| | | |
|---|---|---|
| **Institution:** The University of Leeds | | |
| **Unit of Assessment:** 12 | | |
| **Title of case study:** Accelerating pharmaceutical manufacturing development using automated self-optimisation platforms | | |
| **Period when the underpinning research was undertaken:** 2014–2020 | | |
| **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:** |
| Richard Bourne | University Fellow, Lecturer, Associate Professor | 01/09/2012 – date |
| Franciscus Muller | Professor | 01/08/2011 – date |
| Nikil Kapur | Research Fellow, Lecturer, Senior Lecturer, Professor | 01/07/1999 – date |
| **Period when the claimed impact occurred:** 2014–2020 | | |
| **Is this case study continued from a case study submitted in 2014?** No | | |

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

Optimising pharmaceutical manufacturing processes is expensive, time-consuming, and negatively impacts patients waiting for new or 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 optimise pharmaceutical processes rapidly. 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™ in an accelerated timeframe, which has current annual sales of ~£3Bn.

**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 School of Chemical & Process Engineering and the School of Chemistry at the University of Leeds 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 650 $m^2$ 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), Professor John Blacker (process chemistry, continuous processing), and Professor Frans **Muller** (reaction engineering, kinetic modelling). **Bourne** and **Muller** are returned in UoA12, Blacker in UoA8.

**Bourne** was recruited in 2012 to lead the development of automated continuous flow reactor systems and he has directly supervised eleven industrially-funded/sponsored PDRAs and PhD students in collaboration with four global pharmaceutical companies (AstraZeneca, GlaxoSmithKline, Pfizer, Dr. Reddy's Laboratories), developing Self-Optimising Flow Reactors (SOFR).

Initially, AstraZeneca 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 micro reactors, 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 development of machine learning optimisation algorithms. In 2015, **Bourne** received a Royal Academy of Engineering Industrial Fellowship (ISS1516\8\32) to spend 50% of his time establishing a replica of the University's SOFR system within the AstraZeneca (Macclesfield) Process Research and Development group, 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 continued to sponsor research projects at Leeds to improve automated optimisation platforms. These included 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].

AstraZeneca (Macclesfield) began applying these automated platforms to assess reaction kinetics [5, 6] (co-funded through the University of Leeds EPSRC Impact Acceleration Account). This work explores the use of mixed integer linear programming for model discrimination and automated parameterisation of models. In addition, development of networked systems for parallelised optimisations across different sites was initiated through the £2M EPSRC grant 'Cognitive Chemical Manufacturing' (EP/R032807/1) with AstraZeneca, Swagelok and IBM, who are developing novel algorithms to reduce experimental burden and provide more robust multi-objective optimisations.

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] Holmes N, Akien GR, Blacker AJ, Woodward RL, Meadows RE, and Bourne RA. Self-optimisation of the final stage in the synthesis of EGFR kinase inhibitor AZD9291 using an automated flow reactor. *Reaction Chemistry & Engineering* 1, 366–371 (2016). https://doi.org/10.1039/C6RE00059B

*Novel application of implementing a self-optimising automated flow reactor for a two-step telescoped process in the synthesis of active pharmaceutical ingredient AZD9291.*

[2] Holmes N, Akien GR, Savage RJD, Stanetty C, Baxendale IR, Blacker AJ, Taylor BA, Woodward RL, Meadows RE, and Bourne RA. Online quantitative mass spectrometry for the rapid adaptive optimisation of automated flow reactors. *Reaction Chemistry &*

*Engineering* 1, 96–100 (2016).
https://doi.org/10.1039/C5RE00083A

*Online quantitative mass spectrometry was developed as a tool for rapid analysis during self-optimisation, greatly reducing process development time.*

[3] Schweidtmann AM, Clayton AD, Holmes N, Bradford E, Bourne RA, and Lapkin AA. Machine learning meets continuous flow chemistry: Automated optimization towards the Pareto front of multiple objectives. *Chemical Engineering Journal* 352, 277–282 (2018).
https://doi.org/10.1016/j.cej.2018.07.031

*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] Clayton AD, Schweidtmann AM, Clemens G, Manson JA, Taylor CJ, Niñ CG, Chamberlain TW, Kapur N, Blacker AJ, Lapkin AA, and Bourne RA. Automated self-optimisation of multi-step reaction and separation processes using machine learning. *Chemical Engineering Journal* 384, 123340 (2020).
https://doi.org/10.1016/j.cej.2019.123340

*Multi-objective optimisation and self-optimising platforms were combined for the rapid development of multi-step processes, including steps towards the synthesis of AZD3293.*

[5] Hone CA, Holmes N, Akien GR, Bourne RA, and Muller FL. Rapid multistep kinetic model generation from transient flow data. *Reaction Chemistry & Engineering* 2, 103–108 (2017).
https://doi.org/10.1039/c6re00109b

*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] Taylor CJ, Booth M, Manson JA, Willis MJ, Clemens G, Taylor BA, Chamberlain TW, and Bourne RA. Rapid, automated determination of reaction models and kinetic parameters. *Chemical Engineering Journal, in press*, 127017 (2020).
https://doi.org/10.1016/j.cej.2020.127017

*A kinetic modelling methodology was developed to determine reaction models and kinetic parameters using an autonomous framework involving transient flow measurements.*

All of the above journals are internationally recognised with rigorous review processes and international editorial boards. The quality of the underpinning research being at least 2* is demonstrated by all six references.

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

The development of the SOFR-platform at the University of Leeds has changed business practice 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 transformative approach has enabled AstraZeneca to rapidly develop viable continuous flow process(es) to meet the demands of rapid drug development timelines, and contributes to the company's on-going improvement [text removed for publication] [A].

To date, AstraZeneca have applied this technology to [text removed for publication] projects across different therapy areas and it is now part of their standard workflow [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 was able to develop a manufacturing process in an unprecedentedly short 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 ~£3Bn, and has had significant societal impact by extending cancer patients' lives [text removed for publication] compared to previous standard-of-care treatments [A].

Such success created a route to international innovation, with AstraZeneca transferring SOFR technologies to their Gothenburg site in the Sample Development team. **Bourne** and AstraZeneca (Gothenburg) colleagues developed 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 **Bourne** group at the University of Leeds for a three-year period from January 2019 to advance the technology of the system [D]. AstraZeneca is planning a significant internal investment [text removed for publication] to evolve and deploy these systems to AstraZeneca 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, SK10 2NA, 19 January 2021.

[B] AstraZeneca Press Release, 13 November 2015. 'TAGRISSO™ (AZD9291) approved by the US FDA for patients with EGFR T790M mutation-positive metastatic non-small cell lung cancer'. 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, accessed 2 November 2020.

[C] AstraZeneca Press Release, 30 September 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'. 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, accessed 2 November 2020.

[D] Letter from the Executive Director, Discovery Sciences, AstraZeneca UK Limited, Cambridge, CB4 0WZ, 3 November 2020.

[E] [text removed for publication].

[F] [text removed for publication].