

Institution: University of Bath
Unit of Assessment: 3. Allied Health Professions, Dentistry, Nursing and Pharmacy
Title of case study: Inhaled delivery of life-saving medicines - The Vectura story
<p>1. Summary of the impact</p> <p>Innovative formulation science to create and develop the commercially successful PowderHale[®] technology was undertaken within the Department of Pharmacy & Pharmacology at the University of Bath, and subsequently by Vectura. This has directly provided the basis for novel, potentially life-saving treatments for chronic obstructive pulmonary disease (COPD). Seebri[®] Breezhaler[®] and Ultibro[®] Breezhaler[®] are once-daily, maintenance bronchodilators for the relief of various symptoms due to airways obstruction caused by COPD. Seebri[®] Breezhaler[®] was approved in the EU and Japan at the end of 2012 and has now been launched by Novartis. Ultibro[®] Breezhaler[®] a first-in-class combination bronchodilator was approved in Japan and the EU in September 2013. Under the terms of the licence agreement with Novartis concerning these products, Vectura has already received \$52.5M with an additional >\$100M anticipated upon achievement of regulatory and commercialisation targets. These medicines are major advances to treat and manage a disease that, according to the WHO, affects an estimated 210 million people worldwide and was the third leading cause of death in the developed world in 2012.</p>
<p>2. Underpinning research</p> <p>Pharmaceutical scientists in the Department of Pharmacy & Pharmacology and the Centre for Drug Formulation Studies (CDFS) at the University of Bath conducted a sustained programme of research aimed at improving drug delivery and therapies for inhaled medicines. In the mid-1990s, this research focused on formulation technologies to increase the control and efficiency of drug delivery from dry powder inhalers. Professor John Staniforth, who was employed by the University as a Lecturer, Reader and Professor between 1980 and 2000, headed this research effort. Other key individuals included Professor David Davies, Dr Michael Tobyn, and Dr David Morton who all worked at Bath until 1999 when the team, together with their technology, was absorbed into the biotech company, Vectura, Ltd. Mr Paul Woodcock also worked on various aspects of the technology as an Experimental Officer until 1997, and returned to work at the University in 2011. In addition, Dr Robert Price (now Professor within the same Department) made important contributions to aspects of the research from 1997 to 1999.</p> <p>Inhaled medicines exist in essentially two portable forms: (a) pressurised metered dose inhalers (pMDIs), and (b) dry powder inhalers (DPIs). Both systems generate fine drug particles, less than 5 µm in diameter, which can be inhaled by the patient as a cloud into their lungs. These products are typically used to treat respiratory diseases such as asthma or COPD. pMDI inhalers use pressurised propellants to generate the aerosol cloud, whereas DPI devices utilise the patient's inspirational effort to aerosolise the powder for inhalation. Towards the end of the 20th century, however, both approaches were relatively inefficient with only about 15-30% of the drug being delivered to its target in the lungs.</p> <p>In the development of a DPI, the small (typically 2-3 µm diameter) drug particles are created by milling. Unfortunately, these particles do not flow or aerosolise very well as a single ingredient powder due to the high forces of cohesion between them. As a result, the drug is often blended with larger, "carrier" particles of between 10 and 300 µm in size [1]. While this improves powder flow considerably, the drug particles, upon inhalation, must then be rapidly and efficiently removable from the carrier surface in the moving airstream [2,3]. The key challenge, therefore, is to ensure that the airflow created by the patient's inspiration through the DPI creates sufficient movement in the aerosolised powder to entrain it into this airstream and to uncouple the sticky drug particles from the carrier surface. Only then will the active agent be able to penetrate into the target area of the lung.</p> <p>Aerosolisation studies of pollen grains inspired the development of innovative techniques to 'passivate' carrier particle surfaces using biomimetic physicochemical methods. New excipients and blending methodologies for inhaled therapies were developed at Bath, which led to the filing of</p>

Impact case study (REF3b)

key patents in 1994 and 1995 [4,5]. These excipients, notably magnesium stearate and L-leucine, were added to form ternary blends with the drug and carrier particles. They were selected to create weakness in the adhesion between the drug and carrier thereby enabling rapid entrainment and easy dissociation of the drug from the carrier in the inspired airflow. This concept was further developed in Bath and, subsequently, by Vectura under the trade name 'PowderHale®'. Coupling of this technology with Vectura's device engineering programme resulted in much more efficient DPI products, which enabled significantly higher and more reproducible fine particle dose fractions (up to 80%) of aerosolised drug particles to be delivered into the deep lung [6].

3. References to the research

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2. Begat P, Morton DA, Shur J, Kippax P, Staniforth JN, Price R. The role of force control agents in high-dose dry powder inhaler formulations. *J Pharm Sci.* 2009; 98: 2770-2783. DOI: 10.1002/jps.v98:8
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4. Details of the impact

To best exploit the original research work, the University merged the CDFS, with the recently formed biotech company, Vectura, in 1999. This provided Vectura with the novel technology and innovation, derived from the University's research, to create a high level capability for the development of inhaled products. In the words of Vectura's Chief Financial Officer [7], "*This acquisition provided Vectura with formulation expertise, a contract services business, and a team of research scientists whose primary focus was inhaled product development. It also furnished Vectura with a suite of intellectual property rights relating to inhaled drug delivery from dry powder inhaler (DPI) devices*". This now represents a major success story with respect to the creation of commercial value from academic research [8].

The PowderHale® technology has to-date been licensed by many of the world's largest pharmaceutical companies and is currently used in several globally marketed DPI products. The most significant of these are two products developed in association with Novartis. Vectura NVA23 was approved in Japan and in the EU, respectively, in September and October 2012 [9] and is marketed by Vectura's partner, Novartis, as Seebri® Breezhaler®. This product delivers glycopyrronium bromide, a long-acting muscarinic antagonist with a rapid onset of action. Seebri® Breezhaler® is indicated as a maintenance bronchodilator treatment to relieve the symptoms of chronic obstructive pulmonary disease (COPD) in adult patients. Ultibro® Breezhaler® (indacaterol 85 µg + glycopyrronium 43 µg) is a first-in-class combination maintenance bronchodilator treatment to relieve symptoms in COPD. Ultibro® Breezhaler® was developed under the name QVA149 and was approved in Japan and Europe in September 2013 [10]. The mechanism of action of these drugs leads to an increase in the diameter of the airways in the lungs giving extended relief and easier breathing to patients due to the prolonged bronchodilator effect. The development success of Seebri® Breezhaler® and Ultibro® Breezhaler® are a direct result, therefore, of facilitating the efficacy of known drug substances through the application of novel drug

Impact case study (REF3b)

delivery technology derived from Bath-originated research.

COPD affects an estimated 210 million people worldwide, resulting in 58 million lost workdays each year. The disease is the fourth leading cause of death in the U.S. [11], and it has been calculated that the annual economic cost of COPD is over \$30B. As easy-to-use, cost-effective bronchodilators, with rapid onset of action for fast symptom relief, Seebri[®] Breezhaler[®] and Ultibro[®] Breezhaler[®] are significant therapeutic advances in this area. The products afford greater treatment options for the physician through the provision of better COPD management. The improved therapy possible with Seebri[®] Breezhaler[®] and Ultibro[®] Breezhaler[®] has been demonstrated to result in patient benefit [10] and, as a consequence, one may anticipate added social and economic benefit as well.

The EU and Japanese approvals of Seebri Breezhaler[®] and Ultibro[®] Breezhaler[®] have each triggered milestone payments under the collaboration agreement with Novartis and further substantial milestone payments are anticipated, in addition to royalties on sales [10,12]. The Chief Financial Officer of Vectura affirms that [7], *“To date, Vectura has received \$52.5M from Novartis and, under the terms of the licence agreement, could receive up to an additional \$135M upon achievement of regulatory and commercialisation targets for both products”*.

In addition to delivering new medical therapies, Vectura is a remarkable commercial and business triumph. After several productive years, Vectura completed a successful IPO and floatation on to the London Stock Exchange Alternative Investment Market (AIM) in 2004. This floatation raised £20.1M and placed the company’s initial market capitalisation at around £60M [13,14]. In 2006, the acquisition of Innovata Biomed created the UK’s largest biotech company at that time [15]. The addition of Innovata brought additional capability and capacity in the pulmonary products arena, adding new formulation technologies and devices to the Vectura portfolio [16].

The company has provided key employment opportunities for skilled scientific, ancillary support and administration staff in the Chippenham, Cambridge and Nottingham areas, and it has contributed significantly to the development of the South-West science base. Vectura has grown from 35 staff in 1999 to over 250 employees by 2009; the majority are science graduates, with many of them recruited locally from the South-West. The company has invested in a 1,300 m² state-of-the-art facility specifically designed for the manufacture of inhaled products. Vectura’s acquisitions have enabled the creation of a significant pipeline of products, comprising 5 other approved dry powder inhalers, which are marketed across the globe [12]. Furthermore, the company has strengthened its revenue base by diversification (i.e., it is no longer simply an inhalation-only organisation), and it now also has a strong presence in other sectors with ADVATE[®] for haemophilia A, Extraneal[®] for peritoneal dialysis, and Adept[®] for prevention of surgical adhesions, three products which have all been licensed to Baxter Healthcare [12]. In 2012, Vectura posted annual revenues of £33M.

Major pharmaceutical companies, including GlaxoSmithKline (GSK), continue to draw upon the original Bath research and resulting technology, demonstrating its sustained impact on the use of dry powder inhalers. In 2010, Vectura signed a collaboration agreement with GSK [12,17] worth £20M in stage payments, and royalties of greater than £10M per year, for the use of Vectura dry powder drug formulation intellectual property for late-stage development compounds in GSK’s respiratory product pipeline. The New Drug Application for the GSK’s BREO™ ELLIPTA™ (fluticasone furoate/vilanterol 100/25 µg) was approved by FDA in May, 2013 [19]. This will be the first product to be launched by GSK that will use patents covered by the agreement. A second GSK combination product, similarly protected by the agreement, has also been filed for approval in the US, Europe and Japan [18].

In summary, the Vectura story demonstrates both reach, with regional, national and global impact, and significance, insofar that it has led to the creation of novel medicines, supported the evolution of a successful new enterprise, realised important therapeutic and economical benefits, and enabled the translation of basic pharmaceutical science into obvious benefit for the patient. This conclusion is succinctly captured by Vectura’s Chief Financial Officer [7]: *“As a result of both the inventions acquired from the University of Bath, and the subsequent development of the technologies, Vectura has become a high-value company recognised for innovation in the development of pharmaceutical therapies for the treatment of airway-related diseases”*.

Impact case study (REF3b)

5. Sources to corroborate the impact

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16. <http://production.investis.com/iov/about/profile/>
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18. Vectura Annual Report and Accounts, 2012-13 (page 6).
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