Institution: University of Bath

Unit of Assessment: 3. Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Chiesi Farmaceutici, S.p.A. - Commercialisation of Modulite® technology for pressurised metered dose inhalers

1. Summary of the impact

The transition, at the end of the 20th century, from ozone-depleting chlorofluorocarbons (CFCs) to hydrofluoralkane (HFA) propellants in metered dose inhalers (MDIs), for drug delivery to the upper airways in the lungs, taxed the ingenuity of formulation scientists and device design engineers. The regulatory requirement for clinical equivalence between the CFC and HFA products demanded an unchanged drug dosing regimen and identical lung deposition profiles.

Research funded by Chiesi Farmaceutici (Parma, Italy) in the Centre of Drug Formulation Studies (CDFS) at the University of Bath led to development of the Modulite® technology which met the challenges posed and mimicked the performance of CFC MDI using HFA propellants. The proprietary technology enabled Chiesi to re-formulate and commercialise a number of products, which now represent mainstay therapies in the treatment of asthma and chronic obstructive pulmonary disease (COPD).

The Modulite® technology has provided the greatest contribution to both the turnover and the global development of the Chiesi group, via several successful in-house developmements and collaboration agreements with leading pharmaceutical companies. Global sales of Chiesi's Atimos Modulite®, Fostair/Foster (25% of sales) and Clenil Modulite® (14.4% of sales) MDI products produced revenue of in excess of $450 Million in 2012.

2. Underpinning research

Metered dose inhalers (MDIs) are one of the main treatments for asthma and chronic obstructive pulmonary disease (COPD). For decades, CFCs were the most suitable propellant for use in MDIs, but were subsequently identified as contributing to ozone destruction and damage to the Earth's ozone layer. Although CFC MDIs were granted a temporary "essential use" status under the Montreal Protocol on substances that deplete the ozone layer, they were required to be phased out when alternative technologies and regulatory approval of CFC-free MDIs could be obtained.

The switch from 40 years of research and technical understanding with CFC metered dose inhalers to HFAs was simple in principle but scientifically very challenging. Differences in the physical and chemical properties of CFCs and HFAs created significant problems in the reformulation of existing suspension-based MDI products. For example, conventional surfactants used in CFCs were not soluble in HFA liquefied propellants. The gasket seal materials used in CFC valves were not compatible with HFAs, and the differences in the thermodynamic properties of the liquefied propellants required a new actuator design to obtain correct particle size and plume geometry.

With the need to develop pharmaceutical and therapeutically equivalent products, researchers at the University of Bath developed in collaboration with, and funded by, Chiesi Farmaceutici S.p.A., a novel solution-based technology that enabled a simple yet elegant approach to mimicking the performance characteristics of the existing CFC products [1,2]. A team of three scientists was led by David Lewis, an aerosol scientist at CDFS (1996 – 1999), and supervised by Brian Meakin, Senior Lecturer in the Department of Pharmacy & Pharmacology, and Director of its Centre for Drug Formulation Studies (1960 – 1997). The platform technology allowed the manipulation of HFA-based systems by permuting two inter-dependent variables: the addition of a non-volatile component to the formulation and the geometry of the actuator orifice. Together with two minor variables (quantity of co-solvent and metering volume) to further refine performance, the Modulite® technology enabled modulation of aerosol cloud formation with well-defined aerodynamic particle sizes and plume speeds [3].

The addition of an inert, non-volatile additive provided a means of controlling particle size, as the final particle size distribution of a dry droplet will depend on the concentration of drug within the droplet and any other non-volatile component that has been added. With the addition of glycerol

and polyethylene glycol, the aerodynamic particle size distribution of an aerosol cloud, the mass median aerodynamic diameter (MMAD), can be altered by controlling the volumetric contribution of the non-volatile component using a relatively simple formula [4,5]. Assuming that the aerosol cloud particles approximate to a spherical geometry, the particle diameter (d), is related to the cube root of the volume. For a given combination of drug, non-volatile additive and propellant, and assuming that the spray pattern is maintained, and that density changes are small as composition varies, the increase in the MMAD from a baseline value of $MMAD_0$ to $MMAD_1$ can be theoretically be determined by: $MMAD_1 = MMAD_0 \bullet (m_1/m_0)^{⅓}$, where m_o is the mass of drug in the propellant and m_1 is the mass of drug plus non-volatile additive.

With the Modulite® approach, it is possible to develop HFA-based solution formulations where the cloud characteristics can be tailored to meet specific needs, allowing various drugs such as short- and long-acting beta agonists, corticosteroids and anti-cholinergics to be readily re-formulated in HFA MDIs [4,5]. The outstanding achievement and contribution that Modulite® technology made at a time when the European Union ended the use of CFC-based inhalers was highly significant. Modulite® was awarded the 2006 Frost & Sullivan Technology Innovation Award for demonstration of technological superiority within the industry [6].

3. References to the research

1. Brambilla, G., Ganderton, D, Garzia, R., Lewis, D., Meakin, B.J. and Ventura, P. Modulation of aerosol clouds produced by pressurised inhalation aerosols. Int. J. Pharm., 186 (1999) 53-61. DOI: 10.1016/S0378-5173(99)00137-4
2. Meakin, B., Lewis, D., Ganderton D. and Brambilla, G. Countering challenges posed by mimicry of CFC performance using HFA systems. Respiratory Drug Delivery VII, (2000) 99-107. *Available on request from the HEI.*
3. Ganderton, D., Lewis, D., Davies, R., Meakin, B., Brambilla, G. and Church, T., Modulite®: a means of designing the aerosols generated by pressuized metered dose inhalers. Respir. Med. 96 (2002) S3-S8. http://download.journals.elsevierhealth.com/pdfs/journals/0954-6111/PIIS095461110280018X.pdf
4. Ganderton, D., Lewis, D., Meakin, B., Brambilla, G., Garzia, R. and Ventura, P. Pharmaceutical aerosol composition. (1997) UK Patent Application Number 9712434.1. Patent published in 2008 (WO1998/056349). http://www.google.com/patents/WO1998056349A1?cl=en
5. Lewis, D., Ganderton, D., Meakin, B., Brambilla, G., Garzia, R. and Ventura, P. Pressurised metered dose inhalers (MDI). US Patent filling in 1999. Patent granted in 2008 (US7347199). https://docs.google.com/viewer?url=patentimages.storage.googleapis.com/pdfs/US7347199.pdf
6. Frost & Sullivan Award (2006). http://www.frost.com/prod/servlet/press-release.pag?docid=94679674

4. Details of the impact

The technology, which was invented and developed at the University of Bath, was patented in 1997 and eventually transferred to a purpose-built MDI filling line at Chiesi Farmaceutici S.p.A., Parma, Italy [4,5]. All research and development activities relating to the Modulite® technology remained within the Centre of Drug Formulation Studies (CDFS) at the University of Bath until 2000. For several years thereafter, Chiesi then sponsored further fee-for-service development work employing 17 members of staff before, in 2010, the Italian parent company opened its own purpose-built laboratories in Chippenham. The original University of Bath employees, who had conceived the Modulite® technology, and had been working on the Chiesi-sponsored research and development, formed the core of this new structure (Chiesi UK, Ltd.). The laboratory at Chippenham (which now employs 13 full-time staff) is tasked with producing new formulations having improved drug delivery efficiency resulting in enhanced absorption and therapeutic efficacy of the Modulite® technology.

The Drug Delivery Technologies Director of Chiesi has stated that, *"The team at Bath… showed that addition of a low volatility component to a propellant containing HFA and a co-solvent to*

solubilise the drug could controllably increase the aerodynamic diameter of the aerosol particles on actuation from a metered dose inhaler (MDI). Their input led to [the] patent application on the addition of a low voltaility component in modulating an MDI having HFAs as propellant that was pharmaceutically and clinically equivalent to our exisiting MDIs which used CFCs. This technology was [named] Modulite®."

The Modulite® technology currently generates for the Chiesi group revenues of around $450M per annum [7].

The impact of the Modulite® technology has been widely recognised by the pharmaceutical industry through successful partnership and collaboration agreements with leading pharmaceutical companies, including GlaxoSmithKline (GSK), Novartis and AstraZeneca.

Specific examples include:

- GSK has a semi-exclusive international license and supply agreement for Modulite® beclomethasone dipropionate for treatment of asthma in a number of European and non-European countries.
- Novartis has a semi-exclusive international license and supply agreement for a Modulite® formoterol product for the treatment of asthma in a number of European and non-European countries.

Chiesi's leading marketed product is Modulite® Fostair/Foster, which is a fixed combination of beclometasone dipropionate (corticosteroid) and formoterol fumarate (long-acting β2-agonist) with rapid onset of its therapeutic effect.

Chiesi's Drug Delivery Technologies Director affirms that, *"As a result of [the Bath] invention, Chiesi has successfully developed and launched three products (Atimos Modulite® - Formoterol Fumarate Dihydrate (FFD), Clenil Modulite® - Beclomethasone dipropionate (BDP) and Foster Modulite® - a fixed combination of FFD and BDP) across European and other territories. For certain territories, Chiesi has also licensed the distribution and sales of the Modulite® products through GSK, Novartis and other primary pharmaceutical companies. Foster Modulite® has become Chiesi's top selling product, with sales in 2012 in excess of $300,000,000 and is now being sold in over 35 counties worldwide; further launches are planned throughout 2013-2014."*

In 2010, Foster became Chiesi's top selling product [8] and in the 2012 Chiesi Group annual report, the company's chairman announced that market figures have indicated that: *"Foster is the biggest-selling product resulting from Italian [sponsored] research in the world*" [9].

The Foster/Fostair product was further approved in November 2012 as a maintenance and reliever therapy in 35 European countries thus confirming its efficacy both for maintenance and "as-needed" therapy. Furthermore, a Foster MDI COPD clinical programme was successfully completed in 2013, which will result in a marketing application for this new indication.

The Drug Delivery Technologies Director of Chiesi concludes, *"The 10^{+} year collaboration between Chiesi and CDFS at the University of Bath has led to Chiesi's most successful product development programs and Modulite® continues to be at the forefront of our R&D programs involving new chemical entities for asthma and COPD."*

In sum, the reach of the impact of the Bath-based research described here is evident from the increasing use of the Modulite® technology in products used across the globe; the significance lies not only in the technical success of the science driven by an environmental imperative, but also the key achievement of assuring the efficacy of potent drugs by their effective delivery using formulation skill combined with clever device engineering.

5. Sources to corroborate the impact

7. Letter from the Drug Delivery Technologies Director, Chiesi Farmaceutici, S.p.A., Parma, Italy.
8. 2010 Chiesi Annual report, page 6.
9. 2012 Chiesi Annual report, page 4.