Institution: University of Bath		
Unit of Assessment: A3 Allied Health Professions, Dentistry, Nursing and Pharmacy		
Title of case study: Nanopharm: nanotechnology advancing the development of respiratory medicines		
Period when the underpinning research was undertaken: 2003-2019		
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 Robert Price	Professor of Pharmaceutics, former Reader	1997- August 2020
Dr Jag Shur	Postdoctoral Research Associate, former Research officer	September 2005 – November 2012; May 2013 – November 2018; February 2019 – May 2019
Period when the claimed impact occurred: 2014-2019		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Research at University of Bath into the critical quality attributes that underpin the performance of orally inhaled and nasal drug products (OINDPs) has been translated via Nanopharm, Ltd., a University spin-out. Nanopharm has become a world-leading contract research organisation, growing from 4 to 42 employees, and with sales revenues increasing 10-fold to GBP7,500,000, in the REF period. In 2019, Nanopharm was acquired by AptarGroup, Inc. for approximately USD38,100,000. In parallel, Bath, the U.S. FDA and Nanopharm have collaboratively developed regulatory tools and methods to facilitate patient access to less expensive, safe and effective OINDP generic formulations.

2. Underpinning research

The University of Bath is globally recognised for research investigating the interactive forces, structure and aerosolisation performance of orally inhaled and nasal drug products (OINDPs) and understanding how the efficacy of these complex dosage forms are governed by the physical, chemical and interfacial properties of micron-sized active pharmaceutical ingredients (APIs).

Research at Bath, led by Professor Robert Price in the early 2000s, focused on understanding the influence of the physicochemical and environmental factors on the adhesive and cohesive interactions of respirable-sized particles. Probing these interactive forces at a single particle level provided fundamental insight into the forces, which must be overcome to de-aggregate and disperse drug particles, and enabled prediction of the balance of interparticulate forces required to optimise these complex formulations. These findings led to the breakthrough development of the cohesive-adhesive balance (CAB) technique **[1-3]**, which is still used to measure batch-to-batch variability and the influence of ageing effects and laagering conditions on the interfacial properties of micronized APIs for OINDPs. Furthermore, in understanding the high degrees of cohesion and poor dispersibility of respirable drug particles, a single droplet-to-particle engineering technology was developed to control the physical and interfacial properties of OINDPs and to optimise their aerosol performance **[4]**.

The acquired, in-depth understanding of the complexities of OINDPs led to an extensive and long-term collaboration between Price and the US FDA's Office of Generic Drugs. This has resulted in sustained funding to Bath over the last decade (i.e., 7 projects of 3-4 years duration). In addition to being able to define, measure, control and optimize the critical material attributes of APIs for OINDPs **[5]**, the research has enabled development of a range of orthogonal *in-vitro* techniques to understand the state of aggregation within an aerosolized

dose and with which to determine the rate and extent of drug release for bioequivalence studies **[6]**. Furthermore, the work has enabled more rational optimisation of microstructural physical properties and a clearer understanding of the handling and processing of particulate material to ensure greater consistency between batches.

Following development of the CAB technique at Bath, and initiation of the collaboration with the FDA, the consulting company - Nanopharm, Ltd. - established by Price initially, and then with Dr. Jag Shur, experienced a quantum leap in demand for services from the pharmaceutical industry and underwent significant growth in its business from 2014. This was triggered by translation of the Bath research - specifically, the in-depth understanding of fundamental properties at a single particle level - into Nanopharm's key technology platforms (in particular, Nanosense™ and SmartTrack™) and its range of analytical tools (e.g., CAB/Nanomech/UniDose). These capabilities are fundamentally based on the ability to measure API interparticulate forces and to characterise the associated microstructural properties, which govern the functionality of the resulting formulated products. These bespoke tools have been successfully implemented within the pharmaceutical industry to de-risk and expedite the development of both orally inhaled and nasal drug products.

Most recently, and now in a three-way collaboration between the US FDA's Office of Generic Drugs, the University of Bath and Nanopharm, the development of the UniDose aerosol collection apparatus has been achieved **[6]**. This device has been specifically engineered for the *in vitro* dissolution testing of OINDPs and has increased the discriminatory capability in measuring the *in vitro* release rate of an aerosolised dose. The approach addresses both the limitations of current aerosol collection systems and an important unmet need: specifically, as a potential tool and methodology with which the bioequivalence of switchable, generic OINDPs can be objectively assessed without the need for expensive, prolonged and frequently insensitive clinical endpoint studies.

3. References to the research

[1] Begat, P, Morton, DAV, Staniforth, JN & Price, R 2004, 'The cohesive-adhesive balances in dry powder inhaler formulations I: Direct quantification by atomic force microscopy', *Pharmaceutical Research*, vol. 21, no. 9, pp. 1591-1597. https://doi.org/10.1023/B:PHAM.0000041453.24419.8a

[2] Traini, D, Rogueda, P, Young, P & Price, R 2005, 'Surface energy and interparticle force correlation in model pMDI formulations', *Pharmaceutical Research*, vol. 22, no. 5, pp. 816-825. https://doi.org/10.1007/s11095-005-2599-2

[3] Jones, M, Hooton, JC, Dawson, ML, Ferrie, AR & Price, R 2008, 'An investigation into the dispersion mechanisms of ternary dry powder inhaler formulations by the quantification of interparticulate forces', *Pharmaceutical Research*, vol. 25, no. 2, pp. 337-348. https://doi.org/10.1007/s11095-007-9467-1

[4] Kubavat, HA, Shur, J, Ruecroft, G, Hipkiss, D & Price, R 2012, 'Investigation into the influence of primary crystallization conditions on the mechanical properties and secondary processing behaviour of fluticasone propionate for carrier based dry powder inhaler formulations', *Pharmaceutical Research*, vol. 29, no. 4, pp. 994-1006. https://doi.org/10.1007/s11095-011-0640-1

[5] Depasquale, R, Lee, SL, Saluja, B, Shur, J & Price, R 2015, 'The influence of secondary processing on the structural relaxation dynamics of fluticasone propionate', *AAPS PharmSciTech*, vol. 16, no. 3, pp. 589-600. https://doi.org/10.1208/s12249-014-0222-8

[6] Price, R, Shur, J, Ganley, W, Farias, G, Fotaki, N, Conti, DS, Delvadia, R, Absar, M, Saluja, B & Lee, S 2020, 'Development of an Aerosol Dose Collection Apparatus for In Vitro Dissolution Measurements of Orally Inhaled Drug Products', *AAPS Journal*, vol. 22, no. 2, 47. https://doi.org/10.1208/s12248-020-0422-y

4. Details of the impact

The impact of research from the Price laboratory has been delivered via Nanopharm, Ltd., which has grown significantly during the REF period from a small start-up (spun out of the University of Bath) to a high-end contract research organisation (CRO) that is an international leader in its field **[A]**. Nanopharm now provides an informed, innovative and comprehensive platform for developing formulations of respiratory medicines that enable effective delivery.

Growth, jobs, acquisition: In the 5-year period between 2014 and 2019, the number of Nanopharm employees has increased from 4 to 42 and sales revenue has increased 10-fold from GBP750,000 to GBP7,500,000. The geographical sales of Nanopharm's services are worldwide, with 30%, 30%, 29% and 11% in North America, Australasia, Europe and the UK, respectively. Nanopharm has a wide client base consisting of major international players in the respiratory medicine space (including Janssen, Genentech, 3M, Teva, and Amneal), and a high level of repeat business **[B]**.

Taking advantage of the support, reach and synergies offered by becoming part of a larger organisation, Nanopharm was acquired (but retains its name) by the US-based AptarGroup, Inc., in June 2019 for an enterprise value of approximately USD38,100,000 **[C,D,E]**. The President of Aptar stated **[C]**:

> *"We are delighted to welcome the talented team at Nanopharm... Their expertise and capabilities will deepen our current range of services offered to customers who are developing and testing inhaled medicines".*

and the CEO added **[C]**:

> *"The expertise of Nanopharm, a leader in inhalation and nasal drug development services, … bring[s] additional value to our customers as they navigate the challenging regulatory landscape and seek to bring their products to market faster".*

During the current REF period, the progressive addition of new services offered by Nanopharm (and based on the innovative and disruptive Bath research described above) has led to a rapid and substantial growth of its fee-for-service business **[B]**. These capabilities include (a) an integrated drug development service covering advanced materials characterisation, device and formulation development, and in silico modelling, (b) the SmartTrack™ tool, which identifies the critical formulation and device attributes of OINDPs **[F]**, and (c) UniDose™, a validated aerosol (respirable) dose collection system for *in vitro* dissolution testing and microstructural characterisation by morphology-directed Raman spectroscopy of OINDPs.

Wider economic and societal benefit: As stated above, the success of Nanopharm is directly related to the scientific knowledge and the underpinning research undertaken at the University of Bath. Consequently, Nanopharm's product development services are able to significantly reduce program risk and expedite the drug development process and clinical timelines, which results in significant savings for clients. This may be exemplified by client feedback from Janssen R&D (Belgium) **[A]**:

> *"… we worked with Nanopharm to design a Dry Powder Inhaler (DPI) capsule formulation, manufacturing process and analytical methodology. In a true Quality by Design manner, we started with characterisation of the API and excipient interfacial properties and… Nanopharm succeeded in making a formulation and process that was robust, both for the broad dosing strength range and environmental manufacturing conditions, and that was also stable. The first patient was dosed 9 months after Nanopharm started the work".*

and from the CEO of Advent in Australia **[A]**:

> *"With their scientific rigour and pragmatic approach, as well as their in-depth knowledge of the regulatory situation, [Nanopharm] can really add value to projects".*

In 2017, Nanopharm launched the integrated technology platform SmartTrack™, which has been widely implemented by clients and now comprises more than 45% of sales revenue.

SmartTrack™ ensures that the optimised product (whether propriety or generic) can be manufactured using a quality-by-design (QbD) paradigm **[A,B]**.

Relatedly, it is generally acknowledged that the major barrier to both generic competition and on-going product improvements of OINDPs is the cost and requirements for clinical endpoint bioequivalence (BE) studies. The latter often involve large patient numbers but produce highly variable results and are unable to detect formulation differences. To address this issue, the FDA Office of Generic Drugs has been supporting research at Bath (as indicated above) to explore alternative methodologies that can ensure bioequivalence between reference and generic drug-device combination products without the need for a clinical endpoint BE study. Based on the FDA-funded research at Bath, Nanopharm has advanced the concept of (so-called Q3) structural equivalence for OINDPs. As a result, *in vitro* dissolution testing methodology, combined with Raman spectroscopy and *in silico* mechanistic modelling, is providing an alternative approach **[6]** to compare products such that clinical biowaivers for OINPD development programs may be possible. The ongoing collaboration between Bath, the FDA and Nanopharm is bringing this encouraging idea towards realisation and a significant benefit, therefore, in facilitating patient access to less expensive, safe, efficacious and high-quality complex drug products. As the Director of the Office of Research and Standards in the FDA's Office of Generic Drugs stated in his keynote talk entitled, "New tools for generic orally inhaled drug products to maximize prospects of FDA approval," at the Respiratory Drug Delivery 2018 conference **[G]**:

> *"Rob Price and Jag Shur of the University of Bath and Nanopharm really helped us to understand how difficult it is to develop these products"*.

5. Sources to corroborate the impact

[A] Nanopharm brochure. https://nanopharm.co.uk/

[B] Nanopharm Information Memorandum, February 2019. **Strictly private and confidential**.

[C] University of Bath press release, 26/06/19. https://www.bath.ac.uk/announcements/university-of-bath-professor-sells-nanopharm-ltd-to-aptar-group/

[D] Aptar press release, 10/06/19. "Aptar Acquires Nanopharm and Gateway Analytical, Broadening Pharma Services Platform to Accelerate Customer Drug Development" 10 June 2019 https://www.aptar.com/news-events/aptar-acquires-nanopharm-and-gateway-analytical-broadening-pharma-services-platform-to-accelerate-customer-drug-development/. Note that the enterprise value referred to in this press release (USD50,000,000) is the market capitalisation and value that Aptar had calculated for Nanopharm and another company acquired at the same time. The enterprise value is based on a financial measure of Nanopharm (in this case, profit) which is then multiplied by the perceived value of the business (based on IP and market position).

[E] Aptar 2019 Annual Report, Form 10-K. Furthering a sustainable business and a more circular economy. https://s24.q4cdn.com/576740213/files/doc_financials/2019/ar/Aptar-2019-Annual-Report_Form-10-K.pdf; https://www.sec.gov/ix?doc=/Archives/edgar/data/896622/000155837020001217/atr-20191231x10k2d4ba9.htm

[F] Aptar press release, 06/11/19. Aptar Pharma's Nanopharm Wins "Excellence in Pharma" Award for SmartTrack™ at 2019 CPhI Pharma Awards; https://news.aptar.com/solutions/aptar-pharmas-nanopharm-wins-excellence-in-pharma-award-for-smarttrack-at-2019-cphi-pharma-awards/

[G] Orally Inhaled and Nasal Drug Products (OINDP) Website. https://www.oindpnews.com/2018/05/highlights-from-rdd-2018/6/