Institution: University of Warwick

Unit of Assessment: B9 - Physics

Title of case study: NMR characterisation of the solid-state landscape: enabling the pharmaceutical industry to deliver better quality medicines and improved patient safety (b9ICS-4)

Period when the underpinning research was undertaken: 2004 - (ongoing)

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:**
Steven Brown	Professor	2002-present
Dinu Iuga	Associate Professor, Facilities Manager	2009-present
Oleg Antzutkin	Research Fellow	2008-2015

Period when the claimed impact occurred: 2013 - (ongoing)

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

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

Most newly approved medicines are delivered to patients as a formulated solid tablet. An active pharmaceutical ingredient (API) can pack together in different ways in the solid state, alone or with water or small solvent molecules, crystalline or disordered, affecting key physical properties.

Collaborative research between Prof. Steven Brown's group (Warwick) and large pharmaceutical companies applied, for the first time, experimental ^{1}H magic-angle-spinning (MAS) nuclear magnetic resonance (NMR) technologies, complemented by density-functional theory (DFT) calculations, to solid-state pharmaceuticals. This new technique provides reassurance regarding the solubility and bioavailability of new drugs, and hence the efficacy of pharmaceutical treatments, resulting in cost and time-savings for companies and improved safety for patients.

These solid-state characterisation approaches are now an integral part of development tool-kits to minimise risks in the pharmaceutical development process in major companies, as evidenced for AstraZeneca, *[text removed for publication]*, GlaxoSmithKline, *[text removed for publication]*, Pfizer and the contract research organisation *[text removed for publication]*.

2. Underpinning research (indicative maximum 500 words)

Brown has been working collaboratively with the pharmaceutical industry since 2004. Together with academic colleagues, their research was the first to demonstrate insight into solid-state forms of pharmaceuticals obtained by ^{1}H magic-angle spinning (MAS) NMR, complemented by density-functional theory (DFT) calculations using the Gauge-Included Projector Augmented Wave (GIPAW) method. ^{1}H MAS NMR experiments are particularly well suited for characterising hydrogen bonding and aromatic interactions that play key roles in determining how molecules pack together in the solid state.

The highlights below have led to the uptake of these experimental and computational approaches, as an integral part of the toolkit that is now systematically applied to minimise risks relating to the solid-state form in pharmaceutical development, by AstraZeneca, [text removed for publication], GlaxoSmithKline, *[text removed for publication]*, Pfizer and the contract research organisation *[text removed for publication].*

A significant proportion of this research was performed at the UK High-Field Solid-State NMR Facility, an EPSRC/BBSRC funded National Research Facility based at Warwick, of which Brown has been Director since its inauguration in 2010 (Brown is PI on: EP/F017901/1, GBP3,900,000, 1/2009 to 1/2015; NS/A000061/1, GBP2,700,000, 1/2015 to 1/2020; EP/R029946/1, GBP7,900,000, 5/2018 to 4/2021; EP/T015063/1, GBP2,400,000, 1/2020 to 1/2025).

Specific research linked to the impact include:

- **First use of the ^{1}H double-quantum (DQ) solid-state MAS NMR method to distinguish anhydrous and hydrate solid-state forms of an API, and notably the first application to identify the specific form present in a tablet formulation**
  [**3.1,** with AstraZeneca via an EPSRC CASE PhD studentship, supervised by Brown 2004 - 07, for J.M. Griffin (now a Senior Lecturer in Materials Chemistry at Lancaster University)].
- **Demonstration that the ^{1}H DQ MAS NMR method enables the identification of a minority solid-state form of a pharmaceutical at a limit of detection of 1%**
  [**3.5**, with Daiichi Sankyo – K. Maruyoshi, an employee of this leading Japanese company, was a visiting scientist at Warwick, 2011 - 2012].
- **First applications to pharmaceutical solid-state forms, notably co-crystals and an amorphous dispersion, of ^{14}N-^{1}H MAS NMR experiments**. These experiments identify intermolecular hydrogen bonding interactions via heteronuclear correlation, with the ^{14}N shift being particularly sensitive to the hydrogen-bonding arrangement.
  [**3.3]**, with Daiichi Sankyo (K. Maruyoshi); [**3.4**, with GlaxoSmithKline via an EPSRC CASE PhD studentship supervised by Brown, 2008 - 2012, for A.S. Tatton (now employed as a NMR spectroscopist at GSK); **3.6**, with AstraZeneca, EPSRC Collaborative Computational Network for NMR Crystallography support, EP/M022501/1, for A.S. Tatton to work at AstraZeneca for 4 months in 2017, prior to his employment at GSK].
- **Use of Density-Functional Theory DFT-based GIPAW calculations of NMR parameters to add value to MAS NMR experiment of pharmaceutical solids** These calculations are an invaluable complement to experiment, for example in comparing subtle changes in NMR parameters, notably the ^{1}H chemical shift, for different solid-state forms.
  [**3.2**, **3.6**, with AstraZeneca, who provided funding for the Warwick PhD student, J.P. Bradley, *[text removed for publication]*].

Professor S. P. Brown has been employed in the Department of Physics at Warwick since October 2002, first as a Lecturer and EPSRC Advanced Research Fellow (GR/R75441/01, GBP241,000, 10/2002 to 9/2007), and subsequently Professor (2010). He is chair of the steering group of the EPSRC Collaborative Computational Network for NMR Crystallography (CCP-NC, Co-I on EP/J010510/1, GBP489,000, 10/2011 to 12/2015 and EP/M022501/1, GBP222,000, 05/2015 to 05/2020, currently funded by EP /T026642/1, GBP273,000, 05/2020 to 05/2025). This has facilitated application of the GIPAW method for calculating NMR parameters to pharmaceuticals in collaboration with AstraZeneca and the developers, C.J. Pickard, Cambridge **[3.2**] and J.R. Yates, Oxford **[3.6]**, of the CASTEP code that implements the GIPAW approach.

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

[3.1] John M. Griffin, Dave R. Martin, **Steven P. Brown**. "Distinguishing Anhydrous and Hydrous Forms of an Active Pharmaceutical Ingredient in a Tablet Formulation Using Solid-State NMR Spectroscopy" *Angewandte Chemie International Edition English* 46, 8036-8038 (2007) DOI: 10.1002/anie.200702582

[3.2] Jonathan P. Bradley, Chris J. Pickard, Jonathan C. Burley, Dave R. Martin, Leslie P. Hughes, Stephen D. Cosgrove, **Steven P. Brown**. "Probing intermolecular hydrogen bonding in sibenadet hydrochloride polymorphs by high-resolution ^{1}H double-quantum

solid-state NMR spectroscopy." *Journal of Pharmaceutical Sciences* 101, 1821-1830 (2012) DOI: 10.1002/jps.23078

[3.3] Keisuke Maruyoshi, **Dinu Iuga**, **Oleg N. Antzutkin**, Amjad Alhalaweh, Sitaram P. Velaga and **Steven P. Brown**. "Identifying the intermolecular hydrogen-bonding supramolecular synthons in an indomethacin–nicotinamide cocrystal by solid-state NMR" *Chemical Communications* 48, 10844-10846 (2012) DOI: 10.1039/C2CC36094B

[3.4] Andrew S. Tatton, Tran N. Pham, Frederick G. Vogt, **Dinu Iuga**, Andrew J. Edwards, and **Steven P. Brown**. "Probing Hydrogen Bonding in Cocrystals and Amorphous Dispersions Using ^{14}N–^{1}H HMQC Solid-State NMR" *Molecular Pharmaceutics* 10, 999-1007 (2013) DOI: 10.1021/mp300423r

[3.5] Keisuke Maruyoshi, **Dinu Iuga**, Abigail E. Watts, Colan E. Hughes, Kenneth D.M. Harris, **Steven P. Brown**. "Assessing the Detection Limit of a Minority Solid-State Form of a Pharmaceutical by ^{1}H Double-Quantum Magic-Angle Spinning Nuclear Magnetic Resonance Spectroscopy" *Journal of Pharmaceutical Sciences* 106, 3372-3377 (2017) DOI: 10.1016/j.xphs.2017.07.014

[3.6] Andrew S. Tatton, Helen Blade, **Steven P. Brown**, Paul Hodgkinson, Leslie P. Hughes, Sten O. Nilsson Lill, and Jonathan R. Yates. "Improving Confidence in Crystal Structure Solutions Using NMR Crystallography: The Case of β-Piroxicam" *Crystal Growth & Design* 18, 3339-3351 (2018) DOI: 10.1021/acs.cgd.8b00022

4. Details of the impact

Differences in the solid-state structure at the molecular level of an API manifest themselves in altered solubility and bioavailability. This also affects stability and processability during manufacture. Issues relating to the solid-state form represent a significant contributing factor to the high attrition rate associated with taking a candidate API emerging from discovery through to the patient. Having a way to evaluate and monitor risk associated with solid-state form is of critical importance to the pharmaceutical industry.

World-leading pharmaceutical companies have systematically implemented the experimental and computational ^{1}H MAS NMR based pharmaceutical characterisation technologies developed by Brown, to mitigate risks relating to solid-state form in pharmaceutical development and manufacture.

There are potentially massive costs arising with change of solid-state form during manufacture or tablet storage, with far-reaching consequences for regulatory approval, patent protection and reputation. Specifically, it is essential to assess the risk of a change in the solid-state form, e.g. associated with a change of molecular packing (referred to as polymorphism), hydrate or solvate formation, amorphous / crystalline transformation.

AstraZeneca, *[text removed for publication]*, GlaxoSmithKline, *[text removed for publication]* and Pfizer, with a combined annual revenue in 2019 of USD *[text removed for publication]* in 2019 **[5.1]**, as well as the contract research and development organisation, *[text removed for publication]*, have actively incorporated Brown's research into their toolkits for solid-state characterisation of pharmaceutical molecules in development.

AstraZeneca state that "*Prof. Brown's research in developing solid-state NMR crystallography approaches and their application, especially for improved understanding of hydrogen bonding and API-excipient interactions, has been translated into AstraZeneca's solid state characterisation tool-box"* and confirm that this has "*led to new insights into the risks associated with developing APIs. This knowledge has resulted in better quality medicines and improved patient safety*." Specifically, "*AstraZeneca has applied NMR crystallography approaches to >20 compounds in development, since August 2013.*" **[5.2].** AstraZeneca state that the techniques have been applied to medicines first marketed during the impact period, for the treatment of diverse conditions with total 2019 sales of USD2,871,000,000 **[5.3]**: Farxiga (diabetes), Lokelma (hyperkalaemia),

Lynparza (oncology), Naloxegol (opioid induced constipation), Qtern (diabetes), and Selumetinib (oncology) **[5.2].**

Pfizer have applied Brown's novel ^{1}H MAS NMR and GIPAW calculation techniques to *"approximately a quarter of the Pfizer's small molecule APIs in development since August 2013*." As an example, it was used in the *development of the drug Lorbrena (for treating ALK-positive metastatic non-small cell lung cancer), which achieved regulatory approval in the USA and the EU in 2018 and 2019, respectively.* Pfizer state "*These methods are used to elucidate crystallographic interactions of APIs and examine polymorph changes which minimize risk associated to solid-state form in pharmaceutical development*" **[5.4]**.

Brown's group has been working collaboratively with GlaxoSmithKline (**GSK**) since 2008: solid-state NMR spectroscopists at GSK, Tran Pham and Andrew Tatton, were trained in Brown's group. GSK reiterate that *"[p]olymorphism of an active pharmaceutical ingredient (API) can affect the quality, safety, and efficacy of the medicinal product due to the different chemical, physical and biopharmaceutical properties of the different polymorphic forms of the API".* GSK state that the *"methodology developed by Professor Brown has been employed at GSK to aid the discovery and development of new medicines".* Specifically, the techniques are an *"invaluable tool to tackle difficult solid-state issues as recognized in the pharmaceutical industry*" and that the approach "*now forms an integral part of polymorphism assessment by GSK*" **[5.5]**.

[text removed for publication] **[5.6]**.

[text removed for publication] **[5.7]**.

As a contract research and development organisation, *[text removed for publication]* **[5.8]**.

The pharmaceutical companies' belief in the value and importance of this integral solid-state NMR characterisation is demonstrated by investment in new instrument capability and capacity, for **AstraZeneca** this is more than USD4,000,000 in new solid-state NMR infrastructure *"to apply the NMR crystallography approaches championed by Prof. Brown*." **[5.2]** and for **Pfizer** this has involved "*new infrastructure in order to apply the ^{1}H MAS experiments and DFT-based GIPAW calculations championed by Brown and co-workers to our APIs in development" totalling over USD2,000,000 in both the UK and US locations. Future investments are planned for 2021 (USD1,350,000) and 2023 (USD1,550,000) to further expand capabilities* **[5.4]**. *[text removed for publication]* **[5.6]**. *[text removed for publication]* **[5.7]**. *[text removed for publication]* **[5.8].**

Beyond the commercial value to the pharmaceutical industry, the ultimate value of incorporating Brown's research into solid-state characterisation protocols is for the patients themselves: *"There is little doubt that the field of research that Prof. Brown is a leading figure in has made a direct impact on businesses, such as AstraZeneca, ability to discover, develop and reliably manufacture life changing medicines for patients across the world. This success brings benefits to individual patients, the healthcare systems that we all depend on and wider society through business and economic benefit*." **[5.2]**

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

[5.1] Website confirming combined revenue of the five pharmaceutical companies. https://www.fiercepharma.com/special-report/top-20-pharma-companies-by-2019-revenue Accessed 3rd February 2021.

[5.2] AstraZeneca. Letter evidencing the use of the techniques in the AZ characterisation tool-box and contribution to products in the pipeline, in development and on the market. Letter dated 10th July 2019.

[5.3] **AstraZeneca** annual report 2019 confirming sales figures. Accessed 3rd February 2021. https://www.astrazeneca.com/content/dam/az/Investor_Relations/annual-report-2019/pdf/AstraZeneca_AR_2019.pdf

[5.4] **Pfizer**. Letter evidencing the implementation of the techniques in pharmaceutical development, and investment in new infrastructure to expand capabilities. Letter dated 24th September 2020.

[5.5] **GSK**. Letter evidencing the use of the methodologies by GSK to aid discovery and development of new medicines. Letter dated 4th November 2019.

[5.6] *[text removed for publication]*

[5.7] *[text removed for publication]*

[5.8] *[text removed for publication]*