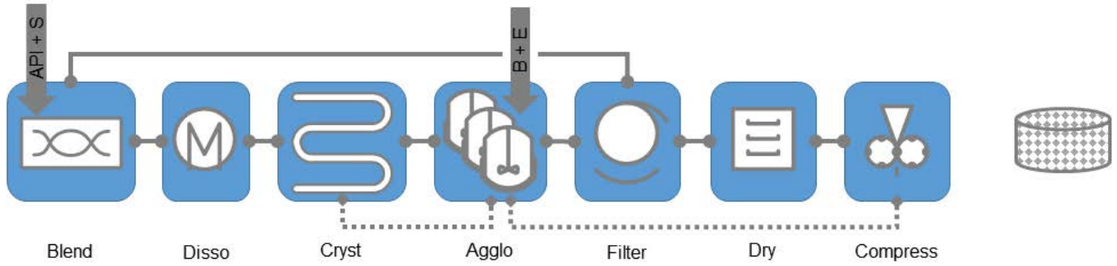


Figure 15: PPA3-----MF3 (example)

Research

Active Pharmaceutical Ingredient End-to-End Manufacturing and Digital Twin

The CMAC Future Manufacturing Research Hub launched its research programme with the development of an end-to-end process for the synthesis, purification, isolation and formulation of Paracetamol. Parallel to this was also the development of a digital twin of the manufacturing process (built in PSE's gFormulate). This short project ran from January to June 2017 and built upon the outputs of the CMAC Centre for Innovative Manufacturing (CIM). The objective of this project was to assess the current capabilities in development workflows, equipment and modelling to inform future research directions.

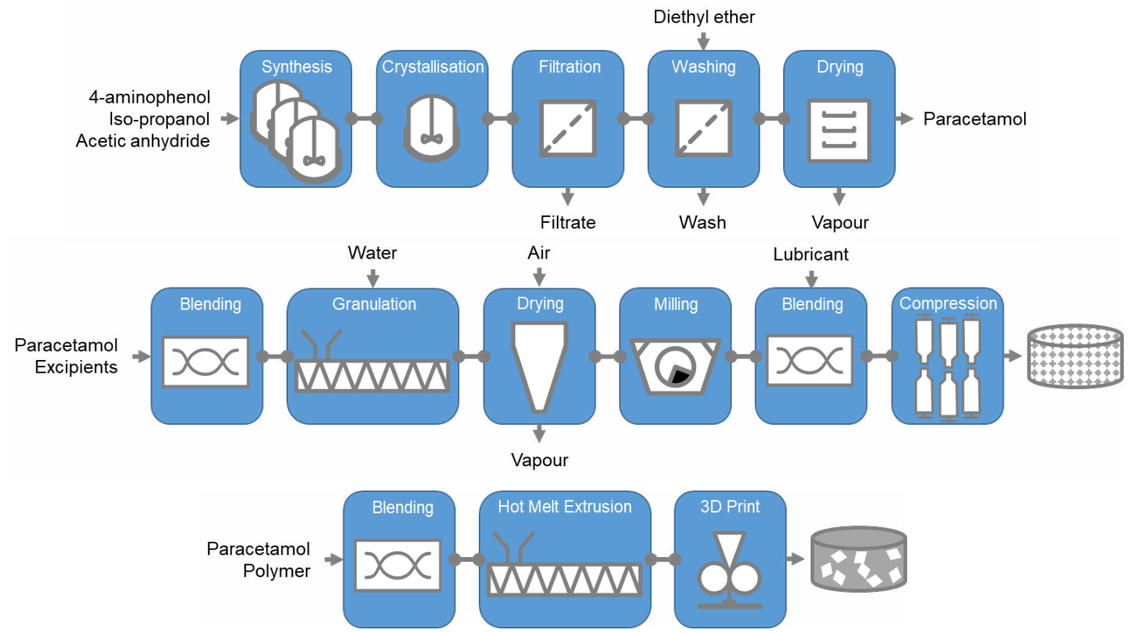
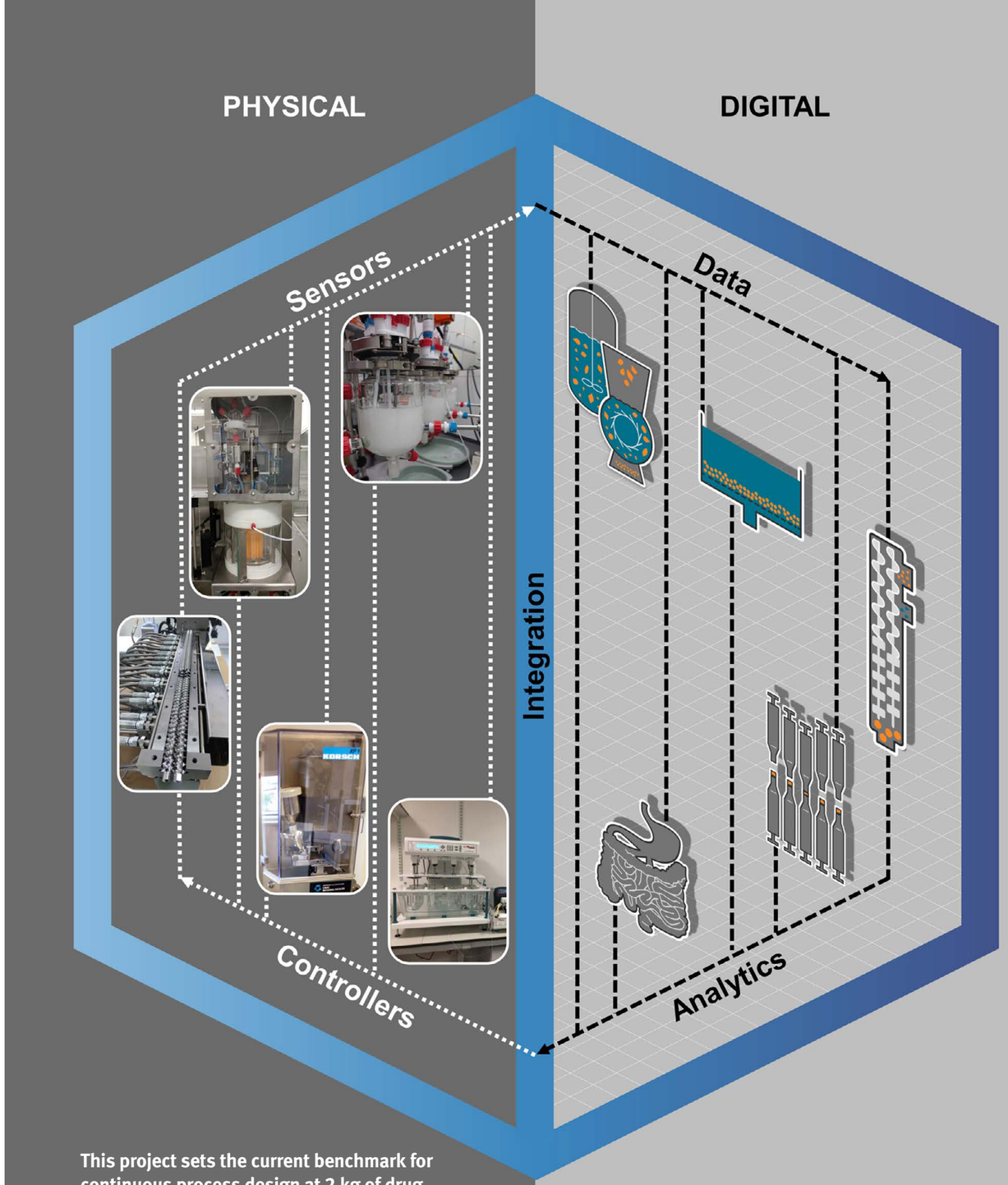


Figure 16: Process for Paracetamol, an example of PPA1

This project demonstrated the capability to produce a minimum of 50 tablets from drug substance synthesised and crystallised in a continuous process. Tablets produced met the target specifications for fast release (via traditional wet granulation) and slow release (via hot melt extrusion and 3D printing). These product deliverables were met by achieving intermediate specifications throughout the process chain, e.g. drug substance particle size distribution. Data was collected with regards to process development time, processing time and researcher effort for comparison to current industrial methods. Tools from CMAC Tier 2 partner Britest were used to identify the critical hold points as well as key in/off-line measurement points. Using the existing CMAC ICT infrastructure complete development and process data were contextualised and archived within the ELNs. Based on the experience in this project, gaps have been identified in key areas relating to filtration, hot melt extrusion and spherical agglomeration. As a result, future activities in Hub projects will focus on addressing these areas.



This project sets the current benchmark for continuous process design at 2 kg of drug substance and 6 month timescale. By 2023 the ambitious challenge for the hub will be to reduce this to 100 g and 2 months whilst achieving improved products. Thus, accelerating the development of products and processes based on continuous manufacturing to meet the needs of industry, consumers and patients.

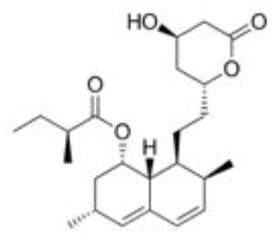
Figure 17: Process and its digital twin for Paracetamol

Research

Towards a Lovastatin Microfactory

From August 2017, the newly assembled Hub research team have been working full time on a project to deliver first a process design and digital twin (WP1), and then a microfactory (WP2) for Lovastatin as a model compound for crystals with a high aspect ratio needle-like morphology (PPA 3 – see page 27).

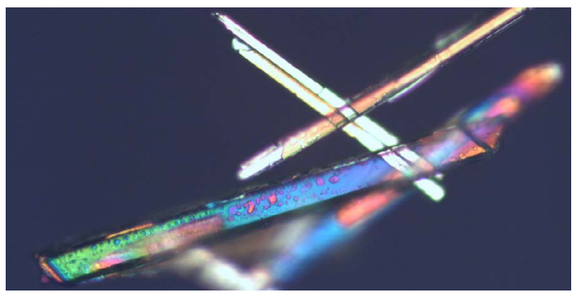
Lovastatin is the active pharmaceutical ingredient (API) in the product Mevacor, a statin for lowering cholesterol invented by Merck. It had $0.6 billion sales in 1999, but the patent expired in 2001. Tablets are sold in 20, 40 and 60 mg doses. Lovastatin is a high permeability, low solubility compound, typically synthesised by a fermentation process.

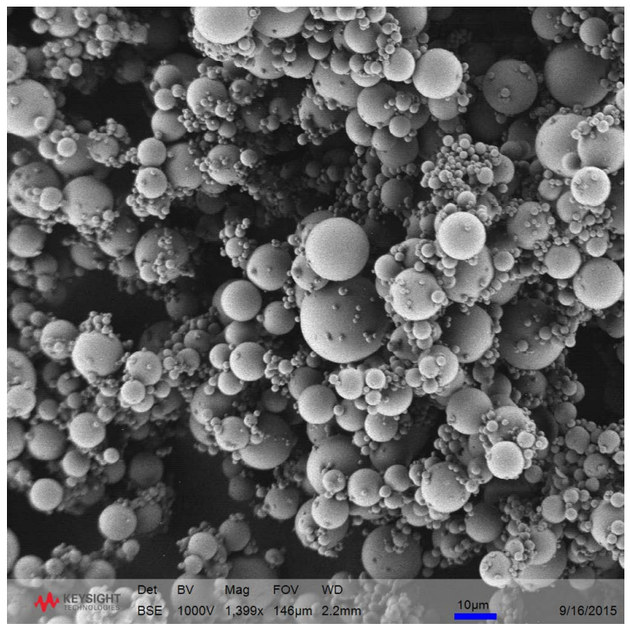


The starting point for the CMAC manufacturing process will be high purity Lovastatin spiked with impurities. The final dosage form will be compressed tablets (20 to 60 mg & ›200 mg dose).

PPA 3 uses spherical agglomeration to address the challenge presented by the needle like form of Lovastatin crystals. The spherical agglomerates will then undergo processing via direct compression to be transformed into the desired dosage form of a tablet. For this project the primary objective is to exemplify the archetype rather than reproduce commercially available tablets. Although Lovastatin is the focus compound for this project other compounds will also be considered to test generic learning points.

Figure 18: Lovastatin





In the next 12 months we plan to develop the end-to-end process for producing Lovastatin via continuous manufacturing from crystallisation to tablet. The outputs will include a process design and digital twin of the process (WP1).

The next stage, which we expect will commence in Q3 2018, will be the development of a Lovastatin microfactory (WP2) with the goal of delivering a testable prototype and its digital twin by June 2020.

In parallel a business case to support the adoption of the new microfactory will be explored by comparing the current and future state scenarios for manufacture of this product (WP3).

Figure 19: Digital render of end-to end process set up

The contributions of the Hub and Spoke partners to the deliverables of the research programme are shown in Figure 20.

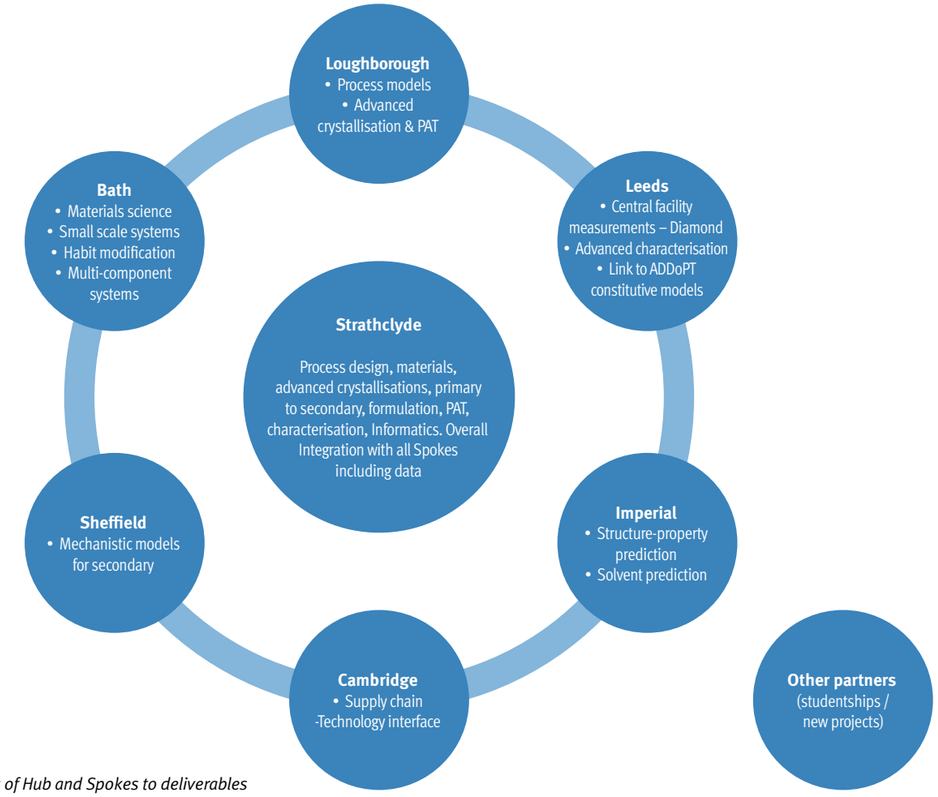


Figure 20: Contributions of Hub and Spokes to deliverables

Research

Hub PhD Programme

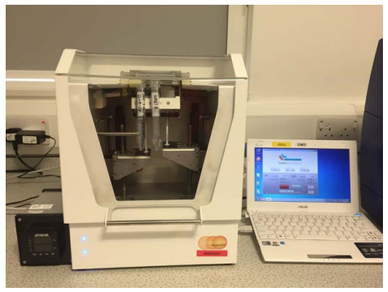


Image: NanoAssemblr benchtop

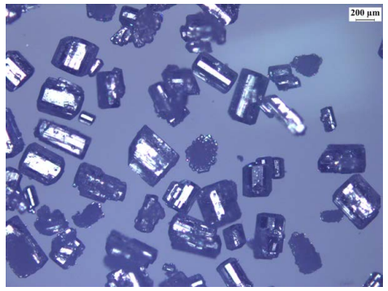


Image: Secondary Nucleated Filtered Seeds

Industry Mentors

All CMAC researchers benefit from support from internationally leading supervisors and experts from industry through the established industrial mentor scheme which was re-launched in 2017 with new groups aligned to the Future CMAC Hub programme.

Industry experts coach students at our regular mentor meetings providing industrial relevance and context for their work. The meetings are a mixture of conference call and face-to-face meetings involving both Tier 1 and some Tier 2 companies. These mentor meetings have enabled access to industrial analytical equipment and facilitated placements within the companies involved. Research and learning in CMAC is transferred into industry and the companies' access and influence the ongoing CMAC research via this scheme. (Details on who is in which group in terms of Researchers, Mentors and Academics can be found in the appendix pages 60-61).

Synthesis into Crystallisation

The CMAC synthesis into crystallisation mentor group brings together researchers with the common interest of bridging the gap between synthesis and crystallisation. The majority of research focusses on the translation of synthesis into crystallisation by investigating specific areas such as crystallisation kinetics, solid dosing and several crystallisation mechanisms. Furthermore, specific technologies are being studied such as MSMPR, NanoAssemblr™ and the monitoring of these techniques with PAT such as FBRM, UV-ATR and molecular dynamics simulation. Industrial partners from AstraZeneca, Bayer, GSK, Lilly and Takeda contribute to the synthesis into crystallisation mentor group through project guidance and support with insight into the industrially relevant areas.

Research Highlight

The progress from batch to continuous manufacture of pharmaceuticals has highlighted the requirement of how to dose solid directly, efficiently and accurately into continuous flow systems. DTC researcher Arabella McLaughlin is working on gaining scientific understanding on operational principles, solid dissolution rate kinetics and problems affecting solid dosing in current batch systems. Firstly, from a parametric study to identify the effects of temperature, solvent content (solubility), mixing intensity, and particle size on dissolution rate. Secondly, using the full factorial design of experiment methodology to establish hierarchy effects of parameters and their interactions in both a stationary and a flow system. The stationary system here refers to a stirred tank reactor where solvents are contained, while the flow system is a twin screw extruder where solvents flow. Paracetamol is the model compound and water/ propan-2-ol the solvent systems. A UV spectrometer with in situ UV-ATR probe is used to monitor the concentration of the solution during dissolution. Dissolution kinetics are extracted from concentration-time profiles, the knowledge gained has been used to set up a continuous flow system with complete dissolution within the residence time of barrel.

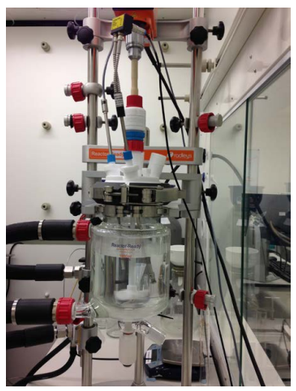


Image: Paracetamol dissolution in a stirred tank reactor with in situ UV-ATR probe

Crystal and Particle Engineering

The CMAC crystal and particle engineering mentor group focusses on the crystallisation stage and how the engineering of particles can have a significant effect on the primary processing step of pharmaceutical manufacturing. The key objective is to develop platforms and processes for the continuous production of crystals where the critical particle properties of size, shape and solid form are precisely controlled. This is being done with various crystallisation methods at different scales. Areas of research within this group are multicomponent nucleation, antisolvent crystallisation, oscillatory flow and small-scale crystallisation with the aim of all areas being translated into continuous processes. Furthermore, specific techniques are being studied such as the scaled down COBC, wet milling and the KRAIC-D platform. Industrial partners from AstraZeneca, Bayer, Lilly and Takeda contribute to the crystal and particle engineering mentor group through project guidance and support with insight into the industrially relevant areas.

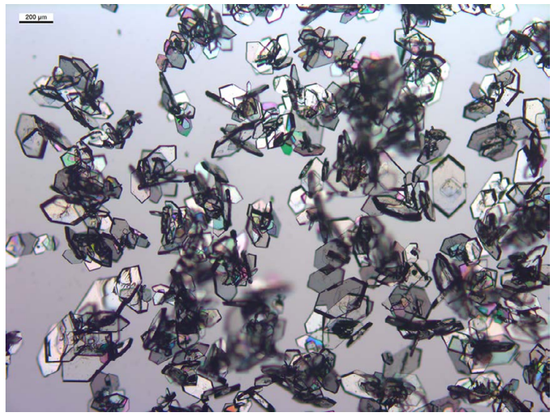


Image: Anthranilic Acid Crystal Plates

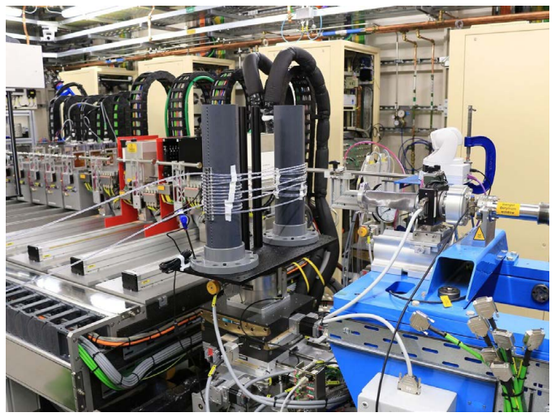


Image: Installation of the KRAIC-D platform at the High Resolution Powder Diffraction beamline I11 at Diamond Light Source

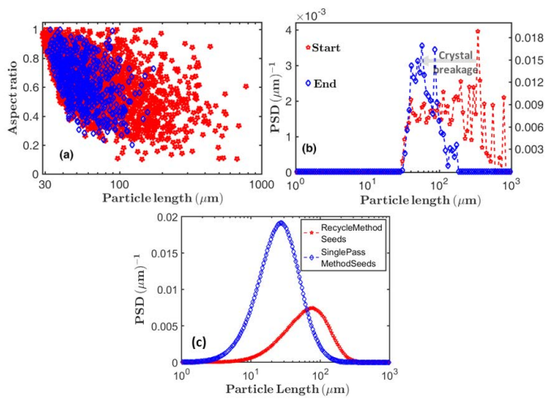


Figure 21: (a) Monitoring the extent of crystal breakage on particle shape change (b) and size reduction (c) from the effect of wet milling. A comparison of particle size distributions from a continuous single-pass and recycle method is displayed

Research Highlight

To deliver robust control over particle properties (size, shape, surface), the crystallisation process must be designed and operated at specific conditions. When the crystallisation is unable to achieve this, incorporating a particle engineering tool such as wet milling with the crystallisation step can often provide an alternative and preferred route to meet the required properties. The theme of this research focuses on two strategic approaches for API's. The first investigates a combined crystallisation and wet milling methodology. The effect of mechanical action on crystal breakage to reduce, manipulate and target specific particle sizes, shapes and surface properties is explored. Secondly, the influence of process parameters of a single-pass wet mill method for seed generation and crystal growth is applied. In comparison to the first approach, the ability to generate seed crystals of smaller sizes ‹15µm with the potential to decouple nucleation and growth domains is realised. DTC researcher Bilal Ahmed is progressing with this project.

Research

Advanced Characterisation

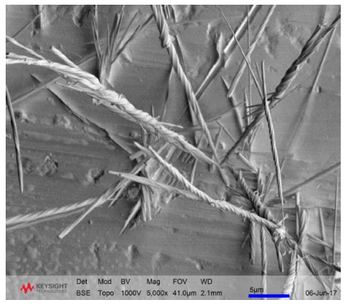


Image: Twisted Oxcarbazepine Form III Crystals Grown via Sublimation onto Silver Foil

The CMAC advanced materials characterisation mentor group is aimed at creating a common platform for researchers working in different areas of material characterisation. The group meetings provide a condensed but useful overview of the major analytical techniques used by researchers in their work. Areas of research with in the group mainly include synthesis and characterisation of amorphous and crystalline materials at ambient and non-ambient conditions using X-ray, microscopic and ToF-SIMS techniques. Industrial partners from AstraZeneca, Bayer, GSK, Lilly and Takeda contribute to the advanced characterisation mentor group through interaction with researchers and provide an opportunity to get answers for specific research related questions.

Image: AFM operation

Research Highlight

ToF-SIMS is a 3D chemical imaging technique that allows the localised measurment of the distribution of compounds of interest in complex matrices, aiding the interpretation of the final performance of finished product, and at the same time providing substantial help in understanding how the manufacturing process impacts on it. CMAC researcher Eleonora Paladino is focussed on surface analysis and metrology in pharmaceutical manufacturing and her research is carried out in collaboration between CMAC and the National Centre of Excellence in Mass Spectrometry Imaging (NCE-MSI) at NPL (UK). The principal techniques that she uses for investigation are ToF-SIMS and Atomic Force Microscopy (AFM). She has successfully demonstrated the use of 2D ToF-SIMS imaging in the analysis of drug-loaded electrospun scaffolds for hernia repair surgery [1, 2], and is now working on the optimisation of 3D imaging methodologies for these systems.

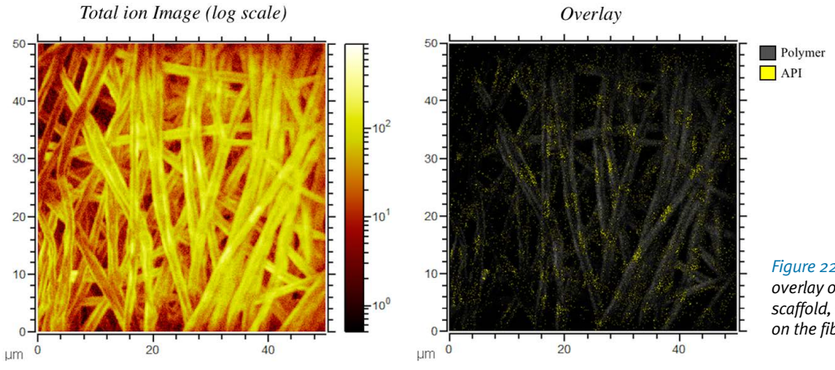
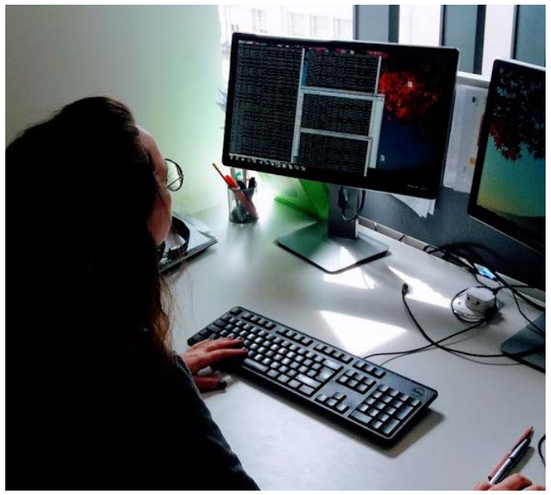


Figure 22: SIMS total ion image and image overlay of polymer and API in a drug loaded scaffold, showing the distribution of the drug on the fibers

ICT Tools, Process Models and Predictive Design



The CMAC ICT tools, process models and predictive design mentor group focusses on the capability and incorporation of process modelling and predictive control to support the processing stages of pharmaceutical manufacturing. Research areas within this group are Artificial Intelligence (AI), model predictive control, solubility data and regression modelling, CFD / PBE model framework, crystallisation control methodologies and data handling, pre-processing, processing and optimisation. Furthermore, specific predictive and modelling techniques are being studied such as Design of Experiments (DoE), gSAFT, COSMO-RS, NRTL-SAC, UNIFAC, population balance modelling, input/output state feedback linearization (SFL), principle Component Regression (PCR) and partial Least Square Regression (PLSR). Industry partners from AstraZeneca, Lilly and Takeda contribute to the ICT tools, process models and predictive design mentor group through project guidance and support with insight into the industrially relevant areas.

Image: CMAC researcher applying predictive and modelling techniques to digital and experimental data

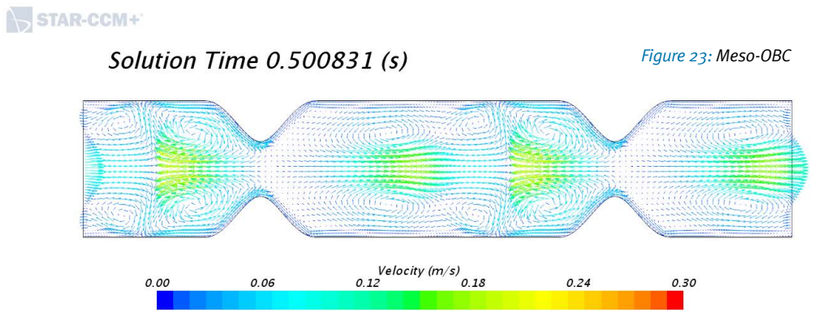
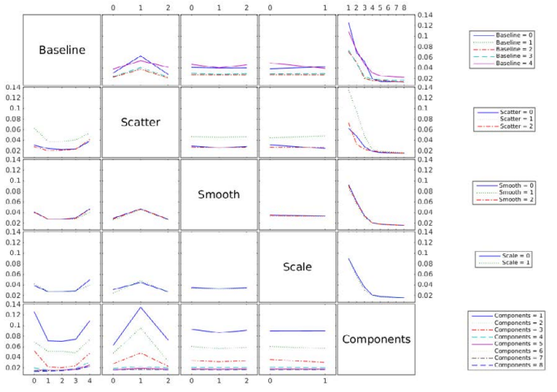


Figure 23: Meso-OBC

Image: Interaction plot between the four major pre-processing steps, baseline correction, scatter correction, smoothening and scaling + number of latent variables based on an example near infrared data set



Research Highlight

Hyperspectral data has large dimensionality and volume requiring novel approaches to data-handling and processing. At CMAC, these are primarily collected using a hyperspectral imaging probe, as well as the ToF-SIMS instrument. Michael Chrubasik, a joint CMAC and NPL researcher is focusing on the processing and optimisation of data gathered using a hyperspectral imaging probe deployed in the analysis of mixing solutions with the aim to explore data-handling, pre-processing and processing of hyperspectral and spectral data. During the optimisation process a DoE based tool for pre-processing spectral data for modelling purposes was established. This tool aids the user in understanding which pre-processing methods are effective for the data analysed and which combination of methods is likely to have the largest impact on error reduction in future models. The tool is currently under active development.

Research

Purification and Isolation

The CMAC purification and isolation mentor group focusses on the separation and isolation of APIs from impurities during crystallisation processes. Ongoing studies within this group are electric field enhanced crystallisation, ultrasound, sonocrystallisation, supercritical CO_2 extraction-drying and the process of solid separation using vacuum filters for filtration, cake washing, deliquoring, and drying. For the solid separation, unconventional automated ultra-scale down, bespoke laboratory scale and continuous filtration platforms are being studied. The studies aim to gain an early understanding of the filtration mechanisms, optimise filtration conditions, screen solvents for cake washing and ultimately inform selection of process conditions for continuous filtration. Industrial partners from AstraZeneca, Bayer and Lilly contribute to the purification and isolation mentor group through project guidance and insight into the industrially relevant areas.

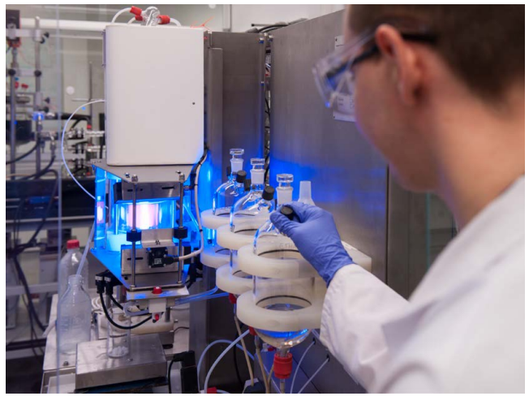


Image: CMAC filtration set-up

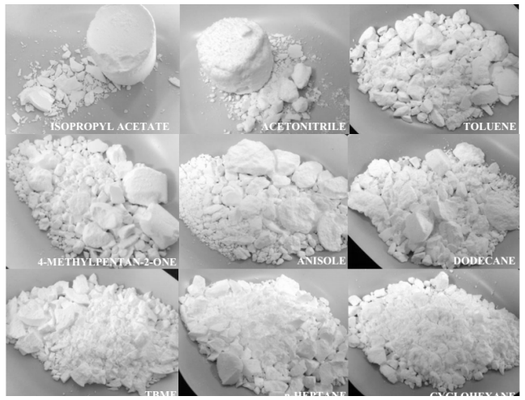


Image: Solvent screening to identify API and solvent properties

Image: Paracetamol powder after supercritical CO_2 extraction

Research Highlight

Supercritical CO_2 extraction-drying is a very promising technique for the future of pharmaceutical manufacturing. Compared with conventional drying and the subsequent milling / de-lumping steps it is a fast process. Using conventional techniques it may take few hours to extract the least volatile residual organic solvents leaving the solid material completely dry. The small CO_2 molecules pass through the pores of the wet cake and come in contact with the solvent which dissolves in the fluid phase. In that way, the undesired particle agglomeration is minimised and the problematic milling steps are eliminated. In addition, $scCO_2$ extraction-drying is very beneficial for thermally labile compounds because the critical temperature of CO_2 is close to ambient. At the end of the extraction process, the CO_2 / organic solvent mixture can be separated cryogenically to minimise organic emissions to the atmosphere and potentially the CO_2 can be recovered and reused. DTC Researcher Georgia Sanxaridou is progressing with this work.

Image: Hot Melt Extrusion (HME)

Primary to Secondary

The CMAC primary to secondary mentor group focusses on downstream processing and formulation technologies of pharmaceutical manufacturing. The key objective is to develop understanding of pharmaceutical material behaviours from primary processing through to formulation. Techniques studied within this group are hot-melt extrusion (HME), twin-screw granulation (TWSG), state-of-art fused deposition 3D printing, inject printing, injection moulding and the monitoring of these techniques using process analytical technology (PAT). Furthermore, we investigate the conventional secondary techniques such as batch granulation, fluidised bed drying and tablet compression. Industrial partners from AstraZeneca, GSK, Lilly, Novartis and Takeda contribute to the primary to secondary mentor group through project guidance and insights into the industrially relevant areas and targets of secondary processing.

Image: Filament samples processed by HME

Research Highlight

Injection Moulding is a tried and tested process in the plastics industry which has gained interest as a method to potentially alter the pharmaceutical manufacturing process. The technique combined with Hot Melt Extrusion as a method of particle production is a novel process to produce solid oral dosage forms. The techniques have the potential to combine polymer with drug to not only stabilise API in the amorphous form-particularly useful for sparingly soluble drugs-but to enable control over the spatial arrangement and order within the dosage form. Through careful formulation and mould design this can lead to an overall better control of drug release whether it be an immediate, pulsatile or extended release. DTC researcher Sarahjane Wood is progressing with this work. She has been on exchange visits to partners RCPE and C-SOPS.

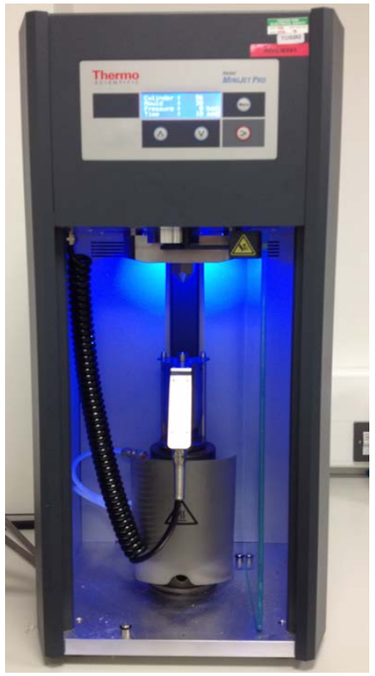
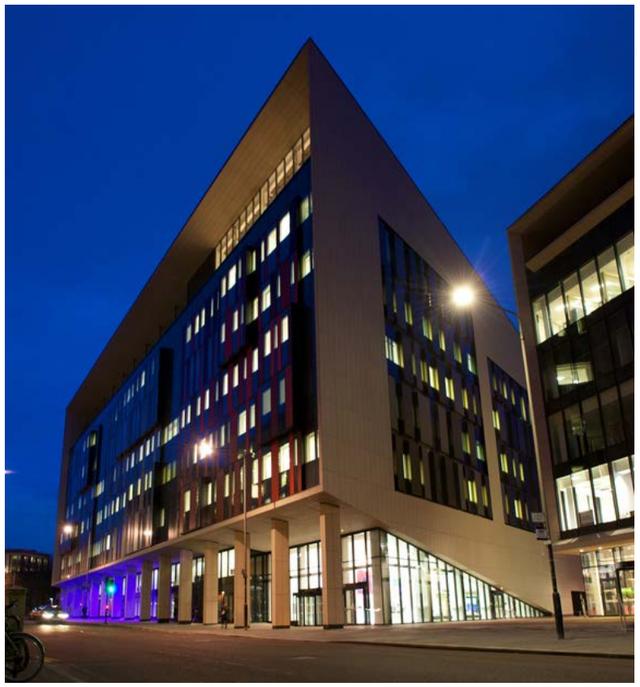


Image: Thermoscientific HAAKE Injection Moulder (Minijet Pro)

Facilities

UNIVERSITY of STRATHCLYDE
CMAC
NATIONAL FACILITY

- **World class facilities for forming, processing and analysing particles and particulate systems**
- **Pilot scale manufacturing capability supporting global partners**



Vision:

To support a world class manufacturing research facility

Mission:

To provide cost effective access and support to all users within a safe, well managed and collaborative environment

The CMAC National Facility delivers world class research, training and knowledge exchange on a global scale supporting users from both academia and industry. Our advanced pharmaceutical manufacturing research facility is easily accessible by academics and businesses both in the UK and internationally.

The National Facility has the additional benefit of co-locating multidisciplinary teams of academic and industry researchers within the state of the art Technology and Innovation Centre (TIC) at the University of Strathclyde.

The facility is equipped using £11.4 m funding awarded by the Higher Education Funding Council for England (HEFCE)'s UK Research Partnership Investment Fund (UKRPIF) and supported with £22.8 in industry and charity contributions. The National Facility features world class capabilities in:

- Primary Processing
- Secondary Processing
- PAT/Spectroscopy
- X-ray Diffraction
- Surface Analysis
- Materials Characterisation

The National Facility has end-to-end continuous manufacturing and crystallisation research capability under one roof. This capability features key items of equipment:

- Modular skid-mounted crystallisation platforms (batch and continuous)
- Pilot scale filtration and drying
- Secondary processing including spray drying, hot melt extrusion (HME), granulation and tableting
- Process Analytical Technology (PAT) providing real time information and feedback
- TOF-SIMS
- Atomic force microscopy (AFM)
- Nuclear magnetic resonance (NMR) spectroscopy
- World class X-ray suite including single crystal, powder (crystalline & amorphous), small angle scattering (SAXS) and nano computed tomography (CT)

Laboratories, Equipment and Services

The laboratory footprint at TIC is over 2000m^2; designed to deliver a fully adaptable space for multi-phase batch and continuous primary processing. There is a dedicated, specialised support team within the National Facility to offer services and assistance to research activity and industrial projects; analytical laboratories for advanced understanding of particulate formation and processing, and a secondary processing suite. Stores and ancillary areas have been constructed to complement the unique activities carried out in the laboratories to support the delivery of the research programme.

Primary Processing Laboratory

Our largest laboratory in TIC houses 12 multi-functional walk-in fume cupboards. These bespoke units are reconfigurable to meet the needs of current research and adaptable to meet future demands of the Hub programme. The fume hoods can be configured to accommodate a 3.8 m long process with pass through ports for PAT probes and fibres plus data communications to monitor and obtain real time data/control over processes.

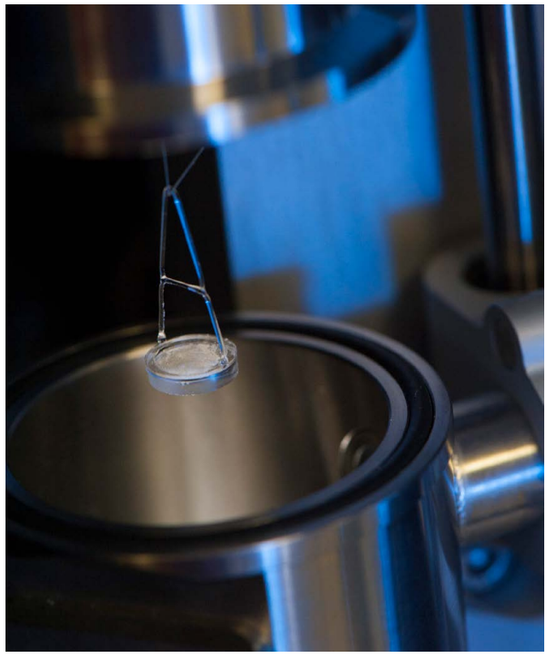
Facilities | CMAC National Facility

Secondary Processing Suite

A purpose built collection of laboratory areas adjacent to the primary processing facility house our entire secondary processing and formulation units. These areas are equipped with flexible exhaust ventilation for powder handling. The units include 11mm and 16 mm Twin Screw Extruders, a mini-injection moulder, bin blender, high-shear wet granulator, fluid bed drier, conical/ hammer mill, dry granulator and a tablet press.

X-ray Analysis Suite

The world-class X-ray suite within the National Facility can deliver a range of services from powder characterisation, fingerprinting, variable temperature measurements, and variable humidity measurements to unit cell determination and full structural solutions. CMAC, together with colleagues from BioNano and Physics at the University of Strathclyde, have purchased a Xenocs Small Angle X-ray Scattering (SAXS) instrument, which can be employed in the investigation of materials with larger intermolecular spacing for the determination of shape and alignment of particles. Our Nano-CT service offers a non-invasive technique for the three-dimensional structural characterisation of solids and can be applied to analyse samples with sizes › ca. 20 um.



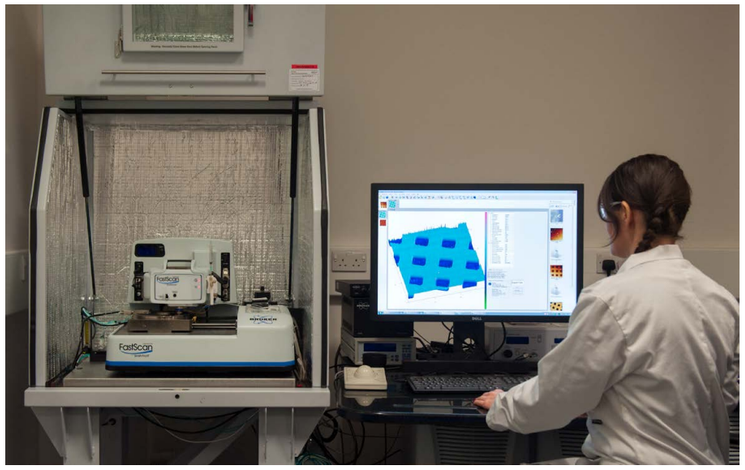
Material Characterisation Laboratory

We have a wide range of advanced analytical equipment available at the facility and our dedicated technical team deliver services across multiple physical forms - powders, tablets, slurries etc. Highlights include: chemical analysis, gas and liquid chromatography and mass spectrometry in addition to physical methods such as porosity, density, surface area analyses, dynamic vapour sorption (DVS), inverse gas chromatography and powder and liquid rheometry. We house the latest technology in delivering innovative particle size and shape analysis. For advanced surface characterisation, we have a TOF-SIMS instrument*. This instrument, in addition to two AFM systems, allows a new level of nanoscale physical and chemical understanding with surface characterisation.

** additional funding from the Wolfson Foundation*

Microscopy Suite

The extensive optical and electron microscopy capability at the National Facility is located within a vibration sensitive laboratory. This includes automated compound and inverted optical microscopes, off-line IR and Raman instruments with surface mapping features plus a benchtop SEM. This service enables physical samples to be imaged and chemically analysed at the facility.



Facilities

Facilities at Spoke Institutions

Systematic analysis, characterisation and performance testing of materials produced though work on Integrated Development Pathways (WP1) and Future Microfactories (WP2) will be supported by utilising capabilities at the CMAC National Facility at Strathclyde and at the Spokes' facilities, including world class national capability in partners Diamond and NPL. The research will be translated though the planned MMIC project.

Innovation Spokes

Figure 25: MMIC

MMIC

CMAC have been working with the Centre for Process Innovation (CPI), Medicines Manufacturing Industrial Partnership (MMIP) and Scottish Enterprise (SE) to make MMIC a reality. MMIC will be a first-in-class, global facility that offers a sustainable and flexible means to accelerate the adoption of emerging and novel manufacturing technologies and transform pharma manufacturing. MMIC will cover the end-to-end manufacturing supply chain within a bespoke, quality driven and safe environment. MMIC will be an enabler in terms of taking advances in manufacturing research and provide a facility for proving concepts before launching them into commercial operations.

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. NPL Scotland is a regional hub formed by the collaboration of strategic partners NPL and the University of Strathclyde. CMAC hosts 3 NPL Scotland PhD students who are doing research on pharmaceutical innovation and manufacturing metrologies supporting continuous manufacturing and crystallisation in the pharmaceutical sector. The 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.

Diamond Light Source and Research Complex at Harwell

CMAC has access to the Research Complex at Harwell and Diamond Light Source on the Harwell Science and Innovation Campus, through new 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. The work is closely aligned with modelling and design through the ADDoPT programme.

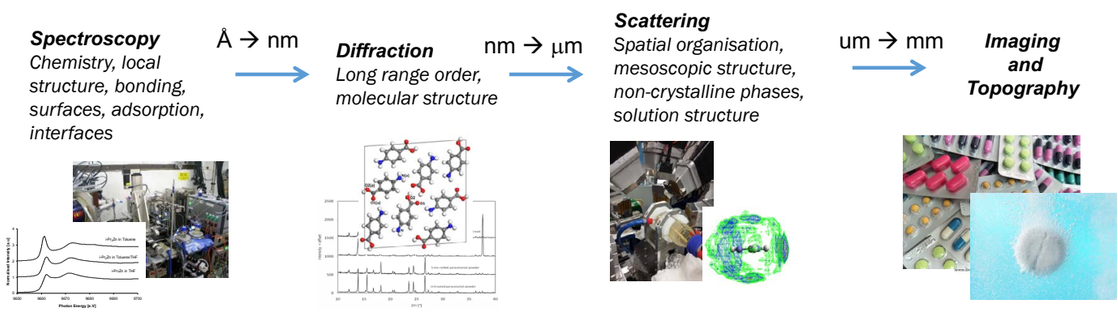


Figure 26: Capability to undertake advanced measurements at all length scales

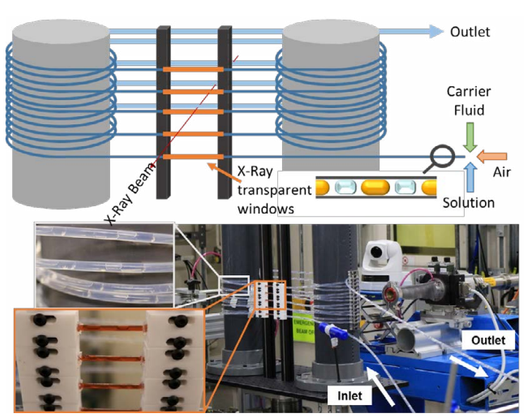


Figure 27: (a) KRAIC D developed at Bath and installed at Harwell (b) Harwell Science and Innovation Campus

Facilities

Academic Spokes

The Diamond at Sheffield

The University of Sheffield has a new state-of-the-art facility, The Diamond, which is a multi-disciplinary teaching space. It houses a Pilot Plant which tests integrated processes with simulations and control systems in a safe, product oriented environment, and a virtual and augmented reality lab which will be used to train researchers for the future.

Image: The Diamond at University of Sheffield

Imperial College London

Statistical Associating Fluid Theory (SAFT) is an advanced molecular thermodynamic model used to predict thermo-physical properties of fluids and complex mixtures developed at Imperial. This predictive approach can be applied to describe the solubility of complex molecules, such as active pharmaceutical ingredients (APIs), in solvents and solvent mixtures.

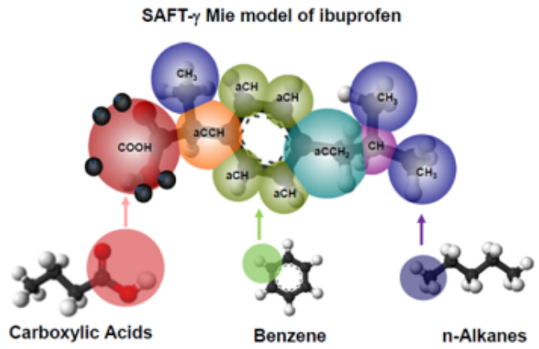


Figure 28: SAFT developed at Imperial

Loughborough University

The team at Loughborough are developing quality by control using intermittent / periodic flow crystallisation. This is model informed design of a continuous MSMPR platform development using periodic / intermittent flow to avoid transfer line blockage and control crystal size and shape by manipulating the residence time and supersaturation.

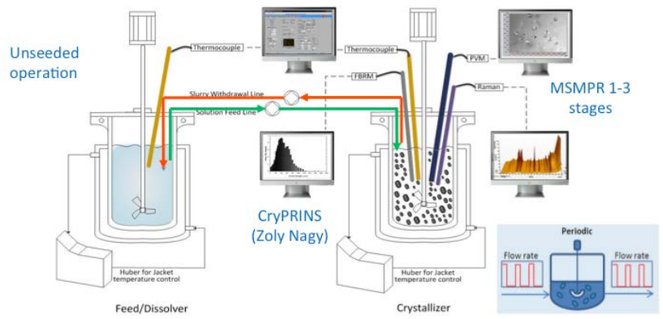


Figure 29: Periodic and intermittent crystallisation configuration at Loughborough

University of Bath

Researchers at Bath have been looking at Development and implementation of continuous crystallisation platforms at laboratory scale, including multi-component and confined environment crystallisation, and have deployed flow crystallisation at Diamond Light Source (Figure 27(a)).

Image: KRAIC platform developed at Bath

University of Cambridge

Researchers at IfM Cambridge will develop network reconfiguration strategies aligned with advanced production, process analytics and supply chain digitalisation, to accelerate integration with emerging technologies. This will drive new redistributed manufacturing supply chain models that offer local volume flexibility addressing drivers of manufacturing closer to the point of need and personalisation.

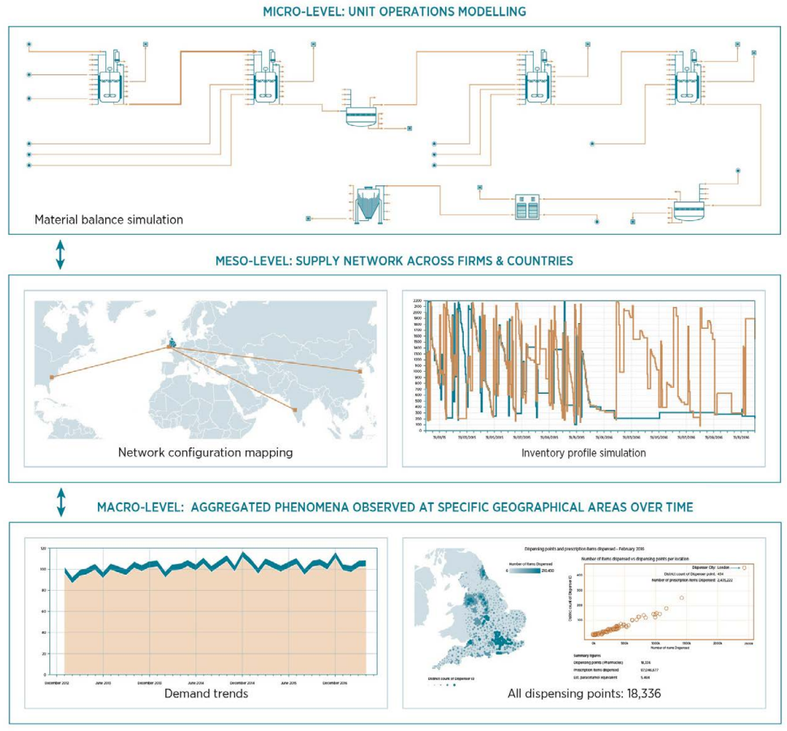


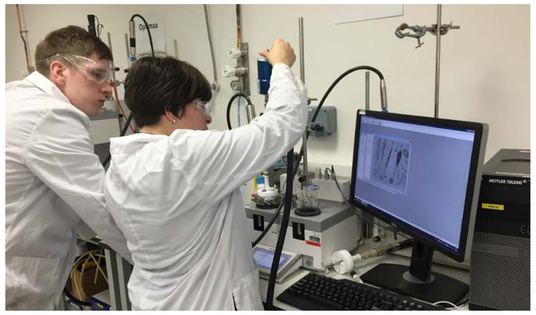
Figure 30: Digital supply chain mapping (https://www.ifm.eng.cam.ac.uk/insights/global-supply-chains/nextgensc/)

University of Leeds

Partners at Leeds are the main link into the facilities at Diamond Light Source at Harwell (Page 43), and with the ADDoPT project (Page 55).

Training

- **Delivering the skilled leaders and workforce of the future**
- **A talent pipeline for industry and academia**
- **World class multi-disciplinary programmes delivering:**
  - **Doctoral and Masters level training**
  - **Industry and international experience**



Training researchers to fill the Industry skills gap is a key deliverable for CMAC. The bespoke training packages CMAC offers have been designed in consultation with Industry partners. CMAC is delivering graduates that move on to world class academic and industry posts. The talent pipeline on pages 22-23 illustrates our success.

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

- MSc in Advanced Pharmaceutical Manufacturing
- CMAC Doctoral Training Centre (DTC) cohort training programme
- Joint international PhD programme in collaboration with NTU Singapore
- PhD programme as part of the NPL Scotland Hub
- Postgraduate development
- Transferable skills training for staff and students

We have created and nurtured a vibrant and dynamic doctoral training 'ecosystem' where individual researchers benefit from leading academic expertise across multiple disciplines, and access to world-class facilities to develop their own views. They develop knowledge and tools to innovate and create solutions within their selected research theme.

The Doctoral Training Centre

The CMAC Doctoral Training Centre (DTC) has established an innovative, world-class, multi-disciplinary doctoral training programme attracting high quality postgraduate students to become the future leaders in continuous manufacturing and crystallisation research. The uniquely qualified researcher cohorts produced are proving to be capable of transforming practice in pharmaceutical and speciality chemical manufacturing. In the longer term this will contribute to the production of improved pharmaceutical and fine chemical products, more efficient manufacturing, and wealth creation in the UK.

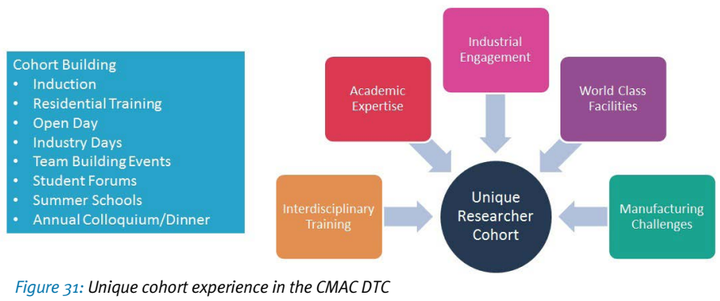


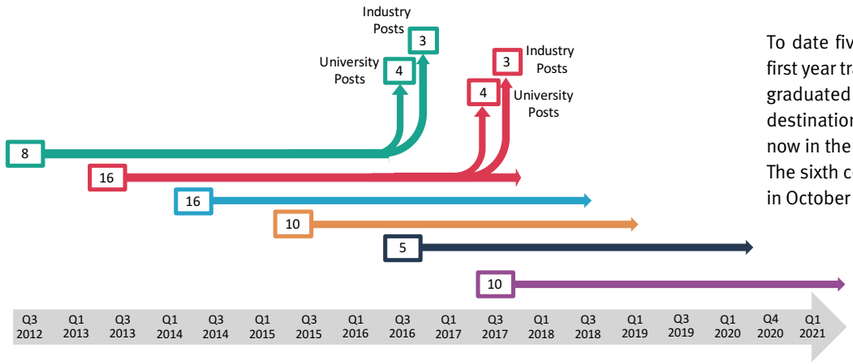
Figure 31: Unique cohort experience in the CMAC DTC

By embedding the DTC within our Future CMAC Hub research programme, our students are exposed to:

- Relevant fundamentals across each discipline
- Current state-of-the-art knowledge including the challenges in continuous manufacturing and advanced crystallisation
- Existing research activities both within the CMAC and internationally
- Unparalleled opportunities to engage in leading-edge research projects as part of a national interdisciplinary team

The formal training programme is coordinated by Prof Jan Sefcik and has three main elements:

- A range of taught modules covering the different aspects of the programme
- Individual and group mini-projects
- Transferable skills training



To date five cohorts have completed their first year training. The first two cohorts have graduated and are moving into their next destinations, and three further cohorts are now in the research phase of their projects. The sixth cohort is has commenced training in October 2017.

Figure 32: First destinations for the graduates of the DTC

The CMAC DTC was established in 2012 through an EPSRC award (£4.2m award, EP/K503289/1) supporting 38 students in 3 cohorts, with additional funds from Industry and partner universities. CMAC continued to train 15 more students in 2015-2016 with support from academic and industry partners. From October 2017 the CMAC DTC training programme will be delivered to the CMAC PhDs supported through the Future CMAC Hub and aligned programmes.

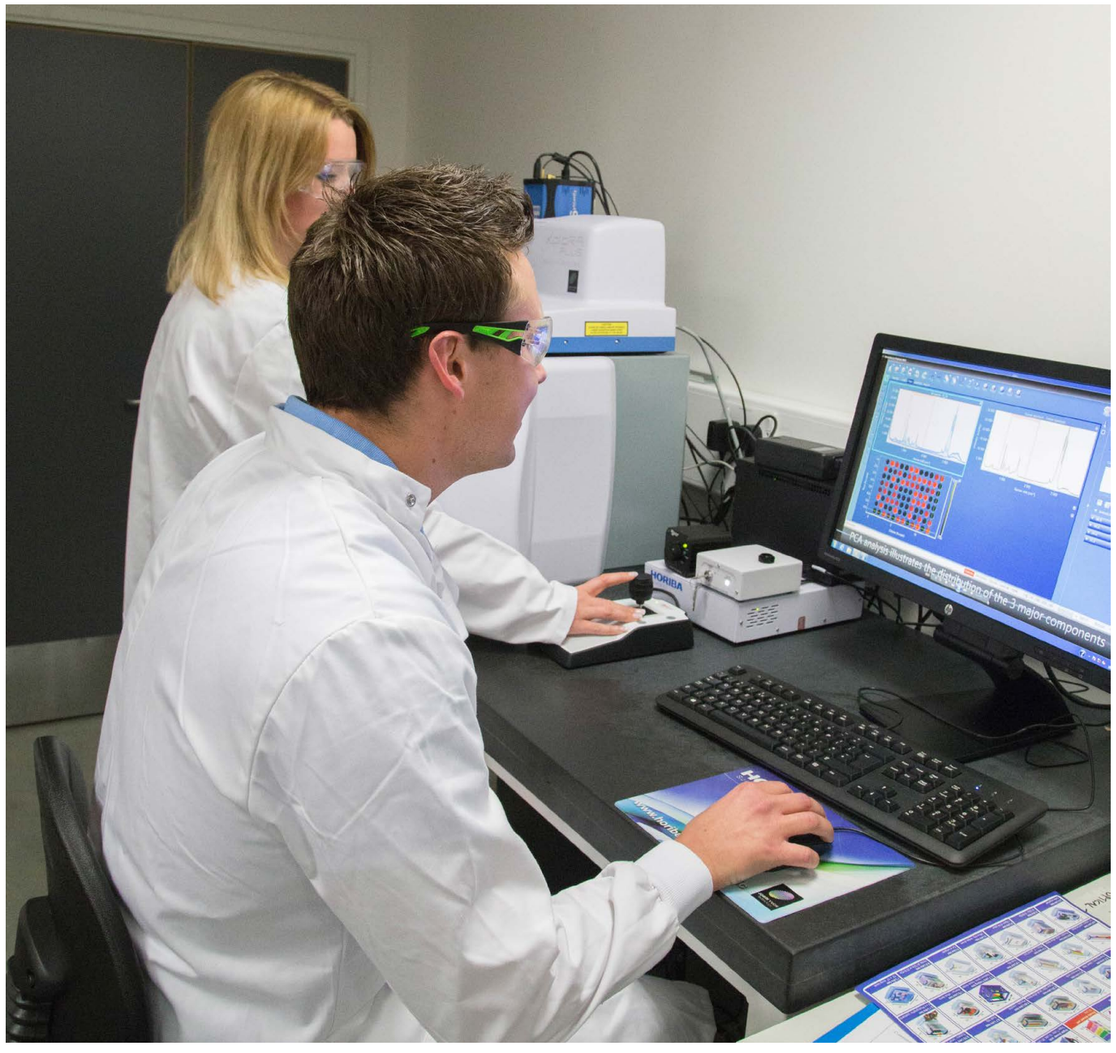
The CMAC DTC has been supported by a partnership that initially included three of the world's largest pharmaceutical companies, Astra Zeneca, GSK and Novartis, who delivered cash and significant in kind contributions. In 2015 Bayer joined CMAC followed in December 2016 Lilly, Roche and Takeda. All have indicated that the strength of the DTC talent pool was viewed as a real asset to joining CMAC.

Training

Joint International PhD Programme

A Joint International Doctoral Training Centre in Continuous Manufacturing and Crystallisation of Pharmaceuticals was initiated as part of an EPSRC Global Engagements award in 2012/2013. CMAC established links with Nanyang Technological University (NTU) in Singapore via workshops and exchanges. We have built on these links, and with support from the University of Strathclyde and established a joint doctoral training programme which commenced in October 2014 with a cohort of 5 students; 3 based at the University of Strathclyde and 2 at NTU. This partnership has extended to support 2 new students at Strathclyde commencing in 2017. The researchers participate in an exchange programme between NTU and Strathclyde during their PhD studies.

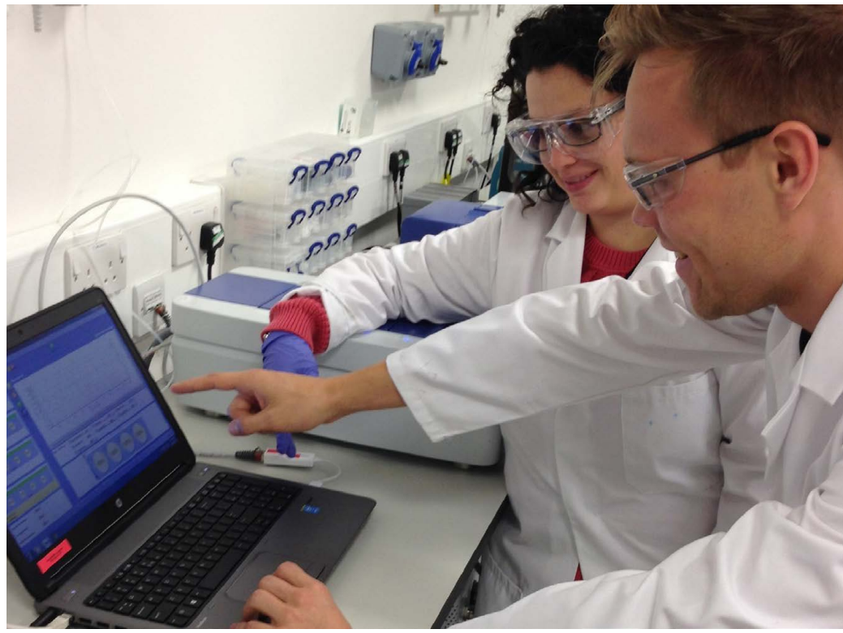
The main research themes of Pharmaceutical Particle Formation, Optimising Pharmaceutical Performance and Multi- Scale Pharmaceutical Systems are being explored via projects at the University of Strathclyde and at NTU.



Pharmaceutical Innovative Manufacturing Metrologies

CMAC is a key theme within the NPL Scotland Regional Hub, a partnership between the National Physical Laboratory (NPL) and the University of Strathclyde. The partners have successfully developed a joint Doctoral Training Programme with underpinning investment in the key research themes: initially three joint CMAC-NPL PhD studentships started in October 2015 with researchers splitting their time between the CMAC National Facility at Strathclyde and NPL laboratories in Teddington. Students receive state of the art training in measurement science applied to a range of scientific disciplines and industrial challenges.

Research projects in Metrology for Pharmaceutical Manufacturing, Measurement of Surfaces and Big Data Management are being explored by three PhD researchers as part of the NPL Scottish Hub at University of Strathclyde.



MSc in Advanced Pharmaceutical Manufacturing

In 2014 the Scottish Funding Council (SFC) awarded CMAC at the University of Strathclyde 20 fully funded places per year for a new MSc in Advanced Pharmaceutical Manufacturing. This unique Masters course provides training in key aspects of modern manufacturing approaches suitable for pharmaceuticals and high-value chemicals. It is designed to produce highly-skilled graduates in continuous manufacturing science and technology to meet the growing demands for expertise in this area. Graduates will be equipped to take up jobs in the food, chemical and pharmaceutical industries. The curriculum was designed with input from CMAC industry partners (AstraZeneca, Bayer, GSK & Novartis).

Students shall undertake the following compulsory classes:

- Continuous Manufacturing of Pharmaceutical Particles and Products
- Crystallisation and Formulation for Manufacture
- Generic Biomedical and Pharmaceutical Research Skills
- Industrial Pharmacy
- Pharmaceutical Project Management
- Process Analytical Technology (PAT) and Quality by Design in Continuous Pharmaceutical Manufacturing

Industry & Knowledge Exchange

- **Industry demand led research programme**
- **Influencing policy through world leading collaborative membership organisation**
- **Enabling supply chains of the future**
- **Impact through effective research translation for multi-nationals and SMEs**

CMAC has always benefited from strong industry engagement and leadership. An industry led membership organisation was created in 2011 and this has grown and developed over the years. The membership organisation operates under a pre-competitive, collaborative research and development model with senior level company support. The main industry partners (AstraZeneca, GSK, Novartis, Bayer, Lilly, Takeda, Roche and Pfizer) get an individual seat on the CMAC Board and an opportunity to influence the direction of future research and Hub activity.

Integral to the CMAC ecosystem are the Tier 2 technology companies. These range from large companies, Siemens and PwC, to micro SMEs. This supportive environment helps translate research into equipment and products. In addition to CMAC members the Hub organises many open events for the broader industry landscape and collaborates with a wide range of additional companies locally, nationally and globally.

Image: Sir Andrew Witty, CEO GSK during CMAC visit

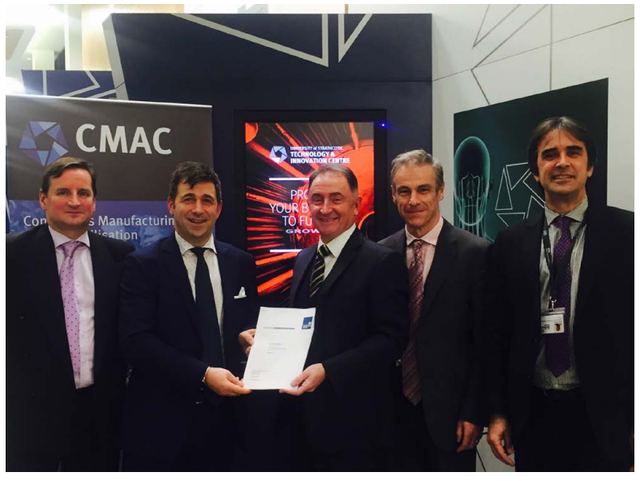


Image: Right to left: Phil Shering, AstraZeneca with Dr Juergen Maier, Siemens meet with Prof Sir Jim McDonald, Principal of University of Strathclyde, Craig Johnston and Prof Alastair Florence of CMAC

Technical Committee

The technical committee has been busy over the last year updating its remit, welcoming four new companies and revising the industry problem statements. The refreshed Industry problem statements will be used to ensure that CMAC continues to research topics that are industrially relevant and are being worked into their final format to be shared in 2018.

The Technical Committee remit is to provide industrial steer and scientific input into the Future CMAC Hub research and training programme:

1. Provide feedback and steer on new PhD projects
2. Help ensure that the Hub research is industrially relevant
3. Manage core projects
4. Coordinate: industrial placements for PhD researchers; mentor group attendees; 1:1 confidential projects
5. Support and disseminate internally as required: new funding bids; existing CMAC collaborative projects

CMAC would like to take this opportunity to formally thank the technical committee for all their time and effort over the last year as well the invaluable scientific discussions with the researchers.

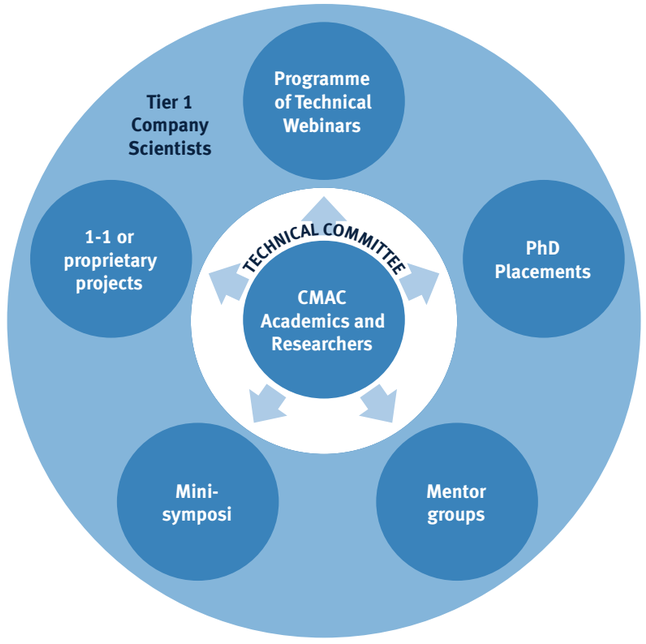


Figure 33: Technical Committee

Members of the Technical committee

Company	Members
AZ	Dr Amy Robertson Mr Phil Shering Dr Helen Wheatcroft
Bayer	Dr Wolfgang Beckamnn Dr Britta Olenik
GSK	Dr Mei Lee Dr Andrew Share
Lilly	Dr Chris Burcham Mr Tim Braden
Novartis	Dr Berthold Schenkel Dr Ruairi O'Meahdra
Pfizer	Dr Kevin Girard Dr Paul Meenan Dr David Walker
Roche	Dr Pirmin Hidber Dr Marcello Bosco
Takeda	Dr Charles Papageorgiou Dr Justin Quon

Industry & Knowledge Exchange

Proprietary Projects

Working on both launched and developmental pharmaceutical compounds, the projects have delivered immediate impact from CMAC's academic research into live projects. Highlights from the year include:

- Three day continuous run making 3.5kg of an API fully meeting commercial specification
- Several multi kg makes of high value materials
- Characterisation and prediction of stability of amorphous formulations

Multi- million pound savings have been achieved through improved consistency as a result of learning gained across the proprietary project.

Tier 1 Core Projects

The Technical Committee have identified five applied research projects to deliver outputs that will be directly implemented into the companies:

- Investigation into the phenomena of "hard and soft" anti-solvents
- Investigation of the scope of a novel scaled-down continuous drum filter
- Linking synthesis to crystallisation: implementation of automation and predictive control of a counter-current L/L separator
- Improved understanding and approaches for impurity rejection in crystallisation
- Technology translation: enabling implementation of research outputs into an industrial environment

Industrial Placements

The placement programme continues to grow with 6 researchers on placement in 2017 and 11 placements arranged for the 2017/18 programme, including placements into our new members in the US.

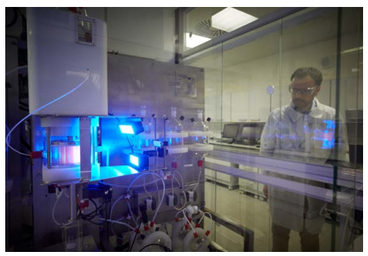
Researcher	Industrial Host	Project
Maria Briuglia	Jorge De Caldron and Julien Douillet, GSK	Workflow for Quantification of Secondary Nucleation
Rajesh Gurung	Lucie Millar-Potika, AZ	Comparison of in-silico Methods for Solubility Prediction
Thomas Kendall	Michal Sowa and Britta Olenik, Bayer	Investigation of Techniques for Nucleationg Difficult to Nucleate Compounds
Lauren Agnew	Amy Robertson, AZ	Investigation of Polymorph Conrol in Continuous Crystallisers
John McGinty	Helen Wheatcroft, AZ	Workflows for Salt Formation in Continuous crystallisation
Lauren Connor	Helen Wheatcroft, AZ	Development of a Workflow for Co-crystal Screening and Formation

Tier 2 Partners

The sixteen Tier 2 members were represented at the CMAC Open Day in 2017 with the majority of them having exhibit stands and a number giving excellent presentations. They also supported the Tier 1 showcase event on 9-10 November 2017 where they engaged and networked with the Tier 1 industrial members and the hub staff and academics. This included updates on industrial challenges, the Future CMAC Hub, MMIC and pitches and exhibitions from the Tier 2 to the Tier 1. These events brought together industrialists, academics and researchers to present their work, technology, challenges, and explore how we can collaborate moving forward.

CMAC has hosted and facilitated face-to-face industrial and academic sessions, workshops and training sessions with the companies including the DTC summer school, and made a large number of business-to-business and academic introductions in 2016/2017, a number of which have resulted in new collaborations. Tier 2 members have been integral to the Hub support, Hub renewal, research support and collaborative projects such as ICT-CMAC, Remedies and ADDOPT.

Figure 1: Tier 2 technology companies



Images: Tier 2 companies at the CMAC Open Day 2017

In addition to our Tier 1 & 2 partners, we also work with a range of technology providers and companies from other chemical sectors including those who contribute to the technical programme, for example, through access to new processing and measurement technologies. We also continue to develop further links with other companies that can contribute a range of expertise to advance the developing programme in continuous manufacturing research. E.g. Mars, Syngenta, BDD, Bruker, CRD, Dow, Merck, Ashland, and Microinnova.

Industry & Knowledge Exchange

REMEDIES: RE-configuring MEDIcines End-to-end Supply

The £23m REMEDIES project is part of the Advanced Manufacturing Supply Chain Initiative (AMSCI) programme working with 22 partners to improve the global competitiveness of UK advanced manufacturing supply chains via funding research and development, skills training and capital investment to achieve world-class standards and encourage major new suppliers to locate in the UK. Although UK pharmaceutical firms (GSK, AZ) lead global markets, significant challenges lie ahead of them relating to the affordability of drugs, product portfolio fragmentation and the ability of existing supply chains to embrace emerging technologies. These challenges compound existing problems of inventory across the end-to-end supply chain, and poor 'right-first-time' processing which costs the industry £20bn per annum globally. The REMEDIES project will seek to address these challenges.

CMAC is leading workstream (App) "A" – Active Pharmaceutical Ingredients and Registered Starting Materials and is technical lead on workstream (App) " B" – Primary to Secondary Formulation.

Objectives:

- The development of **mobile continuous process equipment** capable of a range of chemistries with open access.
- To identify and exploit suitable technologies for continuous processing for specific applications.
- To create an asset network for use by CMOs and primes.

App A Partner Organisations:

Technical Deliverables:

- **Blacktrace** pilot/production scale continuous L/S/G reactions, Liq/Liq rxn, CSTR, separation, particle formation modularised platform.
- **CRD** pilot/production scale continuous:
  - Gas Liquid Mixed Reactors (G/L/S systems)
  - Tubular Reactor Geometry (G/L and G/S systems)
  - Baffled Reactor Geometry (G/L/S systems)
- **C-Tech** pilot/production scale continuous microwave reactor.
- **Intensichem** continuous novel lab scale med-high pressure hydrogenation.
- **Mettler Toledo** providing specific PAT for each technology platform.

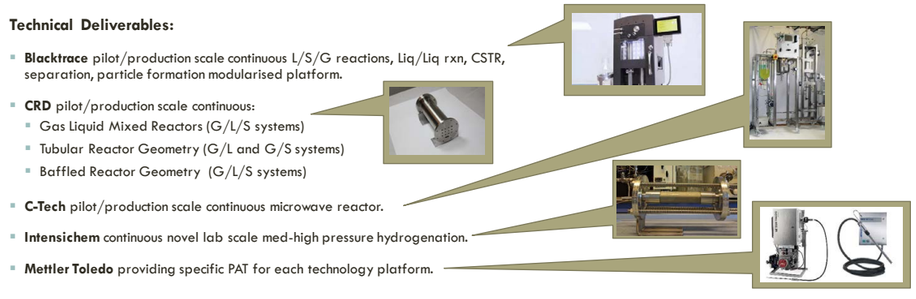


Figure 35: Overview of REMEDIES App A & B

ADDOPT: Advanced Digital Design Transforming Pharmaceutical Development and Manufacture

The ADDoPT (Advanced Digital Design of Pharmaceutical Therapeutics) project is addressing the pharmaceutical industry's desire to deliver medicines more effectively to patients. CMAC is a partner in ADDoPT developing advanced digital design techniques that eliminate non-viable drug candidate formulations as early as possible, streamlining design, development and manufacturing processes. ADDoPT is a £20.4m, four-year collaboration between pharmaceutical companies, solution providers and academia. Part-funded under the Advanced Manufacturing Supply Chains Initiative (AMSCI) and supported by the Medicines Manufacturing Industry Partnership (MMIP), it aims to make existing and new Digital Design approaches widely usable within the pharmaceutical industry and thereby increase efficiency and effectiveness of drug development and manufacture.

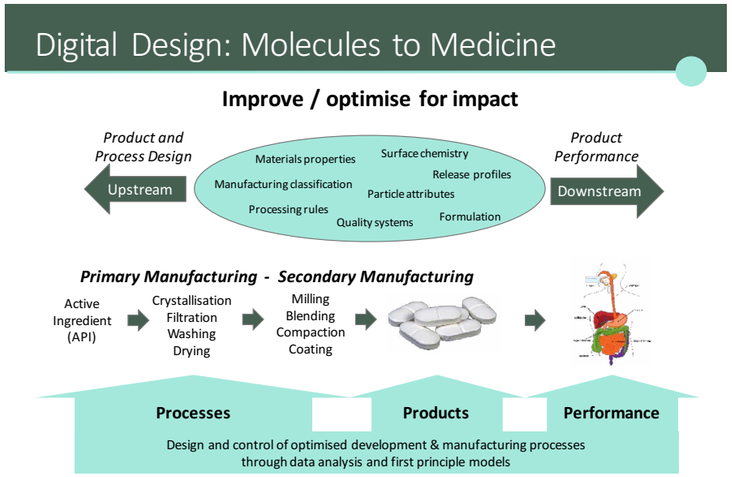


Figure 36: ADDoPT project overview

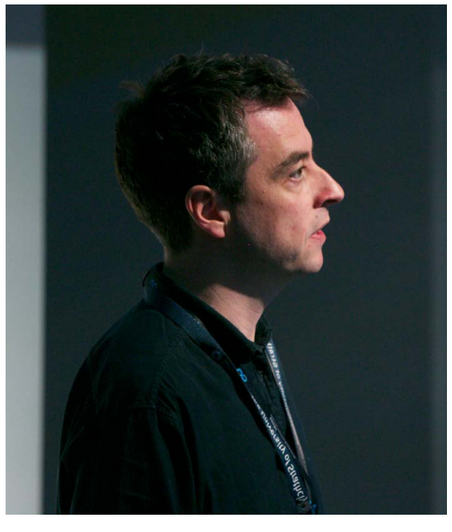


Image: Dr Blair Johnston, CMAC's technical lead in the ADDoPT Project

Within ADDOPT, Blair Johnston (CMAC) is working on the following research challenges:

- Precise control in manufacturing of solid particles using continuous manufacturing technologies.
- Control and exploitation of nucleation and growth of particles via crystallisation under continuous flow.
- Continuous crystallisation platforms; process analysis tools and strategies to manufacture 'perfect particles' for different applications.
- Deliver the tools to achieve exquisite control over crystal structure, particle shape and particle size distribution to meet the needs of advanced manufacturing of innovative chemical products.
- Continuous manufacture of medicines and nanomaterials with kinetic, co-crystallisation and impurity control.
- Understand key particle properties for enhanced formulated product performance.
- Manufacturing operations and supply chain management challenges in continuous manufacturing of chemical particles to include: manufacturing operations and supply chain configuration; management control systems and learning from experiences of other industries.
- Optimise manufacturing industries operations and supply chain to enable the effective adoption of continuous manufacturing.

Alison Clough, Acting Chief Executive of the Association of the British Pharmaceutical Industry, commented,

"This project will help to put the UK in a position to make innovative medicines available to UK patients more quickly by futureproofing our advanced pharmaceutical manufacturing sector."

Appendix

Hub Structure 2017

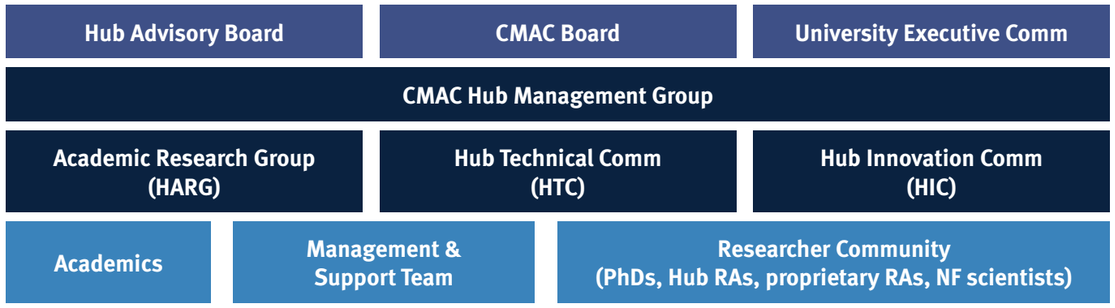


Figure 37: CMAC Governance Structure

Hub Advisory Board

Name	Organisation
Dr Clive Badman	GSK
Dr Neil Baker	Pfizer
Dr Sean Bermingham	PSE
Dr Stephen Brown	Capsugel
Professor Alastair Florence	CMAC, University of Strathclyde
Dr Gerry Flynn	Innovate UK
Professor Ian Gilmore	NPL
Miss Lorna Gray	CMAC, University of Strathclyde
Professor Richard Hague	University of Nottingham
Mr Arun Harish	CPI
Dr Andrea Johnston	CMAC, University of Strathclyde
Mr Craig Johnston	CMAC, University of Strathclyde
Dr Ewan Norton	MHRA
Ms Jo Pisani	PwC
Dr Amy Robertson	AZ
Dr Walkiria Schlindwein	De Montfort University
Professor Nilay Shah	Imperial College London
Professor Sarah Sharples	University of Nottingham
Professor Paul Sharratt	ICES
Dr Nigel Westwood	CRUK
Dr Charlotte Wiles	Chemtrix
Dr Rebecca Williams	EPSRC

CMAC Industry Board

Name	Organisation
Dr Clive Badman (Chair)	GSK
Dr Phil Dell' Orco	GSK
Dr Andrew Share	GSK
Dr Jon Paul Sherlock	AZ
Mr Phil Shering	AZ
Dr Markus Krumme	Novartis
Dr Jan-Olav Henck	Bayer
Dr Charles Papageorgiou	Takeda
Dr Sarah O'Keefe	Lilly
Dr Liam Tully	Pfizer
Dr Brian Chekal	Pfizer
Dr Sean Bermingham	PSE
Dr Pirmin Hidber	Roche
Professor Alastair Florence	CMAC
Mr Craig Johnston	CMAC
Professor David Littlejohn	University of Strathclyde
Professor Graham Wren	University of Strathclyde

Hub Academic Research Group

Professor Alastair Florence, University of Strathclyde (Chair)

Representative each from AZ, Bayer, GSK, Lilly, Novartis, Pfizer, Roche, Takeda

Mr Craig Johnston, CMAC
Dr Ian Houson, CMAC
Dr Stewart Mitchell, CMAC

Professor Claire Adjiman, Imperial College London
Professor Amparo Galindo, Imperial College London
Dr Alfonso Gonzalez Perez, Imperial College London
Professor George Jackson, Imperial College London

Dr Brahim Benyahia, Loughborough University
Dr Wei Li, Loughborough University
Professor Chris D. Rielly, Loughborough University

Professor Chick C. Wilson, University of Bath
Research Associate being recruited

Dr Ettore Settanni, University of Cambridge
Dr Jag S. Srai, University of Cambridge

Professor Kevin Roberts, University of Leeds
Professor Sven Schroeder, University of Leeds
Research Associate being recruited

Dr Omid Arjmandi-Tash, University of Sheffield
Dr Rachel Smith, University of Sheffield
Professor Jim Litster, University of Sheffield

Dr Cameron Brown, University of Strathclyde
Dr Magdalene Chong, University of Strathclyde
Miss Helen Feilden, University of Strathclyde
Professor Gavin Halbert, University of Strathclyde
Professor Joop ter Horst, University of Strathclyde
Dr Andrea Johnston, University of Strathclyde
Dr Blair Johnston, University of Strathclyde
Dr John Mulgrew, University of Strathclyde
Dr Alison Nordon, University of Strathclyde
Dr Chris Price, University of Strathclyde
Dr Elke Prasad, University of Strathclyde
Dr John Robertson, University of Strathclyde
Dr Murray Robertson, University of Strathclyde
Dr Kenny Smith, University of Strathclyde
Professor Jan Sefcik, University of Strathclyde

Technical Committee

Company	Members
AZ	Dr Amy Robertson Mr Phil Shering Dr Helen Wheatcroft
Bayer	Dr Wolfgang Beckamnn Dr Britta Olenik
GSK	Dr Mei Lee Dr Andrew Share
Lilly	Dr Chris Burcham Mr Tim Braden
Novartis	Dr Berthold Schenkel Dr Ruairi O'Meahdra
Pfizer	Dr Kevin Girard Dr Paul Meenan Dr David Walker
Roche	Dr Pirmin Hidber Dr Marcello Bosco
Takeda	Dr Charles Papageorgiou Dr Justin Quon

Appendix

Hub Structure 2017

Management Team

Job Title	Name
Director	Professor Alastair Director
Industrial Director	Mr Craig Johnston
EPSRC Hub Research Manager	Dr Andrea Johnston

Industry Team

Job Title	Name
Industrial Director	Mr Craig Johnston
Tier 1 Technical Project Manager	Dr Ian Houson
Project Manager Remedies	Mr John Mulgrew
Tier 2 Project Manager	Dr Stewart Mitchell
Tier 1 Administrator	Ms Rebekah Russell

National Facility Team

Job Title	Name
Technical Project Manager	Dr Kenneth Smith
Business Development Manager	Dr Claire MacDonald
Technical Operations Manager	Dr Thomas McGlone
CMAC National Facility Administrator	Ms Tanushree Mehta
Senior Instrument Scientist	Dr Humera Siddique
Senior Continuous Processing and Analysis Engineer	Mr Vishal Raval
X-Ray Facility Research Technician	Dr Alan Martin
Physical Analysis Research Technician	Dr Deborah Bowering
Physical Analysis Research Technician	Mrs Monika Warzecha
Chemical Analysis Technician	Ms Laura Harvey

Administrative and Support Team

Job Title	Name
EPSRC Hub Research Manager	Dr Andrea Johnston
EPSRC Hub Training & Outreach Manager	Ms Helen Feilden
Core Project Manager	Ms Claire Lynch
International Collaboration Co-ordinator	Ms Claire Ordoyno (Dr Rebecca Halliwell)
Hub Administrator	Ms Lorna Gray
Postgraduate Development Administrator	Dr Karen Graham
Administration Assistant	(Ms Rebekah Russell)
Assistant Hub Administrator	Ms Rebecca O'Hare

Researcher Teams 2017

EPSRC Future CMAC Hub

University of Strathclyde

Professor Alastair Florence Group

Research Associates
Dr Cameron Brown
Dr Zied Hosni
Dr Ebenezer Ojo
Iyke Onyemelekwe
Dr Nazer Rajoub
Lennart Ramakers
Dr Vijay Srirambhatla

PhD Researchers
Stephanie Yerdelen
Monika Warzecha
Bilal Ahmed
Sebastion Davidson
Frederik Doerr
Hector Polyzois
Michael Devlin
John Mahon

Dr Yi-Chieh (Claudia) Chen Group

PhD Researchers
Carla Ferreira

Professor Alex Duffy Group

PhD Researchers
Leda Todorova-Aleksiev

Professor Gavin Halbert Group

Research Associates
Dr Elke Prasad

PhD Researchers
Elanor Brammer
Albarah Al-Afandi
Carlotta Mendez Torrecillas
Alice Turner
Sarahjane Wood
Eleonora Paladino
Ecaterina Bordos

Professor Joop H. ter Horst Group

Early Stage Researchers
Johannes Hoffman
Sudhansu Sekhar Jena
Raghunath Venkatramana

PhD Researchers
Andrew Dunn
Olayinka Olalere
Carlos Moreno Leon
Corin Mack
Jose Luis Capdevila Echeverria

Dr Blair Johnston Group

Research Associates
Dr Murray Robertson
Dr Antony Vassileiou

PhD Researchers
Bruce Wareham
Thidarat Wongpinyochit
Michael Chrubasik

Dr Alison Nordon Group

Research Associates
Magdalene Chong

PhD Researchers
Joanna Lothian
Antonia Ngama

Dr Iain Oswald Group

Research Associates
Dr Martin Ward

PhD Researchers
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Suse Bebiano
Lloyd Farquhar

Dr Chris Price Group

PhD Researchers
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Muhid Shahid

Dr John Robertson Group

Research Associates
Ali Anwar
Dr Muhammad Tariq Islam

Professor Jan Sefcik Group

Research Associates
John McGinty

PhD Researchers
Vaclav Svoboda
David McKechnie

Spokes

University of Bath

Professor Chick Wilson Group

PhD Researchers
Alex Cousen
Ruth Lunt
Lois Wayment
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University of Cambridge

Dr Jagrit Singh Srai Group

Research Associate
Dr Ettore Settanni

Imperial College London

Professor Claire S. Adjiman Group

Research Associates
Alfonso Gonzalez Perez

PhD Researchers
Oliver Watson

University of Leeds

Professor Sven Schroeder
Professor Kevin Roberts

Loughborough University

Professor Chris Rielly Group

Research Associates
Dr Wei Li

PhD Researchers
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Dr Brahim Benyahia Group

PhD Researchers
Ravi Parekh

University of Sheffield

Professor Jim Litster Group

Research Associates
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PhD Researchers
Jon Tew

Dr Rachel Smith

EPSRC CMAC DTC Universities

Professor Xiongwei Ni, Heriot-Watt University

PhD Researchers
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Arabella McLaughlin
Francisca Navarro Fuentes

Professor Colin Pulham, University of Edinburgh

PhD Researchers
Adam Michalchuk

Dr Ross Forgan, University of Glasgow

PhD Researchers
Sarah Griffin

ICT CMAC

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Research Associates
Jerzy Dziewierz
Okpeafoh Agimelen
Javier Cardona
Akos Borsos

Appendix

Mentor Groups

Synthesis into Crystallisation

Researchers
Meifen Jiang
Arabella McLaughlin
Antonia Ngama
Vaclav Svoboda
Thidarat Wongpinyochit
Andrew Dunn
Carla Ferreira
Sarah Griffin
Francisca Navarro Fuentes
Dr Magdalene Chong
Dr Zied Hosni
Lennart Ramakers

Academics and Technical
Dr Ian Houson
Prof Xiong-Wei Ni
Dr Alison Nordon
Dr John Robertson
Prof Jan Sefcik
Prof Joop Ter Horst
Dr Ross Forgan
Dr Philipp Seib
Dr Claudia Chen
Laura Harvey

Industrial Mentors
Wolfgang Beckmann (Bayer)
Tim Braden (Lilly)
Natalie Douillet (GSK)
Lucie Miller Potucka (AZ)
Takashi Ouchi (Takeda)
Anna Parsons (AZ)

Crystal and Particle Engineering

Researchers
Researchers
Stephanie Yerdelen
Sebastion Davidson
Bilal Ahmed
Alex Cousen
Ruth Lunt
Olayinka Olalere
Lois Wayment
Jose Luis Capdevila Echeverria
Corin Mack
John Mahon
David McKechnie
Pollyanna Payne
Dr Cameron Brown
Dr Wei Lee
Dr John McGinty
Iyke Onyemelukwe

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Prof Alastair Florence
Prof Jan Sefcik
Prof Joop ter Horst
Prof Chick Wilson

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Chris Burcham (Lilly)
Tia Jacobs (Bayer)
Britta Olenik (Bayer)
Sreenivas Reddy Lingireddy (Lilly)
Susan M Reutzel-Edens (Lilly)
Rachel Sullivan (AZ)
Helen Wheatcroft (AZ)
Yihui Yang (Takeda)

Advanced Characterisation

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Frederik Doerr
Eleonora Paladino
Hector Polyzios
Dr Nazer Rajoub
Dr Vijay Srirambhatla

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Prof Gavin Halbert
Prof Sven Schroeder
Prof Kevin Roberts
Dr Alan Martin

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Jeremy Hinds (Lilly)
Tia Jacobs (Bayer)
Marianne Langston (Takeda)
Arlene McBroom (GSK)
Britta Olenik (Bayer)
Sreenivas Reddy Lingireddy (Lilly)
Susan M Reutzel-Edens (Lilly)
Paul Stroud (Lilly)
Stefan Taylor (AZ)

ICT Tools, Process Models and Predictive Design

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Ravi Parekh
Bruce Wareham
Michael Chrubasik
Zhuang Sun
Jon Tew
Oliver Watson
Laura Straughair
Dr Omid Arjmandi Tash
Dr Alfonso Gonzalez Perez
Dr Murray Robertson
Dr Antony Vassileiou

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Prof Alastair Florence
Prof Claire Adjiman
Dr Blair Johnston
Prof Jim Litster
Prof Chris Rielly
Dr Rachel Smith

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Johan Remmelgas (AZ)
Gavin Reynolds (AZ)
Jeff Tan (Lilly)
Yihui Yang (Takeda)

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Clarissa Forbes
Carlos Moreno Leon
Georgia Sanxaridou
Muhid Shahid
Dr Ebenezer Ojo

Academics and Technical
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Dr Chris Price
Prof Alastair Florence

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Chris Burcham (Lilly)
Gareth Ensor (AZ)
Alex Heller (Lilly)
Guilluame Levilain (Bayer)

Primary to Secondary

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Carlota Mendez Torrecillas
Adam Michalchuk
Alice Turner
Sarahjane Wood
Ecaterina Bordos
Dr Tariq Islam
Dr Elke Prasad

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Craig Johnston
Prof Gavin Halbert
Prof Jim Litster
Prof Colin Pulham
Dr John Robertson
Dr Rachel Smith
Dr Deborah Bowering

Industrial Mentors
Susanna Abramsen Alami (AZ)
Frantz Elbaz (Novartis)
Richard G. Elkes (GSK)
Liz Meehan (AZ)
Charles D. Papageorgiou (Takeda)
Mike Quayle (AZ)
Jim Wesley (Lilly)

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Closing Remarks

CMAC has made a significant step forward in the last 12 months, with new academic and industry partners and having established the ambitious new Hub research programme. The new EPSRC Independent Advisory Board brings a wealth of academic and industrial experience of pharmaceutical R&D, manufacturing and regulation and is playing an important role in advising the Director and his team on forward planning aligned with the Hub's aims as well as on routes to maximise CMAC's impact over the coming years. The plans developed by the Hub across research, training, facilities and industry engagement and translation are targeted to accelerate the development of new knowledge and technology and identify effective ways to embed these within innovative industrial partners and the wider continuous manufacturing research community."

Paul Sharratt, ICES

How quickly the first year as a Hub has passed and CMAC continues to thrive and grow. We have our eighth and final Tier 1 member with Pfizer joining us. Progress too on industrialisation of continuous manufacturing with the Medicines Manufacturing Innovation Centre (MMIC) moving a step closer.

CMAC has given rise to both Remedies and the concept of MMIC creating a pathway to impact from fundamental research to industrial application. A wonderful achievement in only 6 years."

Dr Clive Badman OBE, GSK, CMAC Chair

CMAC
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