**Institution: University of the West of England (UWE), Bristol**

**Unit of Assessment: 3**

**Title of case study: Improving the safety and efficacy of therapeutic drugs**

**Period when the underpinning research was undertaken:** 2000 – 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: |
|---|---|---|
| David McCalley | Professor in Bioanalytical Sciences | 2000-present |
| Dr Joseph Russell | EPSRC Research Assistant | 2012-2016 |
| Dr James Heaton | EPSRC Research Associate | 2012-2015 |

**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

UWE's research in chromatography has impacted upon both patient safety in hospitals and on drug development in pharmaceuticals. For patient safety, new tests developed at UWE have allowed clinicians across the UK and Europe to dose and monitor blood levels of toxic antibiotics streptomycin (for multi-drug resistant tuberculosis), and colistin (a drug of last resort for sepsis). Unmonitored, streptomycin can cause permanent hearing and balance loss, and colistin can damage renal function. For drug development, GlaxoSmithKline has adopted UWE's chromatographic techniques allowing identification of potentially dangerous impurities in drug preparations, increasing the speed of drug development via applying high throughput analysis and reducing running costs.

## 2. Underpinning research

Professor McCalley researches the microscopic-level interactions that cause mixtures to separate out in high performance liquid chromatography (HPLC). HPLC is widely used for chemical analysis, but a limited understanding of its principles meant wasteful trial-and-error approaches in developing new tests. As a result of McCalley's research into reversed-phase (RPLC) and hydrophilic interaction (HILIC), hard-to-analyse compounds can now be measured, and, methods for the analysis of new drugs targeted and rapidly optimised. As a result of his work, McCalley was recognised as one of the world's 100 most influential analytical scientists by the online journal *The Analytical Scientist* in 2015 and 2019.

**Improving the speed and effectiveness of drug separation (2000-2010)**

In 2010, McCalley systematically reviewed the previous decade of his own and others' experimental findings related to the difficulties associated with using RPLC to analyse basic compounds (over 70% of pharmaceuticals are basic) (**R1**). He discussed the influence of experimental parameters, such as temperature and particle morphology, on the quality of separations, and most importantly, he offered methodological approaches to improve separation quality (**R1**). This research offered optimisation of tests for drugs in biological fluids and for impurities in pharmaceutical preparations, by improving test speed, resolution and cost

effectiveness. McCalley's research on one common experimental parameter – column overloading – underpinned his development of new methods for precise measurement (**R1**). These new methods have had important applications in assessing impurities in pharmaceuticals, which can be difficult to resolve due to their similarity to the Active Pharmaceutical Ingredient (API). Impurities can lead to undesirable side effects of the formulation and a lack of standards had previously prevented their quantitation. McCalley's work with Russell gave insights into the properties of charged aerosol detection (CAD). Its performance as a universal detector, provided evidence of its use in impurity analysis (**R2**, **G1**), making quantitation possible without the use of standards; impurity levels in candidate drug formulations can now be assessed against regulatory requirements.

**Establishing methods for analysis of highly water-soluble drugs (2010-present)**
McCalley has also demonstrated HILIC's applicability in analysing highly water-soluble drugs, which are difficult to analyse by RPLC. RPLC gives undesirably low and overlapping values of the time taken for a drug to pass through the separation column of the instrument (the 'retention time') (**R3**, **G2**). By contrast, HILIC gives ideal and distinct retention time values, characteristic of each drug, allowing separation and quantification. McCalley has investigated the effect of multiple physical parameters that affect the retention time, including adsorption, partition and ion-exchange, allowing the method to be manipulated to suit analysis of hard-to-analyse drugs. McCalley's studies have increased the speed of HILIC analyses using higher temperatures, smaller particle size columns, and superficially porous stationary phases (**R4**, **G3**, **R5**, **G2**). McCalley and Heaton also demonstrated ways to improve the robustness of HILIC when analysing complex samples while still providing sufficient throughput within a reasonable clinical timeframe (**R6**, **G3**). McCalley and his team transferred the knowledge of the new methodologies to hospital-based staff by working alongside them at the Antimicrobial Reference Laboratory (ARL) based at Southmead Hospital in Bristol, to improve the clinical testing of antibiotics.

## 3. References to the research

**R1** McCalley, D. (2010) The challenges of the analysis of basic compounds by high performance liquid chromatography. *Journal of Chromatography* A. 1217, pp. 858-880. https://doi.org/10.1016/j.chroma.2009.11.068

**R2** Russell, J., Heaton, J., Underwood, T., Boughtflower, R. and McCalley, D. (2015) Performance of charged aerosol detection with hydrophilic interaction chromatography. *Journal of Chromatography A.* 1405, pp. 72-84. https://doi.org/10.1016/j.chroma.2015.05.050

**R3** McCalley, D. (2017) Understanding and manipulating the separation in hydrophilic interaction liquid chromatography-a review. *Journal of Chromatography A.* 1523, pp. 49-71. https://doi.org/10.1016/j.chroma.2017.06.026

**R4** Heaton, J. and McCalley, D. (2016) Some factors that can lead to poor peak shape in hydrophilic interaction chromatography, and possibilities for their remediation. *Journal of Chromatography A.* 1427, pp. 37-44. https://doi.org/10.1016/j.chroma.2015.10.056

**R5** McCalley, D. (2018) A study of the analysis of acidic solutes by hydrophilic interaction chromatography. *Journal of Chromatography A.* 1534, pp. 64-74 https://doi.org/10.1016/j.chroma.2017.12.045

**R6** Heaton, J., Smith, N., McCalley, D. (2019) Retention characteristics of some antibiotic and anti-retroviral compounds in hydrophilic interaction chromatography using isocratic elution, and gradient elution with repeatable partial equilibration. *Analytica Chimica Acta*. 1045, pp. 141-151. https://doi.org/10.1016/j.aca.2018.08.051

## Evidence of the quality of the supporting research

**G1** McCalley, D. *Development of Generic methods for the analysis and purification of polar compounds by high performance liquid chromatography*, EPSRC, 2012 – 2017, £95,443 (including industrial partner contribution).

**G2** McCalley, D. *Study of the mechanism of retention and peak shape of charged compounds in hydrophilic interaction chromatography*, Agilent Technologies, 2015 – 2020, £32,000.

**G3** McCalley, D. *Investigation of the separation mechanism in hydrophilic interaction chromatography*, EPSRC, 2012 – 2014, £151,902.

## 4. Details of the impact

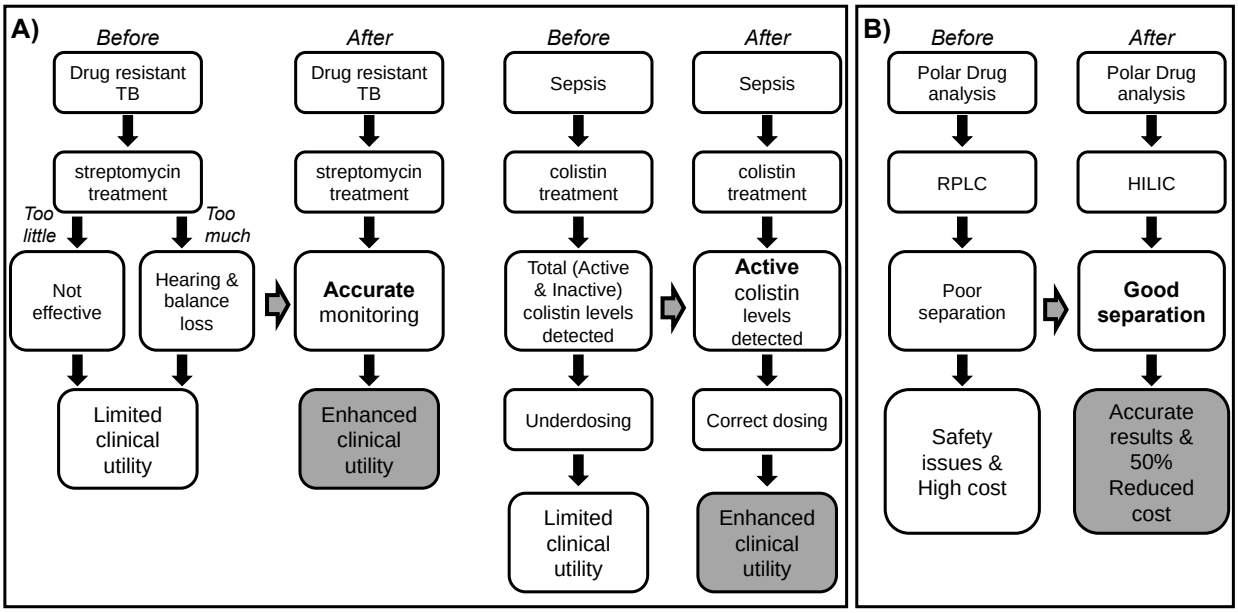


Figure 1. Summary of impact on A) monitoring of toxic antibiotics streptomycin and colistin and B) safe drug development. Processes are shown before and after McCalley's research.

### Improving patient safety through laboratory tests to monitor toxic antibiotics (2013-2020; figure 1A)

Multi-drug resistant (MDR) bacterial infection is a growing issue in Europe and the UK as the region is seeing the highest rate of incidence of MDR-tuberculosis (**S1**, **S2**). Outbreaks can lead to thousands of MDR infections across the UK annually (**S1**). There are few, highly toxic, drug options for the treatment of MDR infections. Drug testing, developed by McCalley (**R6**) and conducted at the Antimicrobial Reference Laboratory (ARL) allows clinicians to monitor levels of toxic drugs in samples of patient blood, optimising efficacy against the pathogens and minimising the toxicity risk (**S1**).

McCalley and his team worked with ARL to develop tests for the drugs streptomycin and colistin (**S3**). Streptomycin treats tuberculosis but has a narrow therapeutic window – too little is ineffective while too much causes permanent hearing and balance loss (figure 1A); and it can only be used safely if monitored (**S1**). Before McCalley's work with ARL, streptomycin could only be tested at a US laboratory, making turnaround times impractical for UK and EU patients and preventing safe use of this important drug (**S3**). Drawing on his research into the mechanisms underlying HPLC separation (**R1**), McCalley developed the sole commercial test for streptomycin in Europe now used by ARL. The lead Consultant in Infection and Professor of Antimicrobial Therapeutics at North Bristol NHS Trust, said '*without this new assay [test], we would struggle to*

*use streptomycin safely*' (**S1**). As the only European-based lab with these capabilities, ARL '*has seen a significant year-on-year growth in use of the service*' (**S3**).

Previously, tests for colistin, which is used to treat sepsis, could not differentiate between the active and non-active form of the drug (figure 1A), leading to over-estimations of the active form and under-dosing of patients (**S1**). Under-dosing with colistin in the first days of hospitalisation leads to poor efficacy, while over-dosing can permanently damage renal function (**S3**). The new liquid chromatography mass spectrometry (LC-MS) test developed by UWE '*far out-performed the bioassay [test] used previously due to improved specificity for the active form*' said the then Head of the ARL (**S3**). It is comparable to tests used internationally, allowing '*clinical staff to optimise patient prescribing in the context of published evidence*" said the Consultant in Infection and Professor of Antimicrobial Therapeutics (**S1**). The Consultant added:

> '*with this improved LC-MS test, we can now use colistin more effectively and more safely in last resort situations*' and '*in my opinion monitoring of colistin by LC-MS is essential to its use, and is leading to better outcomes for sepsis patients suffering multi-drug resistant infection*' (**S1**).

This is particularly significant given that rates of colistin use are rising in acute care (66% increase since 2016-2017) (**S4**).

The laboratory tests McCalley developed provide the basis for a monitoring service helping clinicians and improving patient care throughout Europe by administering safely toxic (streptomycin and colistin) and last-resort (colistin) antibiotics targeted at MDR infections. ARL is the largest provider of antimicrobial Therapeutic Drug Monitoring in the UK and over 240 laboratories using this service across the UK and Europe. ARL tests 10-15 colistin and 5-10 streptomycin samples per week at GBP120 per sample (**S3**), resulting in revenue of approximately GBP125,000 per year.

**Safe drug development at GlaxoSmithKline (GSK): reducing cost and improving speed (2013-2020; figure 1B)**

Approval and launch of a new medicine from drug discovery takes on average 9.5-15 years (**S5**). Drug discovery starts with screening of between 5,000-10,000 compounds out of which typically only 5 make it to Phase 1 clinical trials. GSK Pharmaceutical core annual R&D investment was GBP2,500,000,000 in 2014, 29% of this spent on early-stage research (drug discovery). The strategic aim of GSK was to improve the proportion of high-quality early drug candidates that progress to clinical development, and to reduce the time and cost involved (**S5**).

Collaboration with McCalley enabled GSK to apply HILIC as one of the HPLC procedures used to solve pharmaceutical separation problems in early stage research in identifying impurities in the active pharmaceutical ingredient as well as the preparative separation of pure product from cruder mixtures (figure 1B). McCalley's work showed that HILIC could be used as an analytical process, and also scaled up to allow larger quantities of material to be purified (**S6**, **R2**-**6**). With a shorter, more effective screening process, and simpler scale-up for purification than previously, GSK have reduced their turnaround times and the number of screening rounds required to find optimum analysis conditions. The Head of UK Purification at GSK said their use of McCalley's methods have led to:

> '*approximately a 50% reduction in the running costs of finding suitable separations for scale-up*' *and that they 'speed up the processes required to discover new active chemical entities*' (**S6**, **R3**, **R4**).

McCalley also demonstrated that HPLC CAD could replace GSK's previous method for assessing the solubility of new molecules (**R2**). GSK adopted the CAD system as the universal

detector for drug solubility measurements, which now produces data for hundreds of compounds per week. The Head of UK Purification describes the performance as '*an order of magnitude increase on our previous capacity*'. In contrast to its predecessor, the CAD system is '*robust and easy to operate, allowing quantification of structurally diverse compounds, most importantly in a high throughput fashion*' (**S6**, **R2**). The data from the CAD system allows GSK chemists to rank candidate drugs and identify issues at early stages of development, described as '*reducing attrition rates and speeding up the process toward candidate [drug] selection with obvious attendant cost savings*' (**S6**).

**5. Sources to corroborate the impact**

**S1** Supporting impact data from Consultant in Infection and Professor of Antimicrobial Therapeutics at North Bristol NHS Trust.

**S2** World Health Organisation (WHO) (2017) *Annex 4 TB burden estimates, notifications and treatment outcomes for individual countries and territories, WHO regions and the world* [online] Geneva: World Health Organisation. Available from: https://www.who.int/tb/publications/global_report/gtbr2017_annex4.pdf?ua=1 [Accessed 18 November 2019].

**S3** Supporting impact data from Consultant Clinical Scientist and Head of the Antimicrobial Reference Laboratory, Southmead Hospital, Bristol.

**S4** Public Health England (2018-2019) *English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report*. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/843129/English_Surveillance_Programme_for_Antimicrobial_Utilisation_and_Resistance_2019.pdf.

**S5** GSK (2014) *GSK Annual Report 2014,* pp. 26-27. Available from: https://www.gsk.com/media/2710/gsk-annual-report-2014-interactive.pdf

**S6** Supporting impact data from Head of UK Purification, GlaxoSmithKline Research and Development Limited.