Institution: University of Strathclyde

Unit of Assessment: A3 Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Transforming the development and manufacture of medicine through continuous processing and advanced manufacturing technology research

Period when the underpinning research was undertaken: 2011 - 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Alastair Florence	Professor	01/09/1997 – present
Ian Houson	National Facility Manager	10/12/2012 – present
Cameron Brown	Lecturer	03/03/2014 – present
Gavin Halbert	Professor	01/09/1984 – present
Blair Johnston	Professor	10/06/2002 – present
John Robertson	Knowledge Exchange Fellow	01/05/2015 – present
Joop Ter Horst	Professor	01/08/2014 – present
Craig Johnston	CMAC Industry Director	01/05/2011 – 09/08/2019

Period when the claimed impact occurred: August 2013 - December 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Strathclyde research has been crucial in creating new methods and technologies for industrial pharmaceutical process development associated with continuous manufacturing and crystallisation (CMAC) generating impacts across the UK and international technology and pharmaceutical sectors. This has led to new product lines being developed (Alconbury Weston Ltd), and documented savings in development studies (Lilly) that have gone on to inform commercial manufacturing (AstraZeneca). Since August 2013, approximately GBP45,000,000 of savings and improvements have been realised by the 22 multinational and Small and Medium-sized Enterprises (SMEs) who have invested directly in proprietary analytical and process improvement projects.

2. Underpinning research

The EPSRC Centre for Innovative Manufacturing (CIM) in Continuous Manufacturing and Crystallisation (CMAC) was established at the University of Strathclyde in 2011, based on the joint research and expertise of Florence (A3) and Sefcik (B12). Now an EPSRC Future Manufacturing Research Hub, CMAC undertakes demand-led manufacturing research in partnership with six universities, eight multinational pharmaceutical companies (AstraZeneca (AZ), Bayer, Eli Lilly, GlaxoSmithKline (GSK), Novartis, Pfizer, Roche, Takeda) and 18 equipment, analytical, software and consultancy companies.

CMAC research is conducted by a multi-disciplinary team from Strathclyde's Science and Engineering Faculties to generate a critical-mass ecosystem for advanced pharmaceutical manufacturing research. The development of small scale, modular, agile and flexible continuous manufacturing processes for medicines is essential to meet the rapidly changing demands of modern healthcare. This has never been more evident than in the essential medicines shortages resulting from international supply chain disruption in the ongoing COVID-19 pandemic.

The underpinning research spans understanding of particle formation, continuous processes, advanced technology and innovative digital solutions. Important contributions from Florence, Brown, Ter Horst, Halbert and Johnston among others in the Strathclyde Institute of Pharmacy and Biomedical Sciences have been made to research on:

Particles - Exquisite control of particle quality attributes: Controlling the formation of particles is crucial to realising improved manufacturability, performance and stability demanded by robust, sustainable and cost effective medicines manufacture. Understanding how key particle attributes can be better controlled using advanced process technologies and exploiting this knowledge to

streamline the final production of formulated products is vital to ensure medicines can be made with greater control and lower cost. Examples include the development of an advanced process control system jointly developed with CMAC, an SME (Perceptive Engineering) and AZ. This project delivered methods to directly control particle size, size distribution and significantly improve process yield (26% higher than corresponding batch process), improving productivity and reducing off-spec product and waste [R1]. In addition, extensive characterisation of plug flow reactors coupled with supersaturation and seeding control enabled control over polymorphic form and unwanted nucleation and encrustation during continuous crystallisation [R2].

Processes - Smart workflows for accelerated development of particle formation processes: CMAC research has focussed extensively on the development of robust, scalable workflow processes for continuous crystallisation and drug product processes to enhance process understanding, avoid common failure modes and deliver consistent, high quality products. Several examples have been developed building a comprehensive and rigorous framework for advanced process development that support regulatory requirements such as the US Food and Drug Administration's Quality by Design guidance. An extensive multidisciplinary project developed the first major comprehensive workflow for continuous cooling crystallisation as a key outcome from the EPSRC CIM [R3]. This system-wide view of the crystallisation process coupled scaled down experiments, prediction and multi-scale modelling to deliver robust process design and operation to achieve exquisite control of product attributes and quality. Workflows have also been published for anti-solvent crystallisation, impurity rejection in crystallisation [R4], spherical agglomeration, wash solvent selection in filtration washing and drying, determination of solubility of materials in polymeric systems and manufacturability of formulated products.

Technologies - Advanced continuous platform technology development: CMAC has provided fundamental science to design and develop novel processing equipment, or microfactories, to broaden the applicability and benefits of continuous processing. These platforms include: Novel Nucleator Platform; mixed suspension mixer product removal crystalliser with Digital Twin; meso-scale, moving liquid Continuous Oscillatory Baffled Crystalliser [R1, R2], in line mixers for rapid antisolvent crystallisation and a moving baffle oscillatory baffled reactor cascade.

Digital Design: Manufacturing research spans many length scales from molecular to process and bulk materials. CMAC research has included the development of Machine Learning models to predict the formation of novel solvates and crystallisability thereby creating novel predictive tools to inform and accelerate development. Molecular dynamics and atomic force microscopy (AFM) has informed new understanding of the fundamental mechanisms of crystal formation [R5]. In addition, digital design tools for formulated product manufacture via direct compression provide new tools to accelerate development using predictive modelling approaches [R6]. The role of data science is key and CMAC has developed a database of common excipients to support rapid screening of formulation options in-silico, saving time as well as associated material use.

3. References to the research (Strathclyde affiliated authors in **bold**; FWCI at 02/02/2021)

R1 F. Tahir, K. Krzemieniewska-Nandwani, J. Mack, D. Lovett, **H. Siddique**, **F. Mabbott**, **V. Raval**, **I. Houson**, **A. Florence** (2017) Advanced control of a continuous oscillatory flow crystalliser, *Control Engineering Practice*, 67: 64-75 https://doi.org/10.1016/j.conengprac.2017.07.008

R2 **N.E.B Briggs**, **U. Schacht**, **V. Raval**, **T. McGlone**, **J. Sefcik**, **A.J. Florence** (2015) Seeded crystallization of ß-l-glutamic acid in a continuous oscillatory baffled crystallizer, *Organic Process Research & Development*, 19(12): 1903-1911 https://doi.org/10.1021/acs.oprd.5b00206 [FWCI: 2.15]

R3 **C. Brown**, **T. McGlone**, **S. Yerdelen**, **V. Srirambhatla**, **F. Mabbott**, **R. Gurung**, **M.L. Briuglia**, **B. Ahmed**, **H. Polyzois**, **J. McGinty**, **F. Perciballi**, D. Fysikopoulos, **P. MacFhionnghaile**, **H. Siddique**, **V. Raval**, T.S. Harrington, **A. Vassileiou**, **M. Robertson**, **E. Prasad**, **A. Johnston**, **B. Johnston**, **A. Nordon**, J.S. Srai, **G. Halbert**, **J.H. ter Horst**, **C.J. Price**, C.D. Rielly, **J. Sefcik**, **A.J. Florence** (2018) Enabling

precision manufacturing of active pharmaceutical ingredients: workflow for seeded cooling continuous crystallisations, *Molecular Systems Design & Engineering*, 3: 518-549 https://doi.org/10.1039/C7ME00096K [FWCI: 3.24; REF2]

R4 **S.J. Urwin**, G. Levilain, I. Marziano, J.M. Merritt, I. **Houson, J.H. Ter Horst** (2020) A structured approach to cope with impurities during industrial crystallization development. *Organic Process Research & Development*, 24(8): 1443-1456. https://doi.org/10.1021/acs.oprd.0c00166

R5 **M. Warzecha**, L. Verma, **B. Johnston**, J. Palmer, **A.J. Florence**, P. Vekilov (2020) Olanzapine crystal symmetry originates in preformed centrosymmetric solute dimers, *Nature Chemistry*, 12: 914-920 https://doi.org/10.1038/s41557-020-0542-0 [FWCI: 2.15]

R6 **H.G. Jolliffe, F. Papathanasiou, E. Prasad, G. Halbert, J. Robertson, C.J. Brown, A.J. Florence**, (2019) Improving the prediction of multi-component tablet properties from pure component parameters, *Computer Aided Chemical Engineering*, 46: 883-888 https://doi.org/10.1016/B978-0-12-818634-3.50148-X

Notes on the quality of research: This research has been supported with competitively awarded core funding from EPSRC totalling GBP26,059,706, including:

- Florence (PI), ter Horst, Johnston (CIs), EPSRC Centre for Innovative Manufacturing for Continuous Manufacturing and Crystallisation, 01/10/11-31/12/2016, GBP5,990,295;
- Halbert (PI), Florence (CI), Doctoral Training Centre in Continuous Manufacturing and Crystallisation, 01/07/2012-01/01/2021, GBP4,645,116;
- Florence (CI): Computationally Designed Templates for Exquisite Control of Polymorphic Form, 01/10/13-30/6/18, GBP1,248,345;
- Johnston (PI), Florence (CI): ARTICULAR: ARtificial inTelligence for Integrated ICT-enabled pharmaceUticaL mAnufactuRing, 01/07/18-31/06/22, GBP1,956,119.

4. Details of the impact

Through the establishment, growth and global influence of CMAC, Strathclyde's demand-led research and expertise in forming particles with controlled attributes, in workflow design, on advanced continuous platform technology and development of digital tools has improved pharmaceutical development and manufacturing processes globally. By demonstrating the viability and benefits of advanced continuous manufacturing techniques, Strathclyde's innovative approach to integrated development and operating platforms has enabled adoption within the pharmaceutical industry and created business opportunities for technology providers. As evidenced by the following examples, this has resulted in improved processes which have lowered development time and production costs, increased yields, reduced risk and enhanced product quality to the benefit of manufacturers, suppliers and end-users. Upskilling of staff in new techniques and methods has also been achieved. Since August 2013, CMAC's research has enabled approximately GBP45,000,000 of savings and improvements for the 22 multinational and SMEs who have invested directly in proprietary analytical and process improvement projects.

Contributing more broadly to technology translation for societal and economic benefit, CMAC's work has generated 54 highly-skilled individuals, 31 of whom have gone on to employment in industry (e.g. AZ, Pfizer, GSK, Lilly, Novartis, Roche, Perceptive Engineering, National Physical Laboratory (NPL), Solid Form Solution, Process Systems Enterprise (PSE) Ltd, Mettler Toledo) and 23 to academia (e.g. Strathclyde, Imperial, Loughborough, Massachusetts Institute of Technology (MIT)).

Improved Industrial Process Development:

- CMAC research workflow outcomes [**R3**,**R5**] were applied by AstraZeneca (AZ; 2016-18) to improve a commercial process for a pharmaceutical product delivering GBP10,000,000 saving [**S1**]. The improved process understanding led to reduced waste and increased product quality.
- In 2014, Novartis adopted CMAC Strathclyde's novel methodology for introducing seed crystals into a continuous crystallisation [**R2**,**R3**] in their continuous pilot plant in Basel, Switzerland. This approach has been applied to the development of an anti-cancer product

and at least 2 other active ingredients in development. As noted by the Novartis Development Engineer, *'this effective application of CMAC research reduced chemical exposure risk to operators, minimised plant down time and improved product quality'* [**S2**].

- CMAC doctoral placements (2013-19) installed a novel continuous nucleation and crystallisation platform at AZ which has since been used on 10 live medicinal compounds, 4 of which are in commercial manufacture [**R2**, **R3**, **R5**]. This led to a 90% time reduction to generate the existing amount and quality of information compared to previous approaches. AZ's Principal Scientist confirmed that, *'Without the CMAC collaboration and student placements we would not have had the laboratory continuous crystallisation facilities established in this time frame or have been able to test the feasibility of continuous crystallisation on multiple AZ compounds. Using this new capability AZ scientists are be able to develop continuous crystallisation processes for APIs in-house in a much shorter timescale'* [**S1**].
- The application of CMAC's workflow approaches for particle attribute control at Eli Lilly in 2017 resulted in an improved particle size control from the use of high shear wet milling in the continuous crystallisation of the final active pharmaceutical ingredient for an oncology asset which was then in Phase IIb clinical trials [**R3**,**R6**]. According to a Senior Engineering Advisor at Eli Lilly, by enabling the removal of a post processing dry milling step, this work *'reduced fouling on the crystalliser walls (reducing plant cleaning and down time) and improved the physical product properties improving the product manufacturability. The removal of a milling step has reduced cycle times of each lot of product by 3 days and development time by 3 months. This is now a platform capability embedded at Lilly'* [**S3**].

Enhanced workforce understanding and skills:

- The benefits of process insights from CMAC's multivariate analysis (MVA) and data visualisation approaches were demonstrated on plant data at Lilly's manufacturing plant in Ireland as part of a PhD project. These learnings enhanced process understanding and operations engagement with data analytics tools [**R1**, **R3**, **R6**]. The project delivered real-time data cleansing, organisation and visualisation enabling a reduction in plant downtime and product losses. The work demonstrated the benefits of MVA to senior management and resulted in investment in digitisation of manufacturing processes. As noted by the Eli Lilly Team Leader for Small Molecule Technical Services/Manufacturing Sciences, in Cork, Ireland, this *'really raised awareness of the benefits to manufacturing when data and technology are combined with people with the right skillsets…this work was a significant factor in convincing the site to expand the use of these tools'* [**S4**].
- Working pre-competitively with its 8 large pharma Tier 1 members, CMAC developed an industrially-relevant workflow with 7 case studies providing methods to avoid the incorporation of impurities in crystals [**R4**, **R5**]. Between Jan and Nov 2020, tailored training was provided to over 130 industry staff who subsequently applied the approaches directly into the process development of all their Active Pharmaceuticals Ingredients (APIs) [**S5**].

Advanced process technology and industry adoption:

- An Advanced Process Control (APC) system for continuous reaction and crystallisation was developed and demonstrated in collaboration with Perceptive Engineering, Centre for Process Innovation (CPI) and AstraZeneca [**R1**]. The Managing Director of Perceptive Engineering said, *'The commercialisation of this software directly led to one new client with follow-on sales of GBP207,700, GBP400,000 of related projects, employment of 1 new FTE to support applications on continuous manufacturing and publication of 4 peer-reviewed papers and 2 articles significantly increasing our visibility and reputation'* [**S6**].
- In collaboration with Alconbury Weston Ltd (AWL), CMAC developed and delivered a platform for continuous isolation (filtration, washing and drying) of APIs bridging from process development to manufacturing and reducing scale up risk [**R3**, **R6**]. The platform is now in

commercial production. As confirmed by AWL's CEO, *'Continuous isolation systems are rare at this scale and coupled with the demonstrated benefits of rapid processing times of less than 15 minutes, no particle shear or attrition, precise, repeatable dosing and consistent product, the unit has been demonstrated on >10 commercial molecules (including vitamins, pharmaceuticals, Cannabidiol (CBD) and an energetic material) with more than 15 companies. To date, 8 units have been sold with a further 3 on order, including 2 production scale systems for processing CBD and 2 systems are on hire around the world. The success of the new products based on the outstanding direction and input from Prof. Chris Price has allowed us to refine and commercialise a range of lab, pilot and production scale continuous filtration and drying systems for multiple industries'* [**S7**].

Enhanced the global manufacturing landscape:

- At the request of Janet Woodcock, Head of the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research, CMAC collaborated with the Novartis Centre for Continuous Manufacturing at MIT to initiate biennial symposia to advance continuous pharmaceutical manufacturing. Since 2014, the International Symposium for Continuous Manufacturing of Pharmaceuticals (ISCMP) has been held 5 times (2014, 2016, 2018, 2020 and 2021), demonstrating sustained interest in its potential impact on the global medicines manufacturing landscape. Due to the Covid-19 pandemic, the 2020/21 events were delivered as webinars which attracted over 500 delegates and facilitated discussion between key stakeholders: US and UK regulators (FDA, MHRA), industry bodies (Medicines Manufacturing industry Partnership, MMIP) and the UK Government (Office for Life Sciences and Business Enterprise Innovation and Science, BEIS). By bringing the wider international industry, regulatory and academic communities together to share case studies, develop and share practical guidance on continuous manufacturing (further embedded through the publication of a series of whitepapers and reports) CMAC has accelerated the pace of innovation and change in this strategically important industry sector. Attesting to this, the Chair of the Medicines Manufacturing Industry Partnership (MMIP) notes: *'CMAC, on the basis of its research and recognised expertise, has strengthened international cooperation around continuous pharmaceutical manufacturing through the ISCMP. By facilitating discussion and focusing attention on key developments and issues to be addressed, this initiative has enhanced global relations and positioned the industry well to respond to current and future challenges'* [**S8**].

Strengthened UK Research and Innovation:

- CMAC's critical mass as a collaborative research centre has highlighted the success of the 'triple helix', coupling the power of industry, government and academia working together to accelerate change in the form of the adoption of continuous manufacturing. By working together with the Centre for Process Innovation (CPI Ltd), AZ and GSK, Strathclyde University helped to secure investment of GBP56,000,000 to create the Medicines Manufacturing Innovation Centre (MMIC) in 2018. This new facility, owned by CPI, will be built in 2021 and create 80 high value jobs by 2023 [**S9**].

5. Sources to corroborate the impact

S1 Factual statement from Principal Scientist Crystal & Particle Science, AstraZeneca (01/03/2021).

S2 Factual statement from Development Engineer, Novartis, Switzerland (18/02/2021).

S3 Factual statement from Senior Engineering Advisor of Eli Lilly, Indiana, USA (02/03/2021).

S4 Factual statement from Team Leader, Small Molecule Technical Services/Manufacturing Science, Eli Lilly, Ireland (22/02/2021).

S5 Factual statement, CMAC Translation manager, University of Strathclyde (22/02/2021).

S6 Factual Statement from Managing Director, Perceptive Engineering Ltd (16/02/2021).

S7 Factual statement from CEO, Alconbury Weston Ltd, UK (16/02/2021).

S8 Factual statement from MMIP Chairman in the UK (04/03/2021.

S9 UK Government, 'Faster medicine: £56 million innovation centre for Scotland', 18/06/2018.