



Annual Review

2019

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Introduction

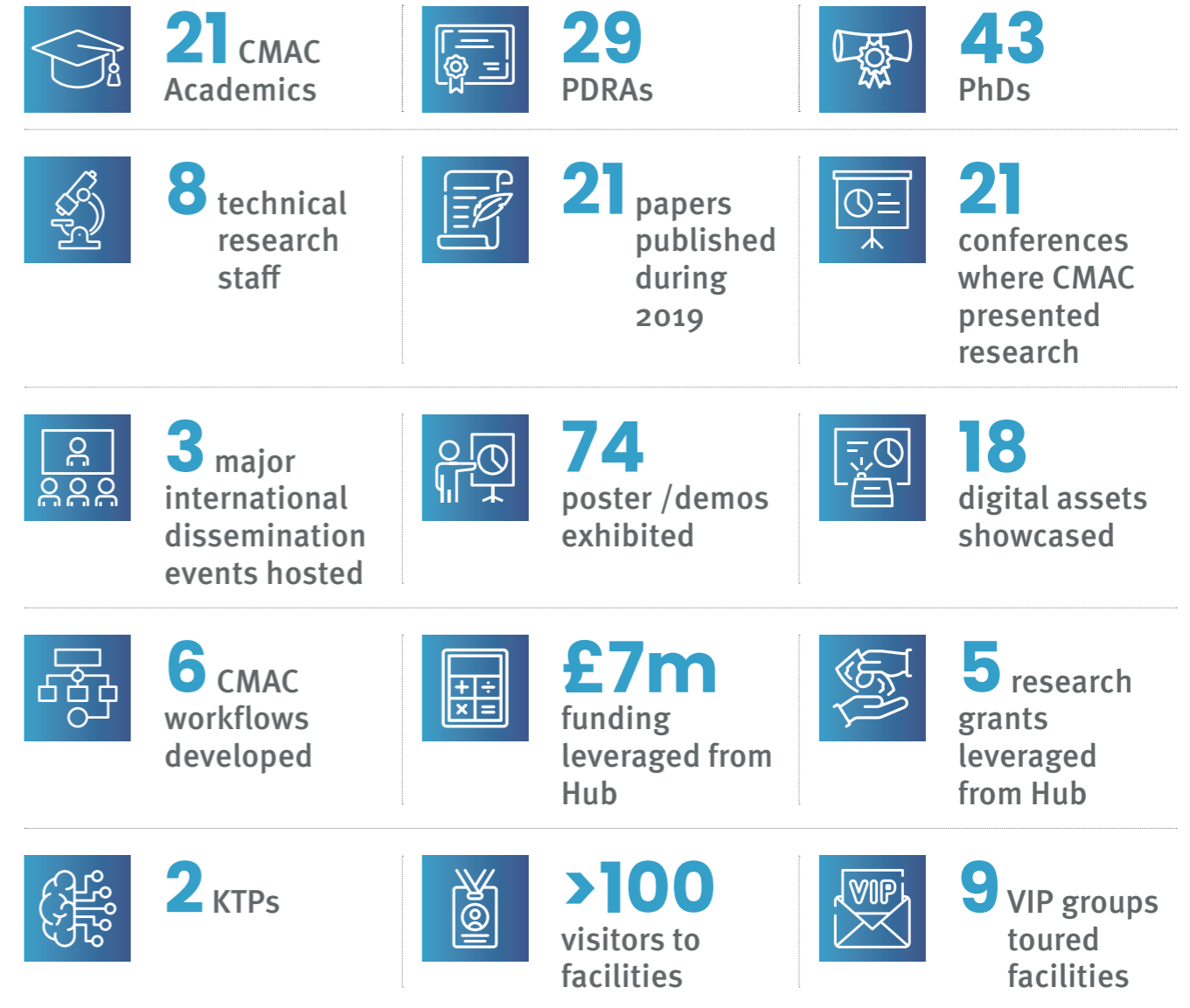


It is a pleasure to introduce the 2019 Annual Review for the EPSRC Future Continuous Manufacturing and Advanced Crystallisation Research Hub (CMAC). The team is working together to establish innovative tools and approaches to transform the way that medicines are developed and produced and enable the future supply of increasingly personalised medicines. The review highlights the significant progress that our manufacturing research programme has made over the last 12 months.

The continued work in enabling digital design of products and processes and translating these designs into new MicroFactory processing platforms has made considerable progress. A key example is the Lovastatin campaign that saw inputs from all Hub partners to deliver the engineering and physical science research to create a novel, integrated drug substance processing platform coupling primary particle formation with spherical agglomeration. This approach showcases the potential for enabling streamlined drug product manufacture that can be realised from delivering the right initial particle properties. Further progress has taken place in exploiting advanced characterisation techniques both in the laboratory and from central facilities and synchrotron radiation to better understand the fundamental structure and transformations that occur during manufacturing processes. This is a crucial aspect to our efforts to build better predictive models and improved manufacturing capabilities. The review also highlights the training and skills development activities across masters and doctoral level ongoing in the Hub in addition to the continued progress in developing the facilities that support our researchers and staff. Translation to industry is core to our mission and I offer my thanks to our previous Industry Director, Craig Johnston, who left CMAC mid 2019 for all his efforts and support developing our industry partnerships. Looking ahead to 2020, I am delighted to welcome Massimo Bresciani who takes over this important role and will be working with all of our stakeholders to continue our success in this area. Also in the coming months we are developing our plans for the second phase of the Hub programme and look forward to sharing these exciting developments with all of our colleagues and partners later in the year. In the meantime, if you would like more information on any of the areas highlighted in the review, please do not hesitate to get in touch.

Prof Alastair Florence, CMAC Director

CMAC by the numbers 2019



3 Integrated process development campaigns during 2017-2019

- ✦ Demonstrated **50% reduction** in material used
- ✦ Demonstrated **prediction first** approach
- ✦ Demonstrated computer aided solvent selection

Prototype integrated Digital Twin demonstrator

- ✦ **5 novel models** developed and integrated in digital twin
- ✦ **2 VR** process simulation demos
- ✦ Hybrid data and mechanistic models



CMAC National Facility Highly Commended in Excellence in Contract Services and Outsourcing category at the CPhI Pharma Awards 2019

Partners

ACADEMIC HUB AND SPOKES:



TIER 1 INDUSTRY PARTNERS:



TIER 2 PARTNERS:



INNOVATION SPOKES:



“The pharmaceutical industry is dealing with significant change as demands from patients, payers and healthcare systems drive increased complexity in the design, development, manufacturing and supply of future medicines. CMAC, with 8 Tier 1 Pharma companies and a thriving Tier 2 community, has been built on pre competitive, industry led collaboration. Delivering an ambitious and impactful research programme and outstanding skills development, whilst excelling at effective industrial translation, is critical to sustainable success and a focus for the industry partners. The environment has changed with the formation of the UK Research and Innovation body (UKRI), the Medicines Manufacturing Industry Partnership (MMIP) and targeted funding through the Industrial Strategy Challenge Fund, CMAC is well positioned in providing a clear and influential voice in this new international ecosystem.”

JON-PAUL SHERLOCK
CHAIR OF CMAC INDUSTRY BOARD AND AZ



“As the Hub approaches its mid-term review, progress remains impressive. Despite a challenging external environment, the team has maintained a strong focus on delivering value to UK manufacturing both through transfer of outputs of the programme to date and by intelligent positioning to bring more value in the future.”

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

CMAC Overview

TRANSFORMING MEDICINES DEVELOPMENT AND MANUFACTURE

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

Established in 2011, CMAC's vision has been developed through close collaboration with industry and the support of its Tier 1 partners; AstraZeneca, Bayer, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, Roche and Takeda. A wide range of technology companies and innovation spokes form part of the CMAC community. CMAC is comprised of more than 120 staff researchers, including academics, 25 post docs, 43 PhD students, 16 MSc students and an experienced support team. To date, we have saved companies in excess of £20M per annum and leveraged a £150M funding portfolio.

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

CMAC

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



SAVED COMPANIES
>£20M p.a.



**7 LEADING
 UK ACADEMIC
 PARTNERS**



MORE THAN
**120 STAFF AND
 RESEARCHERS**



**15 CMAC ALUMNI
 WORKING AT TIER 1
 COMPANIES**



**£25M
 CRITICAL MASS
 FUNDING FROM
 EPSRC**

External Environment

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

SOURCES: KPMG, PHARMA OUTLOOK 2030; PWC PHARMA 2020

WHAT DOES THIS MEAN FOR MEDICINES MANUFACTURING?

<p>Precision medicines driving smaller volume manufacturing and new distribution models</p>	<p>Adaptive and different trial design accelerating clinical and launch phases</p>	<p>Advance drug delivery and increasing molecular and process complexity</p>
<p>Continuous, miniaturised & flexible manufacturing platforms with real time process measurement and control</p>	<p>Advanced analytics and artificial intelligence supporting human decision-making</p>	<p>Digitalisation – embrace emerging technologies towards integrated design manufacturing & supply</p>
<p>Delivering sustainable processes</p>		

CONTINUOUS MANUFACTURING IS A CORNERSTONE

General Summary of companies outlook towards continuous manufacturing.

<p>90%</p> <p>... see CM as important for the supply of their products in the next 5 to 10 years.</p>	<p>>80%</p> <p>... consider their C-level to be well aware about the importance of CM.</p>	<p>59%</p> <p>... have an ambitious adoption strategy driving agenda with regulatory bodies, equipment providers, ecosystem partners etc.</p>	<p>17%</p> <p>... consider their CM strategy as mature whereas CM strategy still at exploratory stage for all others; approximately 1/2 consider themselves early adopters.</p>
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SOURCE: ACCENTURE, ADAPTED BY DR JP SHERLOCK, OPEN DAY 2018

CMAC VISION:

Transforming Medicines Development & Manufacture

MISSION:

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

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

Exploit production tools to accelerate product and process development.

2 Produce digital twins based on multiscale models.

Extract value from data and link multiscale models.

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

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

4 Strengthen understanding of material attributes.

Pharmaceutical materials science underpinning stability, manufacturability and performance.

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

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

6 Strengthen position as Global Manufacturing Research Centre.

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

FOCUS ON CORE PILLARS:

Research Excellence & Intensity



Outstanding Skills Development



World Class Facilities



Exemplary Translation to Industry



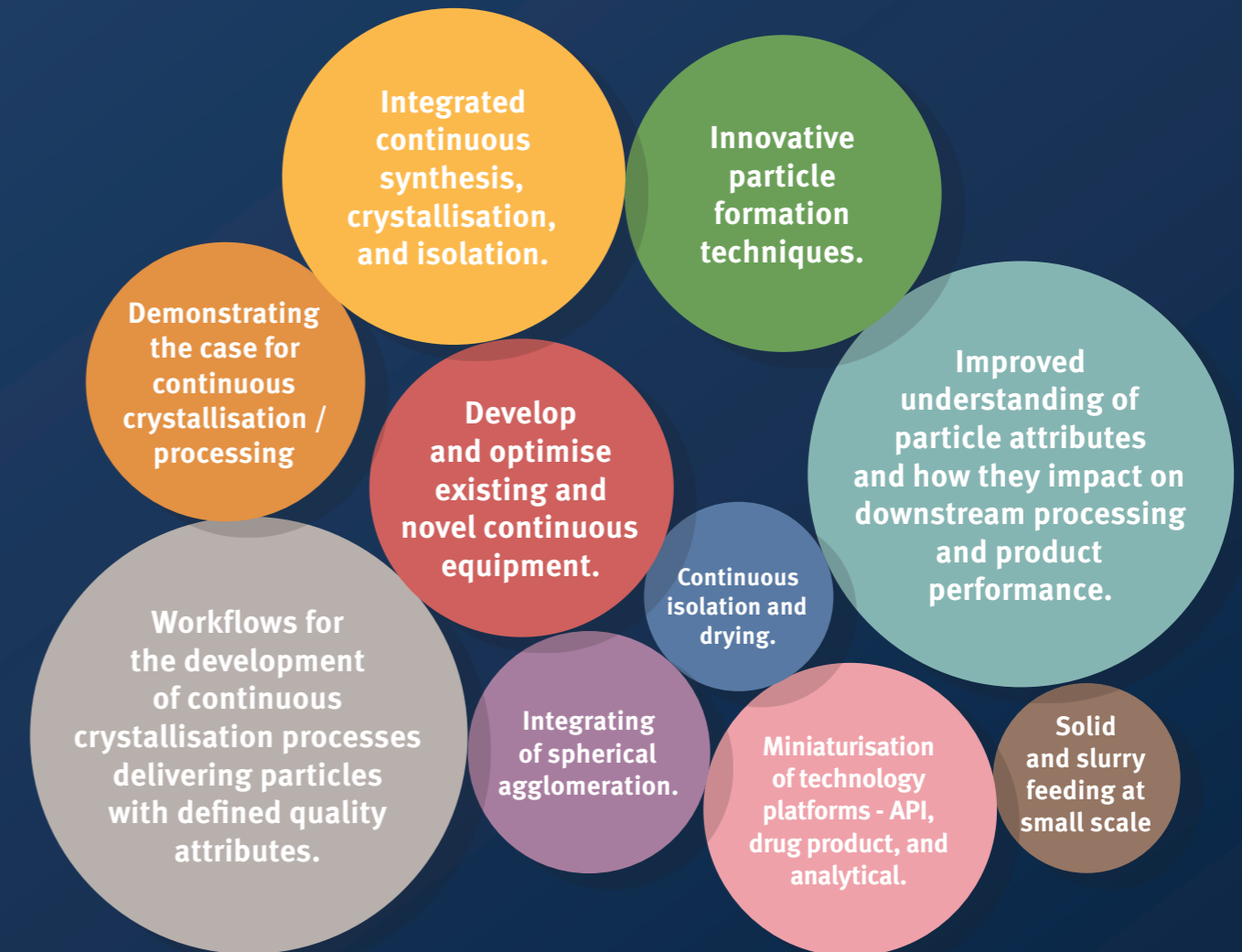
Productive partnerships driven by a collaborative, international outlook and regulator engagement.

Research Excellence & Intensity

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

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

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



RESEARCH ACROSS THE CMAC COMMUNITY IS DRIVEN BY INDUSTRY PROBLEM STATEMENTS

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

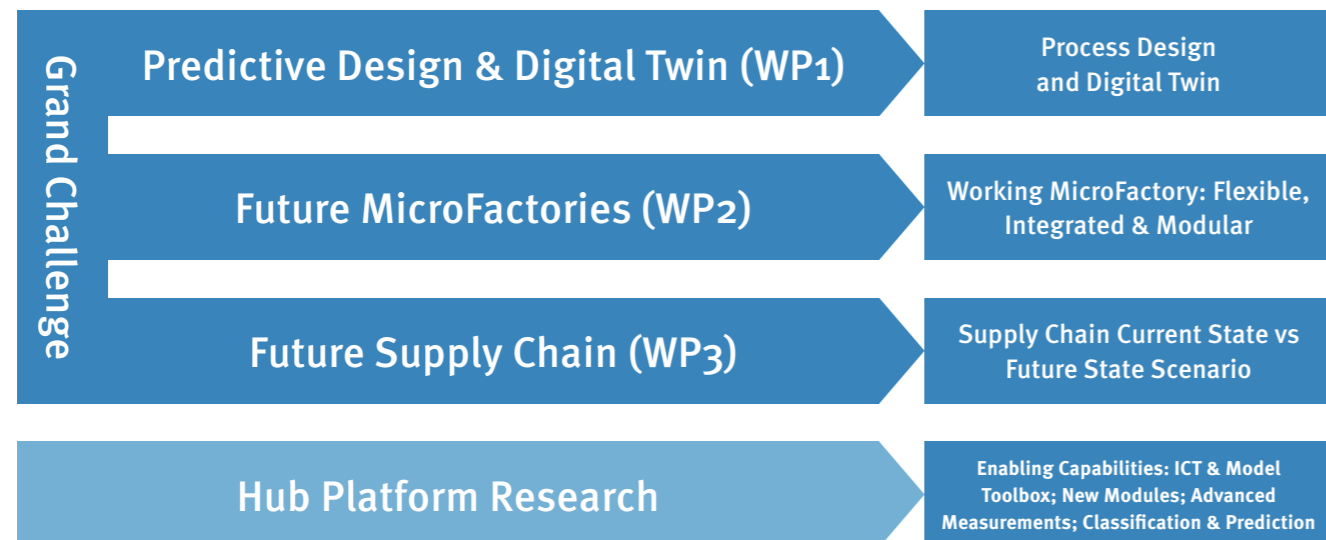
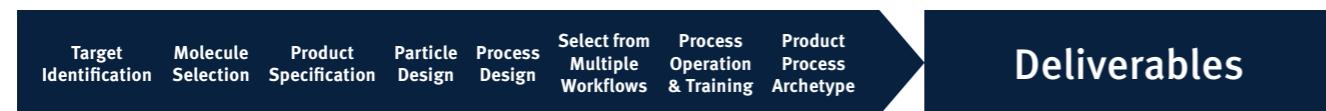
EPSRC CMAC Future Manufacturing Research Hub Programme

HUB VISION

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

HUB 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.



HUB GOALS

- Development using minimal material and experiments exploiting predictive modelling
- Understand and control crystal or material attributes for enhanced manufacturability, stability and performance
- Demonstrate modular, integrated, flexible MicroFactories to enable future supply chains



Hub Platform Research

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

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

HUB GRAND CHALLENGE

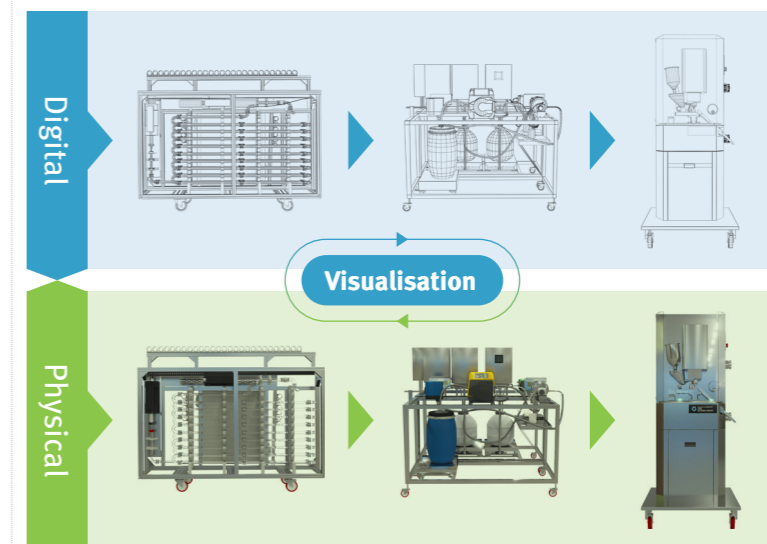
The Hub Programme will deliver a step-change in capability to bring functional high-value solid products to market, with a focus on pharmaceutical products. Small molecule systems of interest to industry and academic partner will be investigated. The work will inform development of radically new approaches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

PROGRAMME VISION

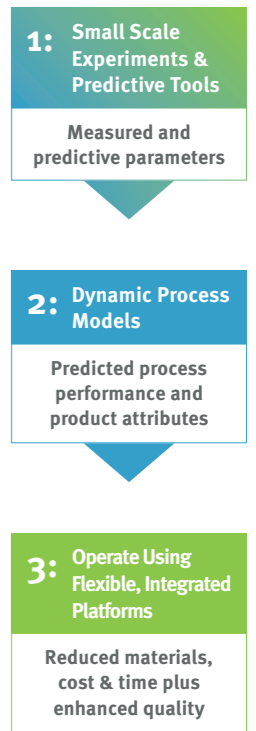
Key goals:

- Minimal material and experiments via predictive modelling
- Crystal attributes for enhanced manufacturability, stability and performance
- Integrated, flexible continuous process streams

Example process: crystallise ▶ isolate ▶ compress ▶ test



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



Three workpackages to deliver the Hub Grand Challenge

WP1: PREDICTIVE DESIGN & DIGITAL TWIN

This work focuses 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.

WP2: FUTURE MICROFACTORIES

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

WP3: FUTURE SUPPLY CHAIN

Future digital supply of personalised products and medicine is being investigated. 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. This will integrate technology capabilities emerging from WP1&2 and explore supply chain digitalisation opportunities that connect the digital factory through to the end consumer/patient.

DIGITALISATION

In order to extract maximum value from the large volume of data generated within CMAC, and from the wider community, efforts have been made to structure and organise these data. Structured data not only allow for fast efficient searching but also opens the possibility of machine learning on these data sets.

DIGITAL ASSETS

Digital assets being developed in CMAC include models – both mechanistic and data driven, structured data sets, and databases.

DIGITAL TWIN

The CMAC Digital Twin is a virtual replica of experiments, equipment and measurements. Digital twins are used to inform experimental design. The goal is to develop better processes more rapidly using less material.

- 🔄 Model integration
- 🔄 Reduce experimental burden
- 🔄 Visual representation of processes
- 🔄 Data visualisation
- 🔄 Enhanced process understanding

Workflows

A key deliverable from the Hub programme is to develop a library of workflows to enable rapid process design. Workflow development and validation, and a rational approach to selecting which workflows to use for a particular process design are aspects of the progress being made in this area. Navigating the workflows being developed and integrated will enable a ‘right first time’ science-based approach to process and product design, development and characterisation.

MicroFactories

CMAC’s vision to transform medicines development and manufacturing requires development of innovative, modular, integrated continuous manufacturing processes for drug substance and drug product. The end-to-end modular lab scale MicroFactories are being developed within the Hub to provide a rapid prototyping capability to control, measure and optimise critical transformations across multiple length-scales spanning crystal and particle engineering, and structured product and dosage form generation. They must also manage variable material properties and increased product complexity.



Inputs from the digitalisation work are used to design, build and operate flexible, integrated continuous manufacturing process chains at scale (kgs/day). A key deliverable is to enable simplified process chains targeting the processes and transformations that improve manufacturability of the drug into a dosage form suitable for good performance in the patient. By developing integrated continuous “direct to dose” approaches, we avoid multiple unit operations and scale up steps.

CMAC UK & US Industry Showcase Events



82
INDUSTRIALISTS
AT EVENT



18 FROM
TIER 2
COMPANIES

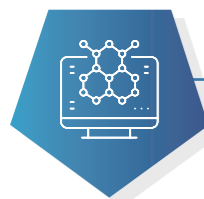


16 ACADEMICS AND
63 RESEARCHERS
SHOWCASING

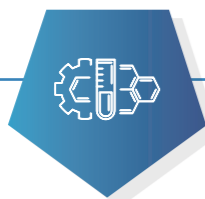


1 WHITE
PAPER
LAUNCHED

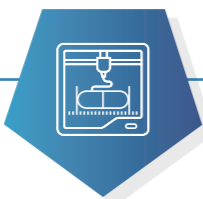
RESEARCH DEMONSTRATORS IN 5 THEMED ZONES WITH 35 POSTERS AND LIVE DEMOS COVERING:



PROPERTY PREDICTION & FUNDAMENTALS



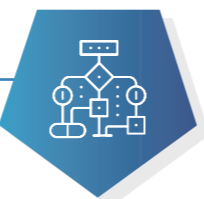
CRYSTAL & PARTICLE ENGINEERING



SECONDARY PROCESSING & ADVANCED MEASUREMENT



DIGITAL & MODEL TOOLBOX



WORKFLOWS

DTC DISSEMINATION EVENT

10 Industry and academic guests

03 Tier 1 & 2 companies

45 Researchers

10 Academics

04 Alumni

46 Posters

26 Presenters

HUB RESEARCH PLANS FOR 2020

Throughout 2019 the Hub Researchers were working on a campaign using the drug Mefenamic Acid as exemplar. This will deliver case studies to showcase at our Open Day in 2020.

1

Mefenamic Acid
Drug Substance
MicroFactory

2

Mefenamic Acid
Drug Product
MicroFactory

3

Digital Twin for
Mefenamic Acid
Drug Substance
MicroFactory

4

Digital Twin of
Crystallisation unit
operation with VR
visualisation

Aligned Core Industry Funded Projects

Pre-competitive industry funded Core projects are aligned with EPSRC funded projects and are steered by the CMAC Technical Committee. (See page 29). Three projects completed in 2019 and two more will continue into 2020.

COMPLETED IN 2019

Spherical Agglomeration

- Joint Sheffield, Strathclyde University project
- Development of a novel wetting pre-nucleation device alongside mechanistic understanding

Impurity Rejection

- Workflow developed to rapidly identify the mechanism for how impurities are incorporated into a crystal
- 3 papers in press, webinars and 1 day training events planned in 2020 for knowledge and technical translation from project into Industry partners

Materials parameterisation database project

- Standardised methods for excipient characterisation in Drug Product area developed
- Model to select excipient for direct compression developed

CONTINUING INTO 2020

Spherical Agglomeration

- Continue mechanistic understanding
- Test manufacturing robustness and impact into Oral Solid Dosage form

Materials parameterisation database project

- Continue mix of experimental and modelling work



World Class Facilities

UNIVERSITY OF STRATHCLYDE



Industrial Engagement

Over the last twelve months CMAC has provided new insights into some of the fundamental processes underpinning key manufacturing operations including ways to monitor and control phenomena which can deliver impactful outcomes to clients, ensuring that solutions are deeply rooted in fundamental science. The facility team was recognised for these services at the prestigious CPhI Excellence in Pharma awards ceremony in November 2019 with an honourable mention in the Services and Outsourcing category.

Academic Excellence

CMAC is built upon a collaborative ethos whether working with multi-disciplinary local academic teams or international researchers. The National Facility team play a critical role in supporting this value by working to support individual researchers to access and use the facilities or the complete provision of research services. Examples of international collaborations include joint research with CUNY in New York and also at the University of Strathclyde and ENSAT INP Toulouse where researchers analysed microplastics obtained from remote mountain locations which made international news.

CMAC National Facility

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

CMAC National Facility in 2019

- ✦ **Ongoing support for CMAC Hub researchers totaling over 50 post-docs and PhD students at Strathclyde, plus visiting Hub researchers**

- ✦ **Analytical support to four Tier 1 member Core pre-competitive projects**

- ✦ **Hosted 24 students conducting final practical projects for a Master of Science qualification in Advanced Pharmaceutical Manufacturing**

- ✦ **Ongoing management and maintenance across the extensive equipment base**

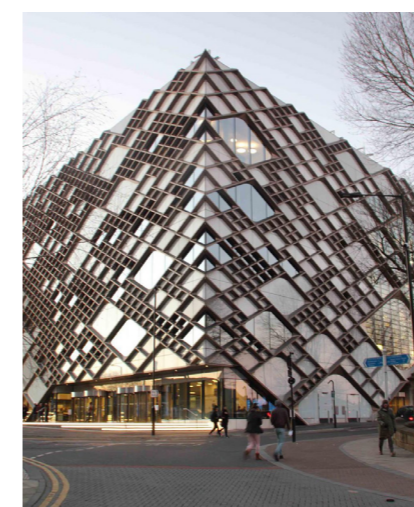
To find out more contact: national-facility@cmac.ac.uk

Facilities at Spokes



Diamond Light Source

CMAC has access to the Research Complex at Harwell and Diamond Light Source on the Harwell Science and Innovation Campus, through academic spoke partner 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.



Sheffield

The Diamond Pilot Plant (DiPP) at 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.

STRATEGIC PARTNER FACILITIES

MMIC

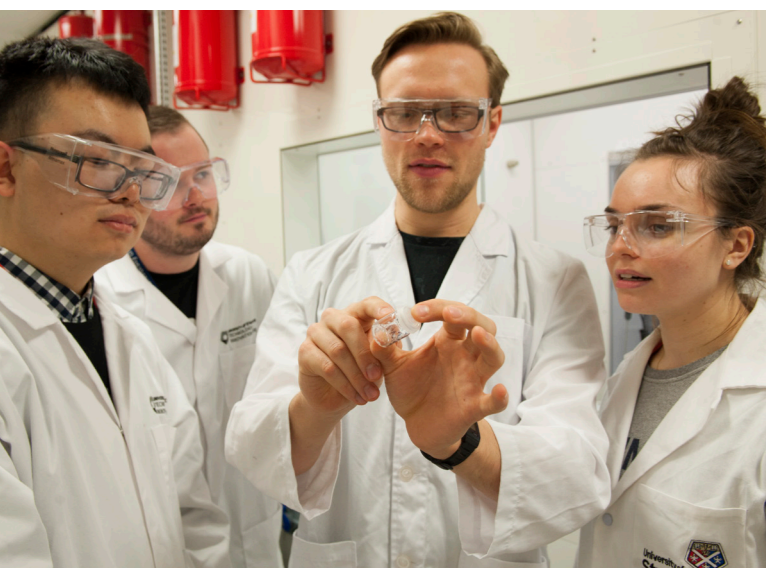
The University of Strathclyde is a strategic partner in a new £56 million UK Medicines Manufacturing Innovation Centre (MMIC), which will revolutionise the way medicines are manufactured. The world-first, industry-led MMIC will offer pharma companies, from start-ups through to multinational organisations, a service to develop and adopt novel manufacturing techniques to adapt into their own manufacturing processes. The Centre is to be located in Renfrewshire and will be operational in 2021. The project is led by the Centre for Process Innovation (CPI), in partnership with Strathclyde, the Medicines Manufacturing Industry Partnership (MMIP), and founding Industry partners, AstraZeneca and GSK. The University is leading the work package of the development phase of a next generation continuous direct compression digital test bed and demonstrator.

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

NPL

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

Outstanding Skills Development



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

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

In CMAC, skills development is tailored to train interdisciplinary researchers ready to move to world-class academic research and industry positions as their first destination after CMAC. The bespoke training programmes are aligned to the Hub research vision and informed by the needs of our Industry partners. The CMAC researcher community benefits from a vibrant and dynamic ‘ecosystem’ of leading academic expertise across multiple disciplines, access to world-class facilities and contribution from leading Industrial partners. Researchers are empowered through training and support to develop their skills, build collaborations and find innovative solutions within their research themes.

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

CMAC INDUSTRY PARTNERS

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

- ✦ MSc in Advanced Pharmaceutical Manufacturing
- ✦ Doctoral Training
- ✦ Early Career Researcher Development
- ✦ Transferable skills training for staff and students

MSc Training

The MSc in Advanced Pharmaceutical Manufacturing delivered at Strathclyde since 2013. The curriculum has been devised in consultation with our Industry partners and is delivered by CMAC academics and industry guest lecturers.

- ✦ 16 students enrolled for 2019/20
- ✦ 92% pass rate for 2018/19
- ✦ 62% who completed 2018/2019 awarded distinction
- ✦ 12% who completed 2018/2019 progressed to PhD

Doctoral Training

In 2019, CMAC doctoral training has been supported by a number of aligned schemes:

- ✦ £4.3m EPSRC award (EP/K503289/1) July 2012- June 2019
- ✦ CMAC PhD programme supported by industry and academic Hub partners
- ✦ Aligned PhDs supported by iCASE: AZ, GSK; NPL; CRUK; NMIS; self-funded

Overview of CMAC DTC



In 2012 the CMAC Doctoral Training Centre (DTC) 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 DTC fully supported 3 cohorts of trainees and further supported aligned CMAC doctoral trainees by providing training and events supporting the researcher community. The uniquely qualified researcher cohorts that benefitted from this support have already proved themselves capable of transforming practice in pharmaceutical and speciality chemical manufacturing.

- ✦ 49 Journal publications
- ✦ 34 PhD Placements
- ✦ 78 Industry mentors
- ✦ 7 Summer School events
- ✦ 44 students who received DTC training have completed by start of 2020
- ✦ 45% of DTC graduates entered industrial careers
- ✦ 55% of DTC graduates entered academic research careers

Early Career Researcher Training

The Hub ran a 2-day Creativity@home event in Q1 2019. This used the “skunkworks” method developed by Lockheed Martin, training from Britest, and the Belbin methodology to help researchers to combine their strengths in teams to come up with creative new project ideas.

- ✦ 40 attendees, 25 were PDRAs
- ✦ 8 project ideas
- ✦ 5 pitches
- ✦ Winning pitch was an idea for an equality and diversity app

PDRA talent pipeline in 2019

- ✦ 25 current PDRA posts in 2019
- ✦ 3 people started new PDRA posts from outside CMAC
- ✦ 4 people changed roles within CMAC to start new PDRA roles
- ✦ 5 left CMAC with 40% going to industry and 60% to academic first destinations



Exemplary Translation to Industry

The shared vision and scope for CMAC has been developed through close collaboration with industry. The continued support from Tier 1 and Tier 2 Industry partners has played a key role in CMAC's success. Industrial partners provide co-ordinated and sustained mentoring, direction, and support for the CMAC's research, training, and outreach portfolios.

CMAC has 8 Tier 1 Industry partners from the global pharmaceutical industry and 17 Tier 2 partners from the community of innovative technology companies that service medicines manufacturing stakeholders.

Changing roles

Craig Johnston, Industry Director, left CMAC in July 2019 to COO position in 3F Bio. We wish him all the best in his new endeavours.

Joining us in February 2020, Massimo Bresciani took over the Industry Director role. Massimo will provide leadership to CMAC's industry engagement, knowledge exchange and research translation activities for our industry and academic partners across major programs including the EPSRC Future Manufacturing Research Hub. Massimo has gathered a wealth of experience from his career, spanning many years in industry and most recently working in a senior role at the academic-industry interface.

We would also like to welcome Iyke Onyemelukwe as the new Technical Translation Manager. Ian Houson (formerly Technical Translation Manager) is now the CMAC National Facility Manager.

TIER 1

The continued support and engagement of Tier 1 Industry partners has been at the core of CMAC's success. Industrial partners provide co-ordinated and sustained mentoring, direction and support for CMAC. CMAC are a strategic partner in CPI Medicines Manufacturing Innovation Centre (MMIC) and we work closely with Industrial partners in a range of collaboratively funded high TRL activities such as Industrial Strategy Challenge Fund Made Smarter Digital Design of Advanced Pharmaceuticals as well as AMSCI funded Remedies and ADDoPT. We are also part of the UK's Medicines Manufacturing Industry Partnership and Medicines Manufacturing Special Interest Group.



TIER 2

CMAC warmly welcomes three new Tier 2 members: Huxley Bertram who will be working with us on the development of a compaction simulator with Terahertz technology, Anatune have joined us to collaborate on using innovative SIFT-MS technology applications, and finally FEI SAS (part of ThermoFisher Scientific) to supply, develop and trial the Amira and Avizo state of the art software for 3D visualisation.



PWC and CMAC have been working with our Tier 1 partners to generate a new white paper titled "Business Case Insights for Continuous Manufacturing" which will be published in early 2020.

We also had multiple visits, upgrades and workshops from our technology partners to work collaboratively with our researchers, partners and customers.

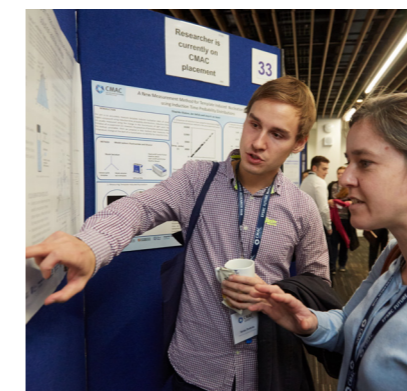
Industry Engagement with CMAC Researcher Community

PHD PLACEMENTS WITH CMAC PARTNERS

9 PhD Placements in 2018/19 (6 in USA, 3 in UK)

Topics included:

- ✦ Developed continuous crystallisation for NCE in phase II trials
- ✦ Developed workflows in co-crystal selection as well as peptide formulation
- ✦ Advanced Characterisation of amorphous materials using PDF
- ✦ Linking performance to surface attributes of spray dried materials using TOF-SIMS
- ✦ Combining model prediction and experimental approach to investigate polymorph landscape



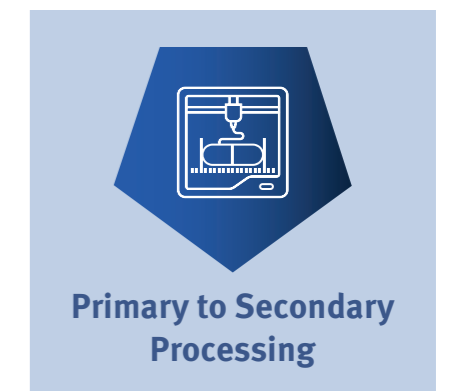
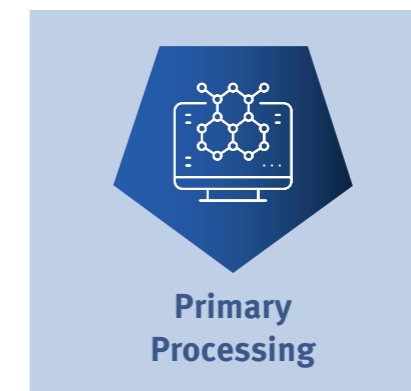
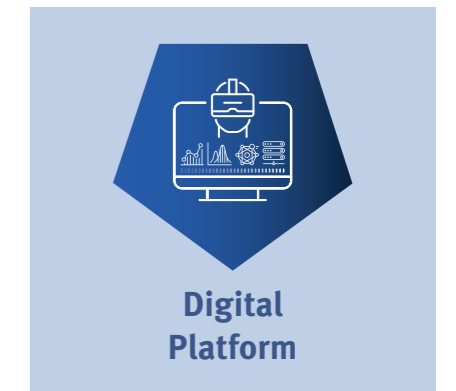
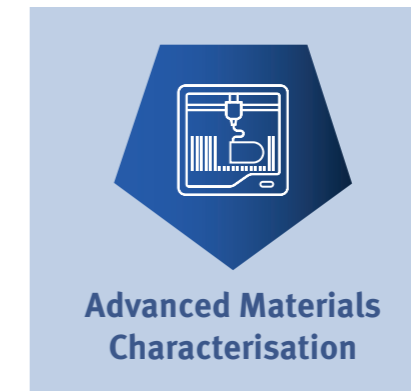
MENTOR GROUPS

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

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

Current groups by topic:

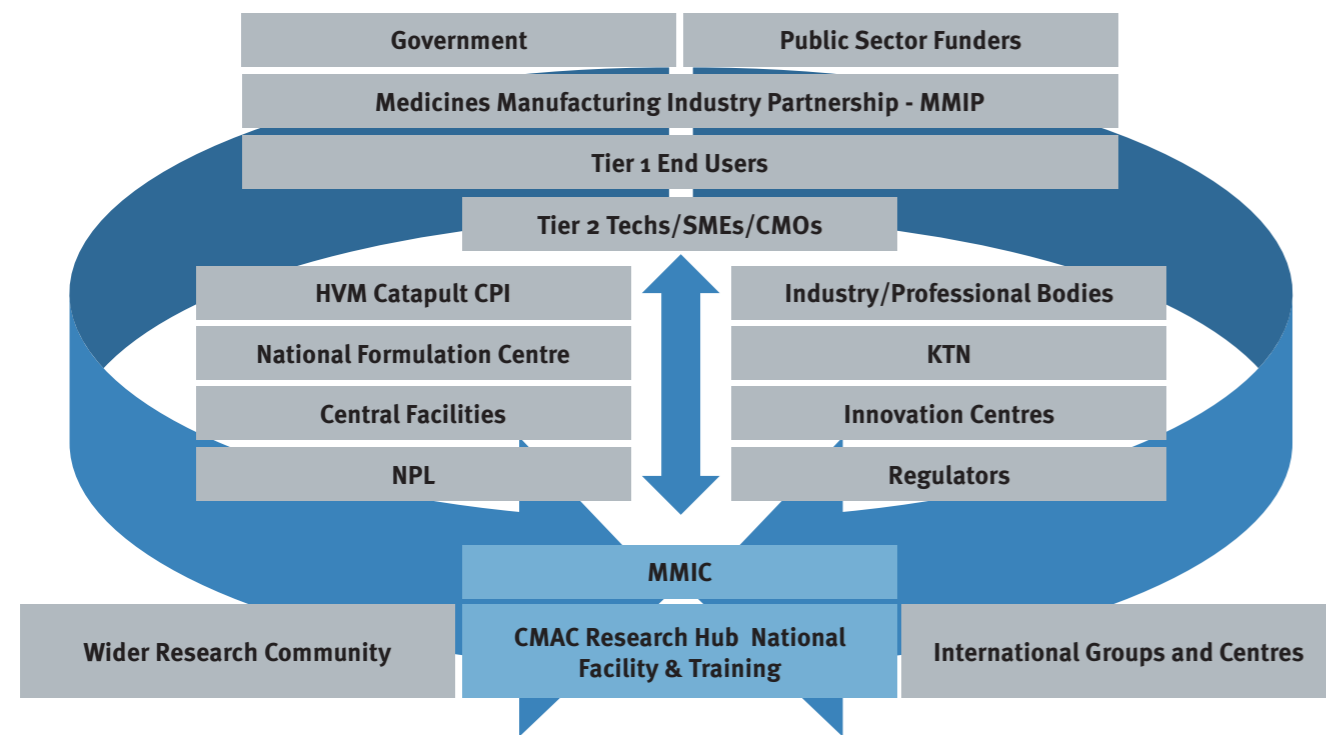
- ✦ Advanced Materials Characterisation
- ✦ Digital Platform
- ✦ Primary Processing
- ✦ Primary to Secondary Processing



Acting as a National Hub

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

LANDSCAPE MAP



KEY THEMES

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

KEY ENGAGEMENTS

CMAC are a strategic partner in CPI Medicines Manufacturing Innovation Centre (MMIC). We are partners and have a research base at Central facilities, and have a MoU and jointly appointed staff with NPL. We have strong interactions and collaborations with the wider research community including other EPSRC funded activities such as Hubs and CDTs. CMAC are represented on exec and leadership teams of many UK and international medicines manufacturing activities. We are part of the UK's Medicines Manufacturing Industry Partnership and Medicines Manufacturing Special Interest Group.



National Physical Laboratory (NPL)

CMAC and NPL have been collaborating since 2014 on how advanced measurements and data science can enhance product and process understanding for medicines development and manufacture. A formal framework agreement was established in May 2017. To date we have established multiple connections between CMAC and NPL staff on project activity, two joint appointments are now in place, five collaborative PhD studentships supported to date and NPL representation on CMAC Hub's Advisory board as one of CMAC's Innovation partners.

Academic Research Community

CMAC are part of the UK research network Connected Everything, an EPSRC-funded research network plus for the Digital Manufacturing community which is addressing the question 'how do we support the future of manufacturing in the UK?'.

Internationally we have links with leading academic medicines manufacturing research centres: MIT through co-organisation of the biannual International Symposium on Continuous Manufacturing of Pharmaceuticals (ISCOMP) events; The Science Foundation Ireland Research Centre for Pharmaceuticals (SSPC) in Ireland; Research Center Pharmaceutical Engineering (RCPE) Austria and Purdue University, US.

Showcase Events

Two industry Showcase events were held during 2019 in Boston, USA and Glasgow, UK in May and October, respectively. This was a highly interactive event for Tier 1, 2 and other partners to see the breadth of research being undertaken across CMAC, network with each other and get updates on the funding landscape. There was also a DTC Dissemination Showcase Event in Glasgow, UK in June to mark the end of the EPSRC DTC Programme.

CMAC ENGAGEMENTS IN 2019:



5
new videos on YouTube



5
Press releases



7
Exhibits



Public Outreach to school age children:
3 School visits,
1 Exploration



10
awards for research outputs



15
Academic keynotes delivered



1
White Paper launched



Webinar Programme launched

Map of CMAC Network

CMAC has worked with Industry partners and academic collaborators globally.



EPSRC:

- 01 EPSRC, Swindon, UK

ACADEMIC HUB AND SPOKES:

- 01 University of Strathclyde, Glasgow, UK
- 02 University of Bath, UK
- 03 University of Cambridge, UK
- 04 Imperial College London, UK
- 05 University of Leeds, UK
- 06 Loughborough University, UK
- 07 University of Sheffield, UK

TIER 1 INDUSTRY PARTNERS:

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

TIER 2 PARTNERS:

- 01 Anature, Cambridge, UK
- 02 AWL, Stoke-on-Trent, UK
- 03 Blacktrace, Royston, UK
- 04 Britest, Daresbury, UK
- 05 CCDC, Cambridge, UK
- 06 Clairet Scientific Limited, Northampton, UK
- 07 EDEM, Edinburgh, UK
- 08 Huxley Bertram, Cambridge UK
- 09 Nitech Solutions, Edinburgh, UK

TIER 2 PARTNERS CONT:

- 10 Perceptive Engineering Ltd, Warrington, UK
- 11 Pion Billerica, MA, USA
- 12 PSE, Hammersmith, UK
- 13 PWC, Glasgow, UK
- 14 Snapdragon Chemistry, Waltham, MA, USA
- 15 Technobis Crystallization Systems – Alkmaar, The Netherlands
- 16 Thermofisher Scientific, Bordeaux, France

INNOVATION SPOKES:

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

OTHER COLLABORATORS:

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

Other Research & Translation

Medicines Manufacturing Innovation Centre - MMIC



FIGURE - AMIDS SITE, RENFREWSHIRE.

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



FIGURE - GERICKE CDC FEED MODULE

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

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



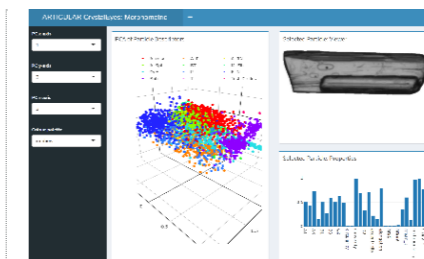
EPSRC ARTICULAR 2019-20 update

ARTificial inTElligence for Integrated ICT-enabled pharmaceUtical mAnufactuRing



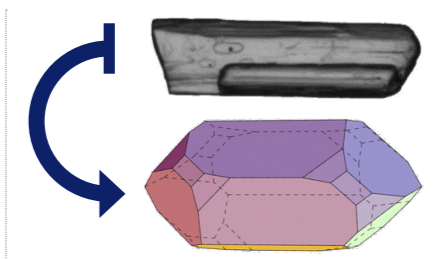
PROCESS DIGITAL TWINS

- Environment and process models for HME, tablet press and crystallisers maturing
- Integrating 24hr HME run data to complete Digital Twin demonstrator
- VR usability study to evaluate usefulness of advanced visualisation approaches coming in Summer 2020



CRYSTALEYES APP

- Unlock more information about particle shape
- Morphometrics analysis and description of particle shape complete
- Expert-enhanced AI via gamification in progress to help the AI see what you see



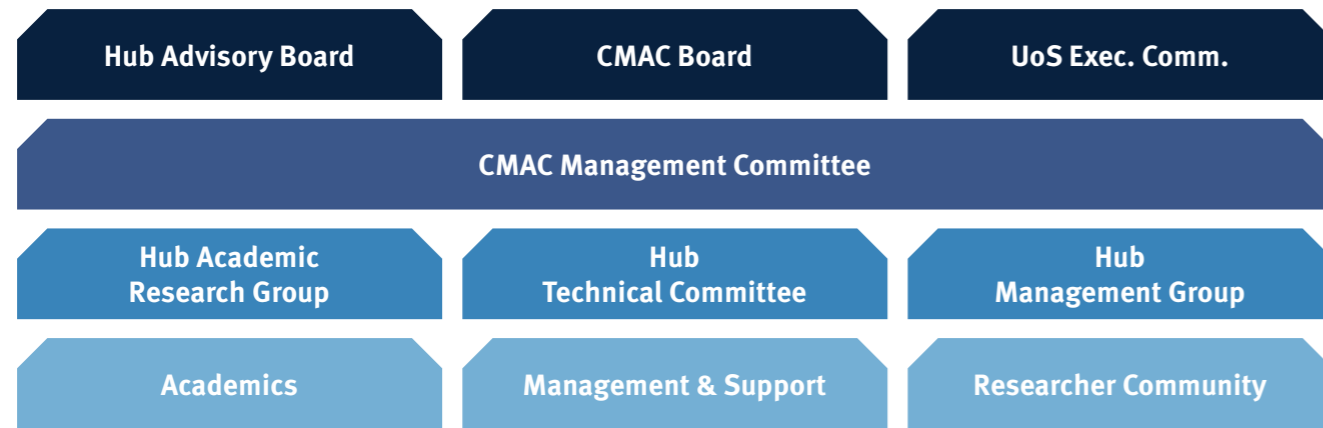
MACHINE LEARNING (ML)

- Developing AI for 2D particle image to 3D morphology estimation
- Predicted morphologies used for DEM simulations etc.
- Predict the outcomes from API crystallisation experiments with AI for predicting likelihood of solvate formation in common solvents



CMAC Governance Structures

CMAC HUB GOVERNANCE STRUCTURES



HUB ADVISORY BOARD

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

CMAC INDUSTRY BOARD

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

HUB ACADEMIC RESEARCH GROUP

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

Dr Andrea Johnston,
CMAC Hub Programme Manager
(**Craig Johnston / Massimo Bresciani**)
Industry Director

Miss Helen Feilden,
CMAC Hub Outreach Manager

Professor Chick C. Wilson,
University of Bath

Dr Lauren Hatcher, University of Bath

Dr Ettore Settanni, University of Cambridge

Dr Jag S. Srai, University of Cambridge

Dr Parminder Kaur Aulakh,
University of Cambridge

Professor Amparo Galindo,
Imperial College London

Professor Claire Adjiman,
Imperial College London

Professor George Jackson,
Imperial College London

Dr Suela Jonuzaj, Imperial College London

Dr Thomas Berger, Imperial College London

Dr Brahim Benyahia,
Loughborough University

Professor Chris D. Rielly,
Loughborough University

Dr Wei Li, Loughborough University

Dr Anuradha Pallipurath,
University of Leeds

Professor Kevin Roberts,
University of Leeds

Professor Sven Schroeder,
University of Leeds

Dr Thokozile Kathyola, University of Leeds

Dr Bilal Ahmed, University of Sheffield

Professor Jim Litster, University of Sheffield

Dr Rachel Smith, University of Sheffield

Dr Alison Nordon, University of Strathclyde

Dr Blair Johnston, University of Strathclyde

Dr Cameron Brown,
University of Strathclyde

Dr Chris Price, University of Strathclyde

Corin Mack, University of Strathclyde

Dr Daniel Markl, University of Strathclyde

Dr Elke Prasad, University of Strathclyde

Frederik Doerr, University of Strathclyde

Professor Gavin Halbert,
University of Strathclyde

Professor Jan Sefcik,
University of Strathclyde

Dr John McGinty, University of Strathclyde

Dr John Robertson, University of Strathclyde

Professor Joop ter Horst,
University of Strathclyde

Dr Magdalene Chong,
University of Strathclyde

Dr Monika Warzecha,
University of Strathclyde

Dr Murray Robertson,
University of Strathclyde

Dr Sara Ottoboni, University of Strathclyde

TECHNICAL COMMITTEE

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



Publications in 2019

Arjmandi-Tash, O.; Tew, J. D.; Pitt, K.; Smith, R.; Litster, J. D., A new mathematical model for nucleation of spherical agglomerates by the immersion mechanism. *Chemical Engineering Science: X* 2019, 4, 100048 <https://doi.org/10.1016/j.cesx.2019.100048>

Briuglia, M. L.; Sefcik, J.; ter Horst, J. H., Measuring Secondary Nucleation through Single Crystal Seeding. *Crystal Growth & Design* 2019, 19, 421-429. <https://doi.org/10.1021/acs.cgd.8b01515>

Bordos, E.; Islam, M. T.; Florence, A. J.; Halbert, G. W.; Robertson, Use of Terahertz-Raman Spectroscopy to Determine Solubility of the Crystalline Active Pharmaceutical Ingredient in Polymeric Matrices during Hot Melt Extrusion. *J. Molecular Pharmaceutics* 2019, 16, 4361. <https://doi.org/10.1021/acs.molpharmaceut.9b00703>

Connor, L. E.; Vassileiou, A. D.; Halbert, G. W.; Johnston, B. F.; Oswald, I. D. H., Structural investigation and compression of a co-crystal of indomethacin and saccharin. *CrystEngComm* 2019. <https://doi.org/10.1039/C9CE00838A>

Dunn, A. S.; Svoboda, V.; Sefcik, J.; ter Horst, Resolution control in a continuous preferential crystallization process. *Organic Process Research & Development*, 2019 23 (9), 2031-2041. <https://doi.org/10.1021/acs.oprd.9b00275>

Edinger, M.; Iftimi, L.-D.; Markl, D.; Al-Sharabi, M.; Bar-Shalom, D.; Rantanen, J.; Genina, N., Quantification of Inkjet-Printed Pharmaceuticals on Porous Substrates Using Raman Spectroscopy and Near-Infrared Spectroscopy. *AAPS PharmSciTech* 2019, 20, 207. <https://doi.org/10.1208/s12249-019-1423-y>

Jiang, M.; Ni, X.-W., Reactive Crystallization of Paracetamol in a Continuous Oscillatory Baffled Reactor. *Organic Process Research & Development* 2019, 23, 882-890. <https://doi.org/10.1016/j.ijpharm.2018.12.052>

Jiang, M.; Ni, X.-W., Effects of solvents and impurity on crystallization kinetics and crystal properties in a reactive crystallization of paracetamol. *Journal of Crystal Growth* 2019, 523, 125150. <https://doi.org/10.1016/j.jcrysgro.2019.125150>

Jimeno, G.; Lee, Y. C.; Ni, X.-W., Smoothed particle hydrodynamics – A new approach for modeling flow in oscillatory baffled reactors. *Computers & Chemical Engineering* 2019, 124, 14-27. <https://doi.org/10.1016/j.ccep.2018.11.002>

Jolliffe, H. G.; Papathanasiou, F.; Prasad, E.; Halbert, G.; Robertson, J.; Brown, C. J.; Florence, A. J., Improving the prediction of multi-component tablet properties from pure component parameters. In *Computer Aided Chemical Engineering*, Kiss, A. A.; Zondervan, E.; Lakerveld, R.; Özkan, L., Eds. Elsevier: 2019; Vol. 46, pp 883-888. <https://doi.org/10.1016/B978-0-12-818634-3.50148-X>

Mendez Torrecillas, C.; Goringe, L. J.; Rajoub, N.; Robertson, J.; Elkes, R. G.; Lamprou, D. A.; Halbert, G. W., The impact of channel fill level on internal forces during continuous twin screw wet granulation. *International journal of pharmaceutics* 2019, 558, 91-100. <https://doi.org/10.1016/j.ijpharm.2018.12.052>

Onyemelukwe, I., Nagy, Z.K., Rielly, C.D. 2019. Solid-liquid axial dispersion performance of a mesoscale continuous oscillatory flow crystalliser with smooth periodic constrictions using a non-invasive dual backlit imaging technique, *Chem. Eng. J.* 2019 <https://doi.org/10.1016/j.cej.2019.122862>

Onyemelukwe, I. I.; Parsons, A. R.; Wheatcroft, H. P.; Robertson, A.; Nagy, Z. K.; Rielly, C. D., The Role of Residence Time Distribution in the Continuous Steady-State Mixed Suspension Mixed Product Removal Crystallization of Glycine. *Crystal Growth & Design* 2019, 19, 66-80. <https://pubs.acs.org/doi/10.1021/acs.cgd.8b00853>

Prasad, E.; Islam, M. T.; Goodwin, D. J.; Megarry, A. J.; Halbert, G. W.; Florence, A. J.; Robertson, J., Development of a hot-melt extrusion (HME) process to produce drug loaded Affinisol™ 15LV filaments for fused filament fabrication (FFF) 3D printing. *Additive Manufacturing* 2019, 29, 100776. <https://doi.org/10.1016/j.addma.2019.06.027>

Stranzinger, S.; Faulhammer, E.; Li, J.; Dong, R.; Khinast, J. G.; Zeitler, J. A.; Markl, D., Measuring bulk density variations in a moving powder bed via terahertz in-line sensing. *Powder Technology* 2019, 344, 152-160. DOI: 10.1016/j.powtec.2018.11.106 <https://doi.org/10.1016/j.powtec.2018.11.106>

Tahir, F.; Islam, M. T.; Mack, J.; Robertson, J.; Lovett, D., Process monitoring and fault detection on a hot-melt extrusion process using in-line Raman spectroscopy and a hybrid soft sensor. *Computers & Chemical Engineering* 2019, 125, 400-414. <https://doi.org/10.1016/j.compchemeng.2019.03.019>

Vesga, M. J.; McKechnie, D.; Mulheran, P. A.; Johnston, K.; Sefcik, J., Conundrum of γ glycine nucleation revisited: to stir or not to stir? *CrystEngComm* 2019, 21, 2234-2243. <https://doi.org/10.1039/C8CE01829D>

Ward, M. R.; Oswald, I. D. H., Antisolvent addition at extreme conditions. *CrystEngComm* 2019. <https://doi.org/10.1039/C9CE00365G>

Watson, O. L.; Galindo, A.; Jackson, G.; Adjiman, C. S., Computer-aided Design of Solvent Blends for the Cooling and Anti-solvent Crystallisation of Ibuprofen. In *Computer Aided Chemical Engineering*, Kiss, A. A.; Zondervan, E.; Lakerveld, R.; Özkan, L., Eds. Elsevier: 2019; Vol. 46, pp 949-954 <https://doi.org/10.1016/B978-0-12-818634-3.50159-4>

Wongpinyochit, T.; Vassileiou, A. D.; Gupta, S.; Mushrif, S. H.; Johnston, B. F.; Seib, F. P., Unraveling the Impact of High-Order Silk Structures on Molecular Drug Binding and Release Behaviors. *The Journal of Physical Chemistry Letters* 2019, 10 (15), 4278-4284. <https://doi.org/10.1021/acs.jpcllett.9b01591>

Zimbitas, G.; Jawor-Baczynska, A.; Vesga, M. J.; Javid, N.; Moore, B. D.; Parkinson, J.; Sefcik, J., Investigation of molecular and mesoscale clusters in undersaturated glycine aqueous solutions. *Colloids and Surfaces A*, 2019 579, 123633. <https://doi.org/10.1016/j.colsurfa.2019.123633>



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