Institution: Cardiff University

Unit of Assessment: UoA3

Title of case study: Inhaled medicines: Leveraging benefits to global pharma and international development

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

i2c Pharmaceutical Services is the trading name for a Cardiff University spin-out company based on Cardiff University research excellence and specialising in pharmaceutical inhaler product research and development. i2c's research in formulation technologies and clinical testing has enabled development of new inhalational medicinal products for the healthcare markets in both developed and emerging countries. Impacts arising from research are at local, national and international levels and evidenced by marketed products, the improved business performance of commercial concerns and the creation of highly skilled jobs.

2. Underpinning research (indicative maximum 500 words)

Effective respiratory medicines depend upon the use of an appropriate inhaler device to deliver an often-complex drug aerosol formulation to the lung in a way that leads to aerosol deposition at appropriate target region(s) of the airways. Professor Glyn Taylor (Lecturer 1980-1993; Senior Lecturer 1993-2010; Professor 2010-present) and his team, including postdoctoral research associates Simon Warren and Paul Dickinson, at the (formerly titled) Welsh School of Pharmacy, Cardiff University have pursued respiratory research programmes to both understand inhaled medicine dose deposition patterns in the lung and optimise novel inhaled drug formulations.

Quantifying drug deposition patterns in the lung

The team's research has contributed to methodological advances in pulmonary pharmaceutical scintigraphy (a form of imaging involving a radiolabelled tracer) for the accurate quantitation of both inhaled drug dose to lung and regional pulmonary drug deposition patterns. In the mid-90s these advances were explored by Taylor and colleagues in animal models, including a definitive report of the relationship between the site of drug deposition in the lung and extent of drug absorption [3.1]. These approaches were adapted to, and exploited in, clinical research in healthy volunteers and in patients to optimise the performance of novel inhalation formulations and devices [3.2,3.3].

Key improvements to scintigraphy imaging in the lung as a result of Taylor's research included the development of novel research strategies, through understanding the nature of appropriate radioligands and their solubility in propellants and solvents, for the efficient radiolabelling of inhaled pharmaceutical formulations, for example pressurised metered dose inhalers (pMDIs) [3.2]. The use of radiolabelled formulations in clinical research studies has shown how the inhalational manoeuvre impacts upon the regional deposition pattern of drug within the lung following delivery from both pMDI [3.2] and nebuliser [3.3] inhalation devices; control of inhalation technique is now a critical component in clinical trial design of novel inhaler devices and formulations. Cardiff workers also identified the need to develop original scintigraphic data analysis approaches to translate 2-dimensional lung tissue scintigraphic imaging data into quantifiable inhaled aerosol deposition information, using appropriate tissue attenuation corrections and ensuring mass balance calculations, and applied these factors in pre-clinical and clinical studies. Taylor's leading research expertise in scintigraphic imaging is evidenced by participation on the International Society for Aerosols in Medicine (ISAM) Sub-Committee for the Standardization of Lung Imaging Techniques. This Committee has recently published expert opinion and guidance to standardize the techniques used by academic/commercial groups for determining aerosol deposition from inhaled products, with Taylor contributing to guidance specifically relating to radiolabelling aerosol drug formulations [3.4] and using 2-dimensional scintigraphic imaging for aerosol deposition assessment [3.5].

Formulating inhaled medicines

Research in experimental inhaled medicines, whether or not they contain scintigraphic tracers, led the Cardiff team to develop formulation research capability. The focus of the Cardiff team in this area involves research in formulating pMDI medicines away from chlorofluorocarbon (CFC) to hydrofluoroalkane (HFA)-based propellants. A propellant is essential in pMDI formulations to expel the drug aerosol upon activation of the inhaler. The switch from 'ozone-depleting' CFC propellants to 'ozone-friendly' HFA propellants is a requirement of the Montreal Protocol. The volatile nature of HFA propellants (they only remain liquid under pressure) makes drug solubility determination in such solvents a challenge. A more convenient model that is liquid at atmospheric pressure yet

could predict drug solubility in the HFA propellant would clearly advance new pMDI research and development. In this context Taylor's team were the first to screen and identify suitable liquid models for predicting the solubility of materials in HFA propellants; their studies showing a linear relationship between compound solubility in 1H-perfluorohexane and common HFA propellants [3.6].

Taylor and colleagues in Cardiff University have also developed innovative formulation strategies to maintain pMDI efficiency following the switch of propellants (HFA propellants are not always as effective as CFC propellants). For example, a butyryl triester prodrug of the common inhaled molecule salbutamol was chemically synthesised [3.7]. This prodrug was shown to be highly miscible in HFA propellant (to enable pMDI formulation) and then able to rapidly hydrolyse when exposed to esterases present in the lung (to enable salbutamol activity in vivo after aerosolisation) [3.7]. A further example involves the association of drug with an inert carrier particle in a pMDI suspension, which has been translated into a "low energy dispersion" platform technology (Patent No. US7481995 filed in 2003). A further novel Cardiff University research approach, incorporating drugs into nanoparticles before dispersion into the pMDI propellant (Patent No. EP1274403 filed in 2001), was further developed by Taylor and colleagues (2006-2010), with the support of 3M Healthcare Ltd. This pMDI delivery technology demonstrates broad applicability to a range of molecules including low molecular weight drugs and macromolecules [3.8].

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

[3.1] **Colthorpe, P., Farr, S.J**., Smith, I.J., Wyatt, D. and **Taylor, G**. The influence of regional deposition on the pharmacokinetics of pulmonary-delivered human growth hormone in rabbits. Pharm. Res. (1995) 12: 356-359. http://dx.doi.org/10.1023/A:1016292232513

[3.2] **Farr, S.J., Rowe, A.M**., Rubsamen, R. and **Taylor, G**. Aerosol deposition in the human lung following administration from a microprocessor-controlled pressurised metered dose inhaler. Thorax (1995) 50: 639-644. http://dx.doi.org/10.1136/thx.50.6.639

[3.3] Nikander, K., Prince, I., Coughlin, S., Warren, S. and **Taylor, G**. Mode of breathing – Tidal or slow and deep – through the I-neb adaptive aerosol delivery (AAD) system affects lung deposition of ^{99m}Tc-DTPA. J. Aerosol Med. Pulm. Drug Deliv. (2010) 23(S1): S37-43. http://dx.doi.org/10.1089/jamp.2009.0786

[3.4] Devadason, S.G., Chan, H.K., Haeussermann, S., Kietzig, C., Kuehl, P.J., Newman, S., Sommerer, K. and **Taylor, G**. Validation of radiolabeling of drug formulations for aerosol deposition assessment of orally inhaled products. J. Aerosol Med. Pulm. Drug Deliv. (2012) 25(S1): S6-9. http://dx.doi.org/10.1089/jamp.2012.1Su3

[3.5] Newman, S., Bennett, W.D., Biddiscombe, M., Devadason, S.G., Dolovich, M.B., Fleming, J., Haeussermann, S., Kietzig, C., Kuehl, P.J., Laube, B.L., Sommerer, K., **Taylor, G.**, Usmani, O.S. and Zeman, K.L. Standardization of techniques for using planar (2D) imaging for aerosol deposition assessment of orally inhaled products. J. Aerosol Med. Pulm. Drug Deliv. (2012) 25(S1): S10-28. http://dx.doi.org/10.1089/jamp.2012.1Su4

[3.6] **Dickinson, P.A., Seville, P.C., McHale, H., Perkins, N.C.** and **Taylor, G.** An investigation of the solubility of various compounds in the hydrofluoroalkane propellants and possible model liquid propellants. J. Aerosol Med. (2000) 13: 179-186. http://dx.doi.org/10.1089/jam.2000.13.179

[3.7] **Seville, P.C., Simons, C., Taylor, G.** and **Dickinson, P.A.** Prodrug to probe solution HFA pMDI formulation and pulmonary esterase activity. Int. J. Pharm. (2000) 195: 13-16. http://dx.doi.org/10.1016/S0378-5173(99)00352-X

[3.8] **Bains, B., Birchall, J.C.**, Toon, R. and **Taylor, G**. In vitro reporter gene transfection via plasmid DNA delivered by metered dose inhaler. J. Pharm. Sci. (2010) 99: 3089-3099. http://dx.doi.org/10.1002/jps.22085

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

To capitalise on the drug deposition research and expertise of Taylor and colleagues at Cardiff University, a spin-out company, Cardiff Scintigraphics Ltd, was founded in 1992 to provide research-led scintigraphy imaging capability to the pharmaceutical commercial sector for both preclinical and clinical drug development. In 2008, as a result of the inhaled formulation research expertise of the Taylor team, this company began trading under the name of i2c Pharmaceutical Services (i2c) to develop its commercial activities in novel inhaler formulation research and development. Taylor is a Director and CSO of i2c. The underpinning of i2c by Cardiff University's

research has, during the assessment period, led to improved business performance for a range of international commercial concerns and is also yielding broader economic, near-future healthcare benefits (new, effective inhaled products) through international development activities.

Business performance of drug development partners and informing practice

During the assessment period i2c in partnership with the clinical research organisation Simbec Research Ltd, has secured £1.6M worth of clinical trial business [5.1] relating primarily to i2c's provision of pulmonary imaging which is itself built upon Cardiff's research expertise and methodological advances in clinical scintigraphy. Working with industry has led to informed changes to practice. For example, one of i2c's scintigraphic studies was a single-centre clinical trial in the pre-assessment period (2006) to evaluate the iNeb® nebuliser. This study showed that using the iNeb® device in Target Inhalation Mode (TIM) as opposed to Tidal Breathing Mode (TBM) (the two breathing pattern algorithms that can be used with this device) it was possible to reduce patient nebulisation times and improve lung deposition. This data was published (2010) by invitation in a specialised journal issue dedicated to the iNeb® (see Section 3 [3.3]) and is currently used by Philips Respironics and their pharmaceutical partners to promote iNeb® and develop regulatory submissions that use the device [5.2]. The research has also informed others seeking to establish guidelines for clinical practice, for example in the work of McCormack et al. 2011 (Alder Hey Children's Hospital) advocating TIM for all cystic fibrosis patients on chronic suppressive therapy and for those with a new growth of Pseudomonas aeruginosa [5.3]: *"Radiolabelled aerosol studies have demonstrated improved lung deposition with TIM compared to TBM"* (citing [3.3]).

Another example of supporting pharmaceutical drug development was i2c's clinical evaluation of inhaled dihydroergotamine for MAP Pharmaceuticals (USA) [5.4]. This data is presented in MAP's New Drug Application (NDA) for Levadex® (dihydroergotamine) as an orally inhaled treatment for migraine (next FDA response due late 2013). In January 2013 it was announced that Allergan would acquire MAP at a cost of $958M, principally to globally commercialise Levadex® as a new anti-migraine therapy [5.5]. Since 2008, i2c's research capability in clinical imaging and drug delivery has also supported patent applications in other therapeutic areas (Aradigm Corporation's deep lung delivery of treprostinil; Patent No. EP 2330893 A1 filed in 2009).

To meet the research needs of drug development partners, i2c has in the assessment period increased its staff from two to five full-time highly skilled employees and three regular consultants. The company has also been consistently able to offer graduates paid project-based work experience and currently sponsors two employees on part-time MSc and PhD programmes. i2c turnover has increased significantly since 2008, now trading at over £500K p.a. for the past 3 years and realising significant pre-tax profits of £200K p.a. In 2012 the company was shortlisted for the Queen's Award for Enterprise in the Innovation category.

International development of inhaled pharmaceutical products

The diversification of business activities based on Cardiff University's formulation research with HFA propellants, and the increasing global reach of i2c's impact is illustrated by i2c's involvement in a consortium with the pMDI valve manufacturer, Valvole Aerosol Research Italiana (VARI, Italy), and the regulatory support/project management company, Pharmadelivery Solutions (PDS, UK). This consortium has won contracts totalling US$3M (2009 to date) from the United Nations Industrial Development Organisation (UNIDO); US$2.4M of this investment was directed to i2c reflecting its pivotal role [5.6]. The UNIDO contracts are to provide research expertise and technology transfer to assist developing countries to fulfil their obligations to phase out the use of ozone-damaging propellants in medicinal pMDIs; specifically providing new HFA formulations and manufacturing capability to replace five CFC pMDI products for two companies in Egypt (with combined annual sales of 7.5 million pMDIs units and producing 163.1 tonnes of CFCs) [5.7], and three CFC pMDI products for one company in Mexico (with an annual production capacity for 4.5-5.5 million pMDIs) [5.8]. The UNIDO-sponsored research and development allows these two countries to comply with the Montreal Protocol while meeting their populations' healthcare demands and developing the capability of local pharmaceutical manufacturers; Arab Drug Company (ADCO, Cairo) and Egyptian International Pharmaceutical Industries Co. (EIPICO, Tenth of Ramadan City) in Egypt, and the Laboratorios Salus (Guadalajara) in Mexico. It is i2c that has the sole responsibility for the research and formulation development to ensure that the HFA alternatives are economically viable and of equivalent performance to more expensive global

inhaler brands. To date, four inhalation products have been developed, approved and transferred to commercial-scale operations through the contributions of i2c, and based on Cardiff University formulation research. Ental HFA (salbutamol) has received regulatory approval (2011) in Egypt, and Assal (salbutamol) and two strengths of HFA-Dobipro (beclomethasone) have received regulatory approval (2011 onwards) in Mexico [5.6]. A further two products are under approval.

The research and development of i2c is also providing commercial benefit for consortium partners and sub-contractors. VARI has seen an unprecedented increase in its manufacturing needs for HFA aerosol valves (ca. 13 million units p.a. to replace those CFC products prescribed in the UNIDO contracts [5.7,5.8]) with inevitable improvements to business performance [5.6]. To meet this increased demand, and providing further evidence of long-term growth and skilled job creation, VARI has recently moved to a custom-built factory [5.6] in which 700m^2 of cleanroom space is dedicated to HFA valve production. Similarly, as a result of the pro-rata demand to meet the new pMDI unit supply needs, as evidenced for valve suppliers VARI [5.6], and the direct replacement of HFA for CFC tonnage [5.7,5.8], the new products brought to market through the UNIDO contracts are increasing the turnover of other pMDI component suppliers: Presspart (Blackburn, UK), sole suppliers of pMDI cans and actuators (est. £1-2M p.a.) [5.9], and Mexichem Fluor (Runcorn, UK), the HFA propellant supplier (est. £20M p.a.).

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

[5.1] Statement from Director Scientific Affairs, Simbec Research (Merthyr Tydfil) confirming £1.6M worth of clinical trial business since 2008 specific to i2c's provision of pulmonary scintigraphy.

[5.2] Contact - Clinical Product Manager, Respiratory Drug Delivery, Philips Respironics USA. Corroborating the role of Taylor's scintigraphic research (e.g. [3.3]) in assisting Philips and their partners to promote the iNeb® device and develop regulatory submissions using the device.

[5.3] Clinical trial in cystic fibrosis patients confirming reduced treatment time of iNeb® operated in TIM and resulting impact on clinical practice. McCormack, P., McNamara, P.S. and Southern, K.W. A randomised controlled trial of breathing modes for adaptive aerosol delivery in children with cystic fibrosis. J. Cyst. Fibros. (2011) 10: 343-349. http://dx.doi.org/10.1016/j.jcf.2011.04.006

[5.4] Collaborative paper co-authored by Cardiff University, MAP Pharmaceuticals and Simbec Research presenting the clinical evaluation of dihydroergotaime for migraine that was subsequently used in MAP's NDA for Levadex®. Shrewsbury, S.B., Cook, R.O., **Taylor, G.**, Edwards, C. and Ramadan, N.M. Safety and pharmacokinetics of dihydroergotamine mesylate administered via a Novel (Tempo) inhaler. Headache (2008) 48: 355-367. http://dx.doi.org/10.1111/j.1526-4610.2007.01006.x

[5.5] Press release confirming Allergan acquisition of MAP Pharmaceuticals Inc. for $958M to globally promote Levadex® for the acute treatment of migraine in adults. http://ir.mappharma.com/releasedetail.cfm?ReleaseID=735129

[5.6] Statement Managing Director, VARI (Italy) confirming i2c's key role in developing new inhaled products for Egyptian and Mexican markets: increased valve production leading to additional turnover for the company and the requirement for additional cleanroom space.

[5.7] UNIDO Request for Proposal (2008) awarded to i2c consortium. Confirming the phase-out of CFC consumption in pMDIs in Egypt stating the types (pp 6-7) and volume (pp 4-5) of pMDI products that require replacement under the UNIDO contract and the ozone depleting potential (ODP) tonnage of CFCs used in pMDIs (p 2 Table). http://www.unido.org/fileadmin/import/86321_15002112AOmp_TOR.pdf

[5.8] UNIDO Request for Proposal (2008) awarded to i2c consortium. Confirming the phase-out of CFC consumption in pMDIs in Mexico stating the types of (p 4) and manufacturing capability for (p 3) pMDI products that require replacement under the UNIDO contract. http://www.unido.org/fileadmin/import/86957_15002116ERA_TOR1.pdf

[5.9] Contact - Business Development Director, Pharmaceuticals, Presspart Manufacturing Ltd., UK. Confirming significant increase in turnover for Presspart Ltd. as a direct result of supplying pMDI components for the newly developed HFA products in the Egyptian and Mexican markets.

All documents, testimony and webpages saved as PDFs are available from the HEI on request.