Institution: The University of Huddersfield

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

Title of case study: Inhaled therapies

1. Summary of the impact

Research by the University of Huddersfield's School of Applied Sciences has played a major role in addressing the difficulties experienced by people who use inhalers. The work has adapted existing methodologies so they can mimic how patients use nebulisers and dry powder inhalers, thereby enhancing understanding of a problem that affects millions globally. Findings and insights have been incorporated in "gold standard" guidelines that are influencing practice and policy around the world, while lead researcher Professor Henry Chrystyn's methods and techniques have become central to academic, practitioner and industry efforts to tackle the issue at national and international level.

2. Underpinning research

According to the World Health Organisation and the Global Initiative for Asthma, 235 million to 300 million people suffer from asthma. In the UK alone more than 5.2 million, a fifth of them children, are affected – roughly equivalent to one person in every five households. The world market for inhaled products is 32 Billion USD per annum. Chronic obstructive pulmonary disease (emphysema and chronic bronchitis) represents a similar problem, with approximately three million patients in the UK. Inhalers are the primary form of treatment, yet many patients have problems using them. Research by the University of Huddersfield's School of Applied Sciences has made a significant contribution to addressing the issue of correct inhaler use.

One key basis for this work has been the recognition that in-vitro studies, because they involve traditional pharmacopoeia methodologies that are essentially unrelated to how patients use inhalers, are able to provide only limited insights. Further limitations arise because in-vivo studies tend to employ patients who are highly trained in the correct use of inhalers, so data does not accurately reflect the difficulties experienced by "average" users in a real-life setting. In-vivo studies are also complicated by the lack of a robust test to identify lung deposition. Huddersfield's research has aimed to overcome all of these shortcomings and to focus on objective measurements rather than subjective criteria to assess a patient's inhaler technique. Professor Henry Chrystyn (Professor and Head of Pharmacy, 2007-present) has led the research in this area since joining the School in September 2007, making full use of a comprehensive and highly competitive inhalation therapeutics laboratory and has adapted the methods to use the characteristics of patient inhalation manoeuvres (referred to as ex-vivo studies).

One key element of the research has been the identification of the variability of the inhalation characteristics of patients when they use inhalers [3.1]. The findings of these studies have been used to inform national and international guidelines on how to train patients to use their inhalers. Another key element is the updating of established in-vitro pharmacopoeia methods to incorporate patient inhalation profiles obtained in real-time clinical settings that more closely reflect how patients use nebulisers [3.2] and dry powder inhalers [3.3]. This has revealed that the traditional focus of standard methods on peak inhalation flow is not as important as other aspects of a patient's inhalation manoeuvre during inhaler use [3.4].

The ex-vivo work has more recently been integrated with Chrystyn's longstanding expertise in urinary pharmacokinetic studies to demonstrate the presence of in-vitro/in-vivo correlations (IVIC) [3.5]. Although well established for oral drug delivery, these correlations have traditionally not been widely acknowledged in the inhalation field. The research team has now validated its urinary pharmacokinetic method for beclometasone, a steroid used ubiquitously in inhalers [3.6].

In summary, Huddersfield's research has identified a range of in-vitro, ex-vivo and in-vivo methodologies to investigate inhaler use. The work is providing enhanced insight into a problem that affects millions of people every day.

3. References to the research

1. Azouz W, Campbell J, Stephenson J, Saralaya D and Chrystyn, H. Improved metered dose inhaler technique when a coordination cap is fitted. (2013) *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, doi: 10.1089/jamp.2012.1031

2. Abdelrahim, ME, and Chrystyn, H. Aerodynamic Characteristics of Nebulised Terbutaline Sulphate Using the Next-Generation Impactor (NGI) and CEN Method. (2009) *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 22, 19-28. doi:10.1089/jamp.2008.0650.

3. Nadarassan, DK, Assi, KH, and Chrystyn, H. Aerodynamic Characteristics of a Dry Powder Inhaler at Low Inhalation Flows Using a Mixing Inlet with an Andersen Cascade Impactor. (2010) *European Journal of Pharmaceutical Sciences*, 39, 5, 348-354. doi: 10.1016/j.ejps.2010.01.002.

4. Azouz, W, and Chrystyn, H. Clarifying the Dilemmas About Inhalation Techniques for Dry Powder Inhalers: Integrating Science with Clinical Practice. (2012) *Primary Care Respiratory Journal*, 21(2), 208-213. doi: 10.4104/pcrj.2012.00010.

5. Mazhar, SH, and Chrystyn, H. Salbutamol Relative Lung and Systemic Bioavailability of Large and Small Spacers. (2008). *Journal of Pharmacy and Pharmacology*, 60, 1609-1613. doi: 10.1211/jpp/60.12.0006.

6. Ahmed, A, Harding, LP, and Chrystyn H. Urinary Pharmacokinetic Methodology to Determine the Relative Lung Bioavailability of Inhaled Beclometasone. (2012) *British Journal of Clinical Pharmacology*, 74(3), 456-464, doi: 10.1111/j.1365-2125.2012.04210.x.

Grants:
All grants were awarded to Professor Chrystyn as PI (unless specified).
In-vitro studies
Characterisation of hydrogel pulmonary formulations. AGT Ltd, Bradford. September 2008 - September 2009. £26.349K.
In-vitro characteristics of Bramitob from a jet nebuliser. Chiesi Pharmaceuticals. September 2008 - February 2009. £15K.
The effect of inhalation flow and inhalation volume on the dose emission of dry powder inhalers. Orion Pharma. April 2009 - July 2009. £37,5K.
In-vitro dose emission characteristics of salbutamol from a PocketFlow Space. NHS Innovations East. June 2009 - October 2009. £15K.
Spray drying of budesonide hydrogel formulations. Intelligent Formulations. May 2011 - October 2011. £13.532K.

In-vivo studies
Inhalation characteristics of patients using a dry powder inhaler, Teva Pharmaceuticals. April 2008 - March 2009. £46.090K.
Comparison of the AeroChamber Plus Flow-Vu and the AeroChamber Plus spacers in asthmatic children. Truddell Medical International InC. April 2009 - April 2011. £36K
Inhalation characteristics of patients when they use a Spiromax and a Turbuhaler dry powder inhaler. Teva Pharmaceuticals. January 2011 - June 2011. £105K
Inhalation characteristics of patients when they use a Spiromax and an Accuhaler dry powder inhaler. Teva Pharmaceuticals. June 2011 - April 2012. £102.5K
The i-Breathe Study. Teva Pharmaceuticals. September 2012 – May 2013. £51K.
A randomised, double-blind placebo controlled trial of the effectiveness of low dose oral theophylline as an adjunct to inhaled corticosteroids in preventing exacerbations of chronic obstructive pulmonary disease. HTA £2.1m (multicentre study – lead applicant Professor David Price, Professor of Primary Care Respiratory Medicine, Department of General Practice and Primary Care, University of Aberdeen). July 2013 – current. £2.1m

Ex-vivo studies

The effect of inhaled volume and acceleration rate on the dose emission of dry powder inhalers. MundiPharma. September 2010 – July 2011. £44K.

The outputs have been accepted in peer-reviewed journals with an international audience and have generated requests for the PI to give invited plenary lectures at international conferences and symposia.

4. Details of the impact

Research by the University of Huddersfield has played a key role in offering solutions to the issues with inhaler therapeutics experienced by the scientific and clinical community. More importantly, the knowledge that has emerged from these studies is passed onto patients suffering from respiratory diseases.

One of the most significant ways in which this has been achieved is through major involvement in developing “gold standard” clinical guidance. Chrystyn was a member (and leading author) of the joint European Respiratory Society / International Society of Aerosols in Medicine Task Force that produced consensus guidelines (2011) for all healthcare professionals on the use of inhalers [5.1]. This multidisciplinary collaboration has provided clear, up-to-date recommendations that enable prescribers to choose the aerosol delivery device most suitable for their patients and to ensure their patients "can and will use" these devices correctly. The recommendations drew on several elements of the research carried out at Huddersfield, chief among them the importance of the delivery device; the widespread failure to adhere to an optimum treatment regime; the relationship between inhalation, resistance and lung deposition in the use of dry power inhalers; the significance of patient inhalation profiles; and the risk of a deterioration in treatment efficacy if an inhaler is substituted for a different device at the prescribing or dispensing stage without involving the patient. Subsequent work [5.2, 5.3] has continued to build on this guidance.

The Global Initiative for Asthma (GINA) has also acknowledged the significance of Chrystyn’s work in informing guidelines on asthma management with inhaler use in particular. GINA’s Global Strategy for Asthma Management and Prevention, (revised 2012 and next revision in 2014), presents a comprehensive plan to manage asthma, with the goal of reducing chronic disability and premature deaths while allowing patients to lead productive and fulfilling lives. Over the past 6 years Chrystyn's work has received international recognition. Professor Tari Haahtela [5.4], a board member of both GINA and the World Allergy Organisation (WAO), has described Chrystyn’s work as “outstanding... both innovative and practical”, adding: “His observations have been rapidly implemented to the practice of therapy – e.g. development of better inhalers in terms of drug delivery and handiness to use.”. Professor Peter Barnes [5.5], a member of the Science Committee of GINA and the Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines, has praised Chrystyn’s “major contribution” in the field and Professor Eric Bateman. [5.6], a member of GINA Science Committee and Chairman of its Board states “Internationally, he is an acknowledged leader in the field and has provided insights and methodologies to optimize the use of inhalation therapies”.

Chrystyn’s expertise has been further recognised through other major international organisations’ use of his techniques. In 2011 the International Primary Care Respiratory Group (with Chrystyn as a major collaborator) – whose overarching mission is to raise standards of care in individual countries and globally through collaborative research, innovation and dissemination of best practice and education – began iHARP [5.7], a study involving 5,000 patients in Western Europe, Scandinavia and Australia, which aims to validate objective methodologies to help healthcare professionals offer patients more effective inhaler training. From 2013 Chrystyn’s methods and findings are being used in two further studies: HITEC is investigating how adults with asthma and chronic obstructive pulmonary disease (COPD) use their inhalers, and ELIOT is assessing how well asthma patients maintain the correct use of their inhalers. Professor David Price [5.8], Managing Director of Research in Real Life (RiRL) Ltd, a key stakeholder in these three studies, has remarked on the importance of Chrystyn’s “unique objective methods” in informing strategies to improve asthma care both nationally and internationally. Such collaboration has been extended to Huddersfield’s involvement in a forthcoming £2.1m National Institute for Health Research Health

Technology Assessment project to identify the synergy between low-dose theophylline and inhaled corticosteroids in COPD [5.9] at seven UK clinical excellence centres.

Chrystyn's research has also resulted in extensive engagement with the pharmaceutical industry. A number of key commercial developers have drawn on his expertise in clinical studies to optimise inhalation techniques and others to introduce new in-vitro methodologies to more closely mimic how patients use inhalers. Such in-vivo/in-vitro work is widely acknowledged as difficult for industry-based researchers to undertake, since there is almost always a perceived conflict of interest. The on-going work is adapting compendial methods to replace mechanical inhalation simulations by those achieved by patients. World-renowned inhalation technology specialist Dr Jolyon Mitchell [5.10], Scientific Director of Canada's Trudell Medical International, is among the leading international experts to acknowledge the value of Chrystyn's contribution.

5. Sources to corroborate the impact

1. Laube, BL, Janssens, HM, de Jongh, FHC, Devadason, SG, Dhand, R, Diot, P, Everard, ML, Horvath, I, Navalesi, P, Voshaar, T, and Chrystyn, H (2011): ERS/ISAM Task Force Consensus Statement: Recommendations on What the Pulmonary Specialist Should Know about the New Inhalation Therapies, *European Respiratory Journal*, 37(6), 1308-133, doi: 10.1183/09031936.00166410

2. Inhaler Error Steering Committee: Price, D, Bosnic-Anticevich, S, Briggs, A, Chrystyn, H, Rand, C, Scheuch, G, and Bousquet J (2013): Inhaler Competence in Asthma: Common Errors, Barriers to Use and Recommended Solutions, *Respiratory Medicine*, 107(1), 37-46, doi: 10.1016/j.rmed.2012.09.017

3. Price, D, Chrystyn, H, Corrigan, C, Rana, S, South, G, and Thomas, M: (2013) The Primary Care Management of Asthma in Real-Life Settings, *Guidelines in Practice*, 49, 1-5. http://www.eguidelines.co.uk/eguidelinesmain/guidelines/summaries/respiratory/wp_asthma_real-life.php

4. Professor Tari Haahtela, board member, Global Initiative for Asthma and World Allergy Organisation.

5. Professor Peter Barnes. Science Committee of Global Guidelines for Asthma (GINA) and COPD (GOLD) and a member of the Aerosol Drug Management Improvement Team (ADMIT).

6. Professor Eric Bateman, member of GINA Science Committee and Chairman of its Board.

7. iHARP project – https://www.iharp.org

8. Professor David Price, Managing Director, Research in Real Life Ltd

9. NIHR HTA project – http://www.hta.ac.uk/project/2990.asp

10. Professor Jolyon Mitchell, Scientific Director, Trudell Medical International