Institution: Cardiff University		
Unit of Assessment: Allied Health Professions, Dentistry, Nursing and Pharmacy (3)		
Title of case study: Improved product performance for a leading global inhalation capsule manufacturer		
Period when the underpinning research was undertaken: 2007 – 2017		
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:**
Sion Coulman James Birchall	Senior Lecturer Professor	01/10/2005-present 01/02/2000-present
Period when the claimed impact occurred: 2013 – 2019		
Is this case study continued from a case study submitted in 2014? No		

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

Millions of patients with chronic lung disease, such as asthma, are prescribed dry powder inhalers which are commonly loaded with a capsule containing the powdered drug. Successful drug delivery relies on the capsule being punctured adequately before inhalation. Prior to Cardiff research, there was no accepted way to accurately evaluate the puncture performance of the different capsules used in these inhalers. Cardiff researchers developed the first robust test to determine how the capsule material and environmental conditions affect capsule puncture performance. Qualicaps®, a global market leader in the field of inhalation capsules, used Cardiff's research to inform company strategy, secure a 91% increase in sales of their premium capsules (worth €3M, or £2.7M) and enter new and emerging markets across the Middle East, Africa and India.

2. Underpinning research (indicative maximum 500 words)

Dry Powder Inhalers (DPIs) deliver medicines into the lung for the treatment of pulmonary disease. One method of loading a powder into a DPI is within a capsule. The capsule is positioned in the inhaler and the patient depresses a button which triggers the movement of steel pins that puncture the wall of the capsule. The powder contained within the capsule then flows through the holes made in the capsule wall and is inhaled into the patient's lung.

Despite the high prevalence of DPI use, there was no established industry test to analyse the critical capsule puncture event needed for the inhaler to work effectively. Quality control tests used in the pharmaceutical industry for hard shell capsules typically relate to the physical properties of the shell (for example, the capsule weight or moisture content) or to the performance of oral capsules (such as how they disintegrate and release the drug contained within it).

Qualicaps®, the largest inhalation capsule manufacturer in the world, produces capsules which they sell to pharmaceutical companies to encase their inhalation drugs before they are loaded into a DPI. To further develop and enhance their capsules, Qualicaps® enlisted the expertise of Cardiff researchers to study their mechanical properties and consistency to the critical puncture event. The research was conducted in two phases:

2.1 Developed a methodology to determine the forces required to puncture two types of capsule in a Dry Powder Inhaler

From 2007, the Cardiff team used a materials testing machine to record the forces required to puncture a capsule with a pin from a commercially available DPI **[3.1]**. This first method was used to compare the puncture performance of Qualicaps®' traditional inhalation capsules (made from gelatin) with their new range of inhalation capsules (made from hydroxypropylmethylcellulose, HPMC). The HPMC capsules were developed by Qualicaps® to provide a solution to the increased brittleness of gelatin capsules at low humidity, which can cause the capsule to crack and shed material upon puncture. Gelatin capsules are also

susceptible to breakage during handling. In 2012, a formal funded collaboration between Cardiff University and Qualicaps® was established to better understand the potential of the company's HPMC capsules in DPIs. This collaboration led the Cardiff team to devise a more refined, sensitive, reproducible, rapid puncture testing high throughput methodology **[3.2]**.

2.2 Determined how the capsule material and storage conditions affect capsule puncture performance

The high throughput methodology outlined in **[2.1]**, the first of its kind, was used to determine the impact of the capsule material (gelatin and HPMC) and the impact of environmental conditions on the capsule puncture performance. The Cardiff research team:

- evaluated the effect of **humidity** on capsule performance **[3.1, 3.2]** and demonstrated that the puncturing performance for HPMC capsules was maintained at low humidity, unlike traditional gelatin capsules. Crucially, this test gave Qualicaps® accurate data for their clients and potential customers, who had expressed concern over the effects of low humidity on the performance and reliability of their DPI formulations and products;
- showed that HPMC capsules are able to maintain puncture performance when stored at **low temperatures.** This finding confirmed that HPMC capsules were less dependent on both temperature and humidity, in contrast to gelatin capsules **[3.3]**;
- developed **imaging expertise** to characterise the dimensions and the morphology of the capsule, the capsule puncturing event and capsule behaviour within an inhaler **[3.4]**. This allowed better understanding of Qualicaps® capsule formulations and performance in DPIs, research outcomes which were communicated through unpublished confidential reports to Qualicaps®.

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

[3.1] Birchall JC, Jones BE, Morrissey A, Jones, BE. 2008. A comparison of the puncturing properties of gelatin and hypromellose capsules for use in dry powder inhalers. Drug Development and Industrial Pharmacy 34(8):870-876 DOI: 10.1080/03639040801928903.

[3.2] Torrisi BM, **Birchall JC,** Jones BE, Diez F, **Coulman, SA**. 2013. The development of a sensitive methodology to characterise hard shell capsule puncture by dry powder inhaler pins. International Journal of Pharmaceutics 456(2):545-552 DOI: 10.1016/j.ijpharm.2013.08.011

[3.3] Chong RH, Jones BE, Díez F, **Birchall JC, Coulman, SA**. 2016. Evaluating the sensitivity, reproducibility and flexibility of a method to test hard shell capsules intended for use in dry powder inhalers. International Journal of Pharmaceutics 500(1-2):316-325 DOI: 10.1016/j.ijpharm.2016.01.034

[3.4] Jones B, Ecenarro S, Whiteside B, **Birchall JC, Coulman, SA**. 2017. Imaging techniques for dry powder inhaler capsules. Inhalation Magazine April 2017:14-19 PDF Link

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

Qualicaps® is the world's biggest supplier of capsules for use in inhalation devices. The Commercial Vice President of Qualicaps® Europe, Beverly Nannini, states: *"Qualicaps® considers the past and present collaboration with Cardiff University as a fundamental factor in our commercial sustainability and success, as well as a key element in our continuous quality improvement efforts"* **[5.1]**.

Cardiff's research benefited Qualicaps® in the following ways:

4.1 Informed Qualicaps®' Research and Development strategy

The Cardiff team provide ongoing scientific advice to Qualicaps®. They sit on the Expert Advisory Panel at Qualicaps® helping to guide scientific and commercial strategy, with the aim of supporting the company in maintaining its leading global position in the field of inhalation capsules **[5.1]**. As a result of Cardiff's advice and guidance, Qualicaps® recently implemented a strategy to expand and enhance its capability in formulation development, as noted by Beverly Nannini at Qualicaps®: "*The steps we have taken in recent years to invest*

in the research and development of our inhalation products have been directly informed and influenced as a result of our collaboration with Cardiff University" **[5.1]**.

Research from Cardiff enabled Qualicaps® to present scientific advances at major international conferences, for example at the American Association of Pharmaceutical Scientists Conference which provides networking opportunities with 6,000 scientists from around the world and is attended by more than 150 potential customers. Cardiff's findings are prominently displayed at such conferences and specifically referenced in Qualicaps® technical manuals and product literature, which Qualicaps® provides to pharmaceutical customers **[5.1, 5.2]**.

4.2 Improved products leading to a 91% increase in sales of Qualicaps®' premium product (£2.7M)

The quality control team at Qualicaps® used results from Cardiff University's capsule puncture test to inform the selection of new raw materials and additional excipients (e.g. colouring agents) in the manufacturing of both their HPMC and gelatin capsules **[5.3]**. Additionally, Cardiff studies demonstrated the clinical advantages of Qualicaps®' premium (HPMC) inhalation Quali-V-I® capsule range over gelatin capsules via research on the capsules' properties and performance **[5.1]**. Qualicaps®' Commercial Vice President states, *"These [Cardiff's] findings influenced our decision to focus our marketing budget and activities for inhalation capsules solely on our hydroxypropyl methylcellulose Quali-V®-I range of capsules"* **[5.1]**. These marketing materials and presentations are aimed at attracting new business and they cite Cardiff evidence throughout **[5.1 -5.2; 5.4 - 5.6]**.

Cardiff's research and the inclusion of the team's findings in marketing materials contributed to a 91% increase in sales of Quali-V®-I HPMC capsules, equating to over €3M (£2.7M) sales between 2013 and the end of 2019. While this range of capsules represents just 3% of Qualicaps®' total capsule sales by volume, it is now 10% of Qualicaps®' overall revenue **[5.1]**. In contrast, sales of Qualicaps® standard capsules have increased by only 11% within the same period, with a 76% decrease in sales for their gelatin capsules. The 91% increase in sales of the Cardiff evidenced Quali-V®-I HPMC capsules raised funds needed for Qualicaps® to launch a new extra dry line extension capsule product in 2018.

4.3 Enabled Qualicaps® to enter new emerging markets

Cardiff's testing not only proved the optimum performance of the Quali-V®-I capsule but also that this capsule was suitable for use in particular climates, compared to other capsule formulations **[3.1, 3.2, 3.3]**. These new research findings enabled Qualicaps® to provide their capsule for business development projects in new and emerging markets where the capsule needed to be transported and stored in humid, hot climates. Cardiff research facilitated Qualicaps®' ambitions to sell the Quali-V®-I to pharmaceutical companies looking to use the capsule for particular drug formulations sensitive to environmental changes **[5.3]**.

To date, Qualicaps® now supply their Cardiff evidenced Quali-V®-I for 20 development projects across the Middle East, Africa and India. A 'development project' is where a pharmaceutical company is looking to formulate and test a new product, specifically here via loading a capsule with a drug formulation and testing the performance and stability of the formulation under various conditions. This is required before a company can move the product into commercial manufacture. Prior to Cardiff's research showing that the Quali-V®-I capsule was robust to humid and hot climates, Qualicaps® had no development projects in these regions **[5.3]**. Of particular importance to the company are 6 development projects in Turkey and 7 in India, countries that present major new target markets for Qualicaps®, aligned to these countries' significant investment plans for their pharmaceutical sectors.

Susana Ecenarro, Qualicaps®' Scientific Business Development Director, confirmed this, writing: *"The results of Cardiff's tests provided the detailed information needed to inform the company's decision to start marketing the Quali-V®-I in emerging markets"*. She adds, "*These development projects have only been operational since Cardiff research demonstrated that the Quali-V®-I capsules could meet the demands of customers in these regions given their specific environmental considerations"* **[5.3]**.

In summary, Cardiff research has been vital to the delivery of Qualicaps®' commercial and product strategy, including significant increased profit for the company and growth across the globe, including in new developing markets.

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

[5.1] Testimonial: Qualicaps' Commercial Vice President, EMEA - Beverly Nannini

[5.2] Qualicaps® Quali-V®-I capsule technical brochure

[5.3] Testimonial: Qualicaps' Scientific Business Development Director - Susana Ecenarro

[5.4] Examples of Qualicaps marketing presentations which include Cardiff reference and findings

[5.5] Quali-V®-I capsule scientific review

[5.6] Qualicaps® Quali-V®-I capsule website screenshot containing puncture performance findings (p.3)