Institution: University of Leeds

Unit of Assessment: UoA 8 Chemistry

Title of case study: Accelerating pharmaceutical manufacturing development using automated self-optimisation platforms

Period when the underpinning research was undertaken: 2014-date

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:
Professor John Blacker	Professor	01/12/2006-date
Dr Thomas Chamberlain	Associate Professor	01/08/2015-date

Period when the claimed impact occurred: 2014-date

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact (indicative maximum 100 words)

Optimising pharmaceutical manufacturing processes is expensive, time-consuming, and negatively impacts patients waiting for new/improved treatments. University of Leeds research has developed automated platforms for the self-optimisation of chemical transformations, which have been deployed within pharmaceutical development by global pharmaceutical companies. These platforms act as autonomous units, combining continuous flow reactors with in-line analytics, reactor control and evolutionary algorithms to rapidly optimise pharmaceutical processes. This has significantly reduced development time, resulting in substantial productivity gains and faster translation of materials to clinical trials. Applications have included development of the AstraZeneca anti-cancer agent TAGRISSO™ (current annual sales ca. GBP3,000,000,000) in an accelerated timeframe.

2. Underpinning research (indicative maximum 500 words)

The Institute of Process Research and Development (iPRD) was established in 2008 as a joint venture between the Schools of Chemistry and Chemical and Process Engineering at the University of Leeds (UoL) to exploit expertise in process chemistry and develop new technologies for, and in partnership with, the fine chemical and pharmaceutical manufacturing industries. Alongside the construction of a new 650m^2 process development laboratory, the Institute was bolstered by four joint appointments between the two Schools, three relevant to this study: Dr Richard Bourne (continuous processing, process optimisation), Prof John Blacker (process chemistry, continuous processing) and Prof Frans Muller (reaction engineering, kinetic modelling). Bourne/Muller are returned in UoA12, Blacker in UoA8. Dr Tom Chamberlain is an Associate Professor in Chemistry with *inter alia* expertise in continuous manufacture of nanomaterials.

With the recruitment of Bourne in 2012, a programme of work was established in iPRD to develop automated continuous flow reactor systems. The project has involved 11 industrially funded/sponsored PDRAs and PhD students across four global pharmaceutical companies (AstraZeneca, GlaxoSmithKline, Pfizer, Dr. Reddy's Laboratories), and has led to the development of Self-Optimising Flow Reactors (SOFR).

Initially, AstraZeneca (AZ) sponsored the development of a platform for self-optimising the synthesis of pharmaceutical compounds using closed-loop feedback at meso-scale. Prior work worldwide had focused on self-optimisation in microreactors, or in niche media such as supercritical fluids. The shift to meso-scale pharmaceutical synthesis critically required development of suitable analytical methods, meso-volume reactor platforms with material saving modifications, accurate pumping solutions and machine learning optimisation algorithms. Supported by Blacker's industrial expertise in continuous processing, a fully operational SOFR unit

was constructed at Leeds. In 2015, Bourne received an RAEng Industrial Fellowship (ISS1516\8\32) to spend 50% of his time at AstraZeneca to establish a replica of the UoL system within the AstraZeneca Process Research and Development group at Macclesfield and apply it to 'live' manufacturing projects such as the kinase inhibitor AZD9291 proposed for lung cancer therapy. The SOFR combined online analysis with evolutionary feedback algorithms to rapidly achieve optimum conditions for the final bond-forming steps in synthesising AZD9291. Optimisations were initially carried out on a model compound, with the data used to track the formation of various impurities and propose a mechanism for their formation. This was then applied to the optimisation of a two-step telescoped reaction to synthesise AZD9291 in 89% yield. **[1]**

Subsequently, AstraZeneca have continued to sponsor research projects at Leeds to improve automated optimisation platforms. These include developing direct mass spectrometry for reaction analysis, which greatly expanded the scope of chemistries to include compounds without chromophores. **[2]** This has proved critical to the development of viable flow processes including a large-scale production for clinical trials. The research also developed techniques for multi-objective optimisation (visualising the trade-off between objectives such as purity and productivity) and optimising multiple unit operations (i.e. reactor and separation). **[3]** This approach was applied to the synthesis of BACE1 inhibitor AZD3293 proposed for Alzheimer's disease therapy. **[4]**

The Leeds team have also developed the use of these automated platforms to assess reaction kinetics. **[5, 6]** This work explores the use of mixed integer linear programming for model discrimination and automated parameterisation of models, and offers a rapid and less labour-intensive approach to gaining process understanding compared with traditional experimentation approaches. This approach has been applied at AstraZeneca (Macclesfield), co-funded through the University of Leeds EPSRC Impact Acceleration Account. **[6]**

In 2019, Bourne was appointed as an AstraZeneca / Royal Academy of Engineering Senior Research Fellow in Digital Manufacturing and Discovery of Pharmaceuticals (RCSRF1920\9\38), in recognition of the impact of his research upon manufacturing and development practices in the pharmaceutical industry.

3. References to the research (indicative maximum of six references)

[1] "Self-optimisation of the final stage in the synthesis of EGFR kinase inhibitor AZD9291 using an automated flow reactor" N. Holmes, G. R. Akien, A. J. Blacker, R. L. Woodward, R. E. Meadows, R. A. Bourne, *Reaction Chemistry & Engineering*, **2016**, *1*, 366–371. DOI: 10.1039/C6RE00059B. (50 citations)
Novel implementation of a self-optimising automated flow reactor for a 2-step telescoped process in the synthesis of active pharmaceutical ingredient AZD9291 (co-authored with AstraZeneca).

[2] "Online quantitative mass spectrometry for the rapid adaptive optimisation of automated flow reactors" N. Holmes, G. R. Akien, R. J. D. Savage, C. Stanetty, I. R. Baxendale, A. J. Blacker, B. A. Taylor, R. L. Woodward, R. E. Meadows, R. A. Bourne, *Reaction Chemistry & Engineering*, **2016**, *1*, 96–100. DOI: 10.1039/C5RE00083A. (62 citations)
Online quantitative mass spectrometry was developed as a tool for rapid analysis during self-optimisation, greatly reducing process development time (co-authored with AstraZeneca).

[3] "Machine learning meets continuous flow chemistry: Automated optimization towards the Pareto front of multiple objectives" A. M. Schweidtmann, A. D. Clayton, N. Holmes, E. Bradford, R. A. Bourne, A. A. Lapkin, *Chemical Engineering Journal*, **2018**, *352*, 277–282. DOI: 10.1016/j.cej.2018.07.031. (39 citations)
Application of machine learning global multi-objective optimisation algorithm for the self-optimisation of reaction conditions and visualisation of the trade-off between competing economic and environmental objectives.

[4] "Automated self-optimisation of multi-step reaction and separation processes using machine learning", A. D. Clayton, A. M. Schweidtmann, G. Clemens, J. A. Manson, C. J. Taylor, C. G. Niño,

T. W. Chamberlain, N. Kapur, A. J. Blacker, A. A. Lapkin, R. A. Bourne, *Chemical Engineering Journal*, **2020**, *384*, 123340. DOI: 10.1016/j.cej.2019.123340. (7 citations)
Multi-objective optimisation and self-optimising platforms were combined for the rapid development of multi-step processes, including steps towards the synthesis of AZD3293 (co-authored with AstraZeneca).

[5] "Rapid multistep kinetic model generation from transient flow data", C. A. Hone, N. Holmes, G. R. Akien, R. A. Bourne, F. L. Muller, *Reaction Chemistry & Engineering*, **2017**, *2*, 103–108. DOI: 10.1039/c6re00109b. (25 citations)
A method for kinetic model generation from transient flow data was developed resulting in a significant reduction in the time and material required compared to conventional approaches.

[6] "Rapid, automated determination of reaction models and kinetic parameters", C. J. Taylor, M. Booth, J. A. Manson, M. J. Willis, G. Clemens, B. A. Taylor, T. W. Chamberlain, R. A. Bourne, *Chemical Engineering Journal,* in press (available online 12/9/2020,127017. DOI: 10.1016/j.cej.2020.127017. (0 citations)
A kinetic modelling methodology was developed to determine reaction models and kinetic parameters using an autonomous framework involving transient flow measurements (co-authored with AstraZeneca).

The quality of the underpinning research is evidenced by (a) outputs [1]-[6] being published in international peer-reviewed journals and (b) the citations (Web of Science, 14/1/21) of each output that support their influence and scientific impact within the community.

4. Details of the impact (indicative maximum 750 words)

The development of the Self-Optimising Flow Reactor (SOFR) platforms **[1-4]** at the University of Leeds has changed business practices and outcomes.

AstraZeneca established their own SOFR platform at their Macclesfield site, facilitated through Bourne's RAEng Industrial Fellowship secondment, which included his training of AstraZeneca staff. **[A]** This contributes to the AstraZeneca Pharmaceutical and Development department's on-going improvement [text removed for publication]. **[A]**

To date, AstraZeneca have applied this technology to "[text removed for publication] *projects within our development and commercial portfolio across different therapy areas within the last year and is part of our standard workflow*". This has led to faster and more robust processes, with *"productivity gains of up to 50% in some areas*", **[A]** leading to significant financial impact and impact on patient health. AZD9291 is an example of such a product in the public domain:

- AZD9291, a kinase inhibitor for the treatment of lung cancer, was fast-tracked for approval by the Federal Drugs Administration (FDA) due to an unmet patient need. **[B]** By applying the SOFR technology developed at the University of Leeds, AstraZeneca were able to develop a manufacturing process in an unprecedentedly short timescale: the technology "*helped to reduce the overall development time to 2.5 years from a normal medicine development cycle of approximately 8 years*". **[A]**. The SOFR technology played a key role [text removed for publication] in the final stage of the synthesis. AZD9291 was launched in 2018 as TAGRISSO™, which is now an approved first line treatment in over 75 countries, **[C]** so the speed at which AZD9291 became available has significantly impacted patient health worldwide. This is now AstraZeneca's biggest selling medicine with current annual sales of ca. GBP3,000,000,000, **[A]** and has had significant societal impact by extending cancer patients' lives *"*[text removed for publication] *compared to previous standard-of-care treatments*". **[A]**

The success of these examples created a route to international innovation, with AstraZeneca transferring SOFR technologies to their Gothenburg site in the Sample Development team. University of Leeds and AstraZeneca (Gothenburg) colleagues designed a new proof-of-concept

system in 2017 (based on the original SOFR), **[D]** [text removed for publication]. In addition, a scientific role was created by AstraZeneca within the group at the University of Leeds for a 3-year period from January 2019 to advance the technology further. AstraZeneca is planning a significant internal investment [text removed for publication] to evolve and deploy these systems to AZ research sites [text removed for publication]. **[D]**

[text removed for publication]

5. Sources to corroborate the impact (indicative maximum of 10 references)

[A] Letter from the Principal Scientist, Pharmaceutical Technology & Development, AstraZeneca UK Limited, Macclesfield, UK (17th July 2020)

[B] 'TAGRISSO™ (AZD9291) approved by the US FDA for patients with EGFR T790M mutation-positive metastatic non-small cell lung cancer', 13 November 2015. https://www.astrazeneca.com/media-centre/press-releases/2015/TAGRISSO-AZD9291-approved-by-the-US-FDA-for-patients-with-EGFR-T790M-mutation-positive-metastatic-non-small-cell-lung-cancer-13112015.html#

[C] 'Tagrisso is the only 1st-line treatment for EGFR-mutated non-small cell lung cancer to deliver a median overall survival of more than three years', 30 September 2019. https://www.astrazeneca.com/media-centre/press-releases/2019/tagrisso-is-the-only-1st-line-treatment-for-egfr-mutated-non-small-cell-lung-cancer-to-deliver-a-median-overall-survival-of-more-than-three-years.html

[D] Letter from the Executive Director, Discovery Sciences, AstraZeneca UK Limited (3rd November 2020)

[E] [text removed for publication]

[F] [text removed for publication]