
Monograph:
Slack, R., Ward, S., McCabe, C. et al. (2 more authors) (1998) The transition to CFC-free inhalers. Other. ScHARR Occasional Paper (98/1). ScHARR (School of Health and Related Research), University of Sheffield , Sheffield. ISSN 1900752069

June 1998

THE TRANSITION TO CFC-FREE INHALERS

Russell Slack
Sue Ward
Chris McCabe
Jean Peters
Ron Akehurst

ScHARR
(School of Health and Related Research)
University of Sheffield

ScHARR Occasional Paper no. 98/1

Published by ScHARR (School of Health and Related Research), University of Sheffield

ISBN 1 900752 06 9

For further copies:

Alison Ring
Information Resources
ScHARR
Regent Court
30 Regent Street
Sheffield
S1 4DA

Tel: (0114) 222 5420
Fax: (0114) 272 4095
Email: scharrlib@sheffield.ac.uk

Price: £10.00 per copy (inc. p & p)
By cheque payable to: University of Sheffield

School of Health and Related Research

AN INTRODUCTION TO ScHARR

ScHARR, The School of Health and Related Research, is a large, multidisciplinary research centre located near the centre of Sheffield. It forms the northern arm of the Trent Institute for Health Services Research which also includes centres at Nottingham and Leicester Universities. The staff at the School are drawn from a wide range of disciplines and backgrounds, embracing epidemiology, health economics, management sciences, medical sociology, medical statistics, nursing research, operational research, primary care, psychology, information science and public health medicine. This broad base of skills, together with the School's close ties with local NHS Trusts and Health Authorities, makes it uniquely placed to conduct applied and methodological Health Services Research to the highest quality.

AIMS OF ScHARR

The aims of ScHARR are:

- to conduct and promote within the University, Health Services Research (HSR), judged to be excellent both nationally and internationally;
- to deliver the highest standard of teaching in HSR and related subjects;
- to provide research and consultancy services in HSR to clients outside the University, particularly to NHS Trusts and Authorities but also to other public sector bodies and private organisations;
- to be an active and vigorous member of the Trent Institute for Health Services Research.

Professor Ron Akehurst, Director

AUTHORS

Russell Slack is a Research Associate at ScHARR

Sue Ward is a Senior Operational Research Analyst at ScHARR

Chris McCabe is a Lecturer in Health Economics at ScHARR

Jean Peters is a Research Fellow at ScHARR

Ron Akehurst is Deputy Dean & Chair of the School Board at ScHARR

ACKNOWLEDGEMENTS

The authors would like to acknowledge the assistance of all the persons who attended the seminar to discuss an earlier draft of this paper, particularly Peter Golightly, Keith Doran, Charles McGarrity and Helen Hulme. We would also like to acknowledge the assistance of Professor Tim Higginbottom as well as Dr Paul Anderson and Maria Read of the Sheffield Asthma Interest Group.

The work presented in this paper was funded by 3M Healthcare Limited. 3M Healthcare Limited produce Airomir™ inhalers.

The views expressed within the paper are those of the authors alone, and any errors are their responsibility.

CONTENTS

LIST OF TABLES AND FIGURES **Page**

EXECUTIVE SUMMARY

The pressurised metered dose inhaler (pMDI) is the mainstay of treatment for asthma and is widely used in the treatment of other chronic obstructive airways diseases. The majority of pMDIs use chlorofluorohydrocarbon (CFC) based aerosols, however, the United Kingdom is committed to the removal of CFCs from all medicinal products by 1999, in accord with the Montreal Protocol. Asthma is one of the largest areas of prescribing within the NHS and therefore the potential impact of the transition to CFC-free therapies is large. This enforced change offers a unique one-off opportunity for the Health Service to approach, and manage, the transition in a co-ordinated manner which maximises patient benefit and minimises potentially large costs.

Patients and doctors will wish to achieve the change with the minimum of inconvenience whilst maintaining effective patient management. Those companies which manage to produce CFC-free versions of their products will emphasise this in order to maximise the probability of maintaining their current market share. Those companies which produce alternative therapies will put significant efforts into capturing as large a share as possible of those patients forced to switch. The potential cost implications of the change appear sufficient to justify careful management of the transition by Health Authorities.

This paper explores two sets of change scenarios. Under the minimum change scenarios the potential cost to the NHS of the transition of bronchodilators ranges from £169k through to just under £4 million; the transition for steroids might incur costs of up to £3 million. Whilst these figures are small relative to total expenditure they are still significant sums of money. The maximum change scenario suggests that the cost of transition for bronchodilators could lie between £1.4 million and £120 million, whilst for steroids these figures range between a potential saving of nearly £10 million and a cost of £150 million. These figures are large in a

relative as well as an absolute sense. These figures are obviously worst case scenarios, however, at the present time there is no information which would allow purchasers to predict where between the minimum and maximum change scenarios the actual change will lie.

On the basis of these analyses, it is argued that there could be significant advantages to the NHS in taking a co-ordinated regional and/or national approach to guidance for clinicians on switching patients from their current CFC-containing to CFC-free products. Producing evidence-based guidance would help to manage the financial implications of the transition and potentially improve the quality of care provided to people with asthma. It would be consistent with the commitment to excellence set out in the recent White Paper and would avoid the problems of duplication of activity in different parts of the NHS and the risk of conflicting recommendations.

1. INTRODUCTION

The pressurised metered dose inhaler (pMDI) is the mainstay of treatment for asthma and is widely used in the treatment of other chronic obstructive airways diseases. In 1995 83% of all prescriptions for short acting β2-agonists and 78% of all prescriptions for inhaled steroids were for pMDIs.[1] The transition from chlorofluorohydrocarbon (CFC) containing pMDIs is not an optional process. The Montreal Protocol on Substances that Deplete the Ozone Layer banned all manufacturing and use of CFCs on 1st January 1996 with an 'essential use' exemption for pMDIs.[2] The United Kingdom Government has stated that the Medicines Control Agency is complying with European Regulations and the Montreal Protocol, and ***'...is committed to the removal of CFCs from all medicinal products by 1999'*** .[3]

This 'forced' transition should be seen by the Health Service as an opportunity to influence current prescribing trends. It is widely acknowledged that existing patterns of prescribing for asthma are less than optimal. The proportion of generic prescribing, although variable, is surprisingly low in many areas and the 1995 British Guidelines on asthma management suggest that '...many well controlled patients are overtreated with inhaled steroids'.[4] Therefore, if managed efficiently, the transition to CFC-free therapies offers a unique one-off opportunity to address poor prescribing. Carefully managed, this transition offers scope for cost-savings, where feasible, by transition to generics or cheaper branded therapies. Consideration should also be given to 'stepping down' the doses of inhaled steroids for patients whose asthma is well controlled.

The objective of this paper is to consider the implications of this change for prescribing practice costs. For simplicity, the paper considers options involving the transition from current Salbutamol usage to a range of alternatives, and the transition from current Beclomethasone usage to a range of alternatives. These examples, which represent the majority of the current

pMDI asthma market, are meant purely as an initial guide to the ***potential*** financial consequences which might result from the forthcoming change.

The paper starts with a brief summary of the epidemiology of the relevant respiratory conditions and a description of the range of treatments currently available. The second section considers the published evidence on the effectiveness and safety of CFC-free pMDIs compared to current pMDI devices. The third section considers the context within which the transition is taking place and describes the analytical approach adopted in the paper to assess the potential cost implications of the transition to CFC-free inhalers. The final section of the report describes the results of the analysis, assesses their importance to the NHS and explores possible options for purchasing authorities, and the NHS generally, to manage the transition to CFC-free therapies.

2. EPIDEMIOLOGY

2.1 Background

Lung related breathing problems can be divided into two groups: '*obstructive*' in which the airways are narrowed and air movement through them in a given period of time is reduced and; '*restrictive*' in which the useful volume of the lung is reduced by damage or scarring. It is in the first group that symptoms can be eased through the use of bronchial smooth muscle relaxants and anti-inflammatory drugs.

The group of diseases which cause chronic air flow obstruction, such as asthma (ICD9 493), chronic bronchitis (ICD9 491) and emphysema (ICD9 492) account for a substantial proportion of ill health. This is evident by the impact these diseases have upon the health service in terms of workload and expenditure. It has been estimated that, in England and Wales, over 30% of patients consult their general practitioner for respiratory illnesses and 11% of the total pharmacy expenditure is attributable to chronic obstructive pulmonary disease (COPD) and allied conditions, representing the greatest single item.[5]

Table 1 gives mortality rates for the three diseases based on reported underlying cause of death.

Table 1: Mortality Rates by underlying cause (England and Wales) per one million population

	All ages		< 16 years		> 64 years	
	Males	Females	Males	Females	Males	Females
Total Population	24.4 million	26.4 million	5.4 million	5.2 million	3.3 million	6.1 million
Chronic Bronchitis (ICD 491)	70	36	0	0	474	138
Emphysema (ICD 492)	52	23	0	0	343	83
Asthma (ICD 493)	21	34	1	2	94	108
COPD and allied diseases (ICD 490-496)	652	443	2	3	4474	1700

Source: Mortality Statistics, Series DH2 number 22. Cause, England and Wales. London: Stationary Office 1995 (modified).[6]

2.2 Management of 'Obstructive' Diseases

Relief of obstructive diseases can be facilitated through various options but the two main methods are by bronchodilators (relievers) or anti-inflammatory preparations (preventers). Bronchodilators relax airway smooth muscle through the stimulation of β_2-adrenoceptors. There are two classes of β_2-agonists, short-acting and long-acting. Short-acting treatments (including Salbutamol and Terbutaline amongst others) have a rapid onset of action and relieve symptoms for 3 to 6 hours. These should be used in patients with normal lung function and infrequent symptoms or prophylactically before exercise and, should be administered by inhalation as required rather than on a regular basis. Anybody who has significant symptoms, either with or without, normal lung function should be on more than just a simple bronchodilator. Long-acting alternatives can be used to improve symptom control, particularly at night or with exercise induced symptoms. Anti-inflammatory corticosteroids prevent attacks by reducing airway hyper-responsiveness and bronchial mucosal inflammatory reactions such as oedema and mucous secretion. Inhaled steroids such as Beclomethasone, Budesonide and Fluticasone, are the mainstay of prophylactic therapy in both adults and children who need to inhale a bronchodilator more than once daily or who have nocturnal symptoms.

Medication may be taken orally or by inhalation with the latter being the more common mode of treatment. Most health professionals consider the inhaled route to be the best method of delivering drugs to the respiratory system. Inhaled treatments are dispensed in the form of particulates or as a metered dose aerosol spray. For the latter a propellant is required. Currently CFCs are most frequently used but CFC-free pressurised inhalers are now available.

Four types of inhaled delivery system are in use.[7] Inhaled drugs are most frequently prescribed as pMDIs. These devices deliver medication as an aerosol and are available in two

forms: one actuated manually to co-ordinate with inspiration and another that is breath actuated. However, both require co-ordination between actuating the delivery of drug by squeezing the device coupled with slow inspiration by the patient and are therefore unsuitable for the young, people with arthritis and many elderly persons. In the UK pMDIs are the cheapest type of device on the market and are often the device of choice for those patients able to use them.[7]

Dry powder devices (DPIs) are either single or multiple dose. These devices are similar to breath-actuated devices in that they require no co-ordination between actuation and inhalation by the patient. Such devices do require that the patient has sufficient breath to drive the 'fan', and are therefore unsuitable for some users.

Other options include, pMDIs in combination with a large volume spacer, which facilitates delivery of the drug to the lungs by reducing the need for good co-ordination by patients when actuating the pMDI, thus enabling the delivery of inhaled drugs to the young and elderly. Finally, Nebulisers driven by compressors deliver higher doses of drug to the airways than is usual with standard inhalers. Nebulisers are used to treat acute exacerbations of asthma to patients (such as children) unable to use other devices.

2.3 Scale of the Problem for a Typical Health Authority

In 1993, prescriptions for asthma accounted for 7% of all NHS prescriptions. Their net ingredient cost was 11% of that for all prescriptions.[8] In the last 10 years, prescriptions for asthma have increased by 75%, and over the same period GP consultation rates have more than doubled. The National Studies of Morbidity in General Practice reported doctor consultation rates for asthma of 8% in children aged 0 to 15 and 4% overall for all patients.[8]

The prescription dispensing cost for asthma in 1995/96 has been calculated as £101 million of the total £834 million spent on all diseases. On the assumption that the item prescribing profile across all the Regional Health Authorities is similar; that overall costs of prescribed items per disease are similar, and given that Trent as a region accounted for 10.3% of the total number of NHS prescription items dispensed in 1996, as a very crude approximation, it can be estimated that Trent spent around £10.4 million on NHS prescription items for asthma in 1995/6.[9]

3. EVIDENCE ON EFFECTIVENESS

3.1 Background

One CFC-free metered dose inhaler, containing Salbutamol, is currently available (Airomir™ inhaler; 3M Pharmaceuticals) for the treatment of asthma, and it is expected that others will be developed and marketed by those pharmaceutical companies with CFC-containing asthma products in due course. Airomir™ inhaler has been shown to be clinically comparable to CFC-containing pMDIs. [10,11] For the purpose of the analysis contained within this paper it is assumed that there will be equal efficacy between the new and old treatment options.

A number of randomised clinical studies have been conducted to compare the safety and/or efficacy of Airomir™ inhaler versus a CFC-Salbutamol inhaler or placebo. The published studies are described in Appendix 1 and the unpublished studies in Appendix 2. All of these papers (published and unpublished) concluded that there were no statistically significant differences between the Airomir™ inhaler and CFC Salbutamol. These studies[10,12,13] were all randomised studies, published in clinical journals, whose findings were that safety and efficacy data indicated that the CFC-free inhaler provided similar results to CFC Salbutamol inhalers. Literature on alternatives to Beclomethasone treatments are not yet available.

3.2 Conclusion on Direction of Evidence and its Quality

The quality of evidence is limited, restricted as it is to a small number of published papers. These papers however are randomised, blinded trials encompassing a range of sample sizes. They offer evidence of statistical comparability between a new CFC-free pMDI (Airomir™) and older CFC-Salbutamol inhalers. In addition, other evidence has shown that the dose delivered by a standard pMDI can vary depending upon whether it is stored 'valve up' or 'valve down'. Reformulation in the new hydrofluoroalkane (HFA) propellant has necessitated the development of a new valve system for the pMDI, which is not affected in the same way.

4. PHASING OUT CFC-CONTAINING pMDIs

At the present time a small number of (large) companies supply the vast majority of pMDI therapies to the NHS. The cost of prescribing pMDIs is one of the largest single cost items in the NHS budget. Prescribing in COPDs is generally considered to be less than optimal, and the change to a culture of alternative therapies is gradual. Thus, the context in which phasing out will take place is one where the NHS would like to see significant changes in current prescribing activity, but there are significant structural barriers to that change.

The implication of the Montreal Protocol is that change is unavoidable. Patients and doctors will have no choice but to change to another therapy. The great uncertainty is what therapies will be available. At the present time, there is only one CFC-free inhaler licensed for use in the UK. [14] However, one large producer of pMDIs has already produced literature advising doctors and patients that CFC-free equivalent products will be available at the time of the phase out, although the company does not presently market any CFC-free products. Given the large value of the current pMDI market, it is reasonable to assume that all the big producers of CFC-containing asthma products have development programmes aimed at delivering CFC-free replacements on the market in time for the phase out of CFC-containing products. This said, the investment necessary to produce a CFC-free pMDI is such that it can be safely assumed that ***not all*** products presently available will be available after the Montreal Protocol has been implemented.

It is expected that individual companies will be launching their own range of CFC-free products over an extended period of time, thus the introduction of new therapies will be a gradual process, rather than occurring all at once. This extended availability period is partly due to formulation problems, especially with Beclomethasone. During the transition period there will be dual availability of both CFC and CFC-free pMDI versions of the same product,

therefore it is essential that a large amount of educational information is available for professionals and patients alike, and that additional patient counselling is available for patients during the transition period. Therefore, a proactive approach at a local level could help reduce unnecessary disruption to effective patient care and help minimise the potential financial pressures which an unplanned transition could impose.

5. COST ANALYSIS

When CFC-containing pMDIs are phased out in 1999, GPs will face the option of converting patients to a CFC-free pMDI or to a dry powder inhaler. In order to investigate the cost implications of transition a model was set up to examine a range of transition scenarios.* The cost and dose assumptions for these scenarios are presented in Appendix 3. A minimum and a maximum change scenario have been described. It is assumed within the scenarios that a switch to the alternatives is possible, though of course in practice not all individuals are capable of using alternative treatments. It should be stressed that these figures are only meant as a general guide. These costings apply to the National situation only, figures for a Health Authority setting are presented in Appendix 4.

5.1 Description of Costing Scenarios

There is a possibility that the market will undertake the transition to alternative CFC-free options under its own accord. Here, the issue is to try and quantify the results of a minimal change whereby only a very small proportion of the market will *not* be able to undertake the transition to CFC-free equivalents, thus the **minimum** transition that will be required. A recent unpublished study (confidential personal communication, J Raftery) found that 60% of prescribing for bronchodilators was for generics, and around 40% of prescribing for steroids was for generics. Applying these figures to the national situation[15] provides an estimate of the total number of units of generic products which might be contestable. In keeping with the assumption that only the minimum shifts to alternatives will be adopted, the analysis examines the potential cost of just 5% of these generic units not having an equivalent CFC-free alternative following the transition, and thus facing the potential of a shift to the alternatives identified within the scenarios.

* These figures are available from the authors

There is also the other extreme, that of the **maximum** transition and these scenarios examine a total switch from current prescribing of pMDIs to a single alternative CFC-free therapy. It is acknowledged that a complete switch to any one of the alternative methods of treatment is unlikely, but these options provide an insight into the likely cost implications.

Other options exist, but those presented were considered to be a representative selection of the extremes of choices that purchasers will be forced to consider during the phasing out of CFC-containing pMDIs.

5.2 Salbutamol Options

Currently, the only bronchodilator available in non-proprietary form is Salbutamol. One CFC-free pMDI (Airomir) is presently available which has been shown to be at least as effective as its CFC-containing predecessor. The product is priced above its generic equivalents, but at the same price as the CFC-containing equivalent. The costs of moving to alternative therapies are presented in Table 2.

Table 2: National cost of moving to alternatives for Salbutamol users

Scenario	Minimum	Maximum
Salbutamol CFC-free	£169,680	£1,454,400
Terbutaline DPI	£3,745,080	£120,634,400
Cheapest branded alternative	£315,120	£6,302,400

5.3 Beclomethasone Options

Currently, there are no CFC-free Beclomethasone steroids available, though it is expected that two pharmaceutical companies will launch products during 1998. Therefore, the scenarios presented in table 4 are hypothetical. Options for transition include CFC-free products which are expected to be priced at present generic prices, dry powder alternatives, or transition to Fluticasone. The latter represents an expensive option.

Table 3: National cost of moving to alternatives for Beclomethasone users

Scenario	Minimum	Maximum
Beclomethasone extra-fine CFC-free	(£5,601)	(£9,663,448)
Budesonide (1:1)	£3,188,689	£150,051,362
Budesonide (2:1)	£701,087	£25,671,233
Fluticasone	£2,197,232	£101,278,365
Cheapest branded alternative	£312,770	£6,255,392

note: *brackets denote a saving*

5.4 Discussion

The phasing out of CFC-containing pMDIs is certain. Equally certain is that the pharmaceutical companies will approach this event with the intention of minimising the negative impact and maximising the positive impact of the changes on their revenues. Patients and doctors will wish to achieve the change with the minimum of inconvenience whilst maintaining effective management of the patients' disease. Those companies which manage to produce CFC-free versions of their products will emphasise this in order to maximise the probability of maintaining their current market share. Those companies which produce alternative therapies will put significant efforts into capturing as large a share of those patients forced to switch as possible. At the present time there is no way of knowing what proportion of the market will fall into each category. However, the potential cost implications of the change appear sufficient to justify careful management of the transition by Health Authorities.

In addition to minimising the cost of transition, there are several other advantages for Health Authorities preparing a co-ordinated changeover within a geographical area. Such a changeover reduces the likelihood of dual availability of both CFC-containing and CFC-free products. Leading on from this, the changeover of most patients during a focused time period will facilitate minimising the primary/secondary care problems where patients can be prescribed products which may, or may not, contain CFCs, aiding compliance with the slightly different new inhalers.

There are a number of potential fora in which Health Authorities can consider influencing the way the transition is managed and which patients are switched to which therapy.

- Joint Areas Prescribing Groups
- National Asthma Campaign/Local Asthma Interest Groups
- Primary Care Commissioning Groups
- Postgraduate Medical Education Programmes
- British Thoracic Society

Guidance on rational prescribing in the context of the phase out of CFC-containing pMDIs can be both developed and disseminated in any, or all, of these fora. However, this would require purchasing authorities to decide that the risk of not managing the transition process was sufficient to justify the allocation of resources for that purpose.

There are a number of factors which this analysis is not able to take into account but which should be borne in mind.

- The legislated change in prescribing offers the opportunity to improve the quality of health care provided by supporting rational prescribing choices; e.g. moving patients for whom inhaled steroids and/or β2-agonists are not the best therapy, onto different therapies rather than CFC-free equivalents, and possibly moving stable patients 'down' the scale of therapies recommended by the British Thoracic Society.[16]

- Those companies which do not manage to have CFC-free versions of their products are likely to attempt to encourage switching to alternative products in their own range rather than allow switching to CFC-free products from other companies. Even those companies which do produce CFC-free equivalents are likely to compete for a share of those patients

for whom CFC-free equivalent products are not available. They will not necessarily aim for direct substitution if they also produce a dry powder product.

The transition offers GPs and Health Authorities, a unique opportunity to develop strategies which both minimise the costs of the transition and advocate the push towards more cost-effective prescribing; a strategy that offers maximum benefit to both patients and the health service.

6. OPTIONS FOR PURCHASERS

In identifying the potential way forward for purchasing authorities, the uncertainty about the likely situation at the time of the transition is a significant limiting factor. Therefore, the following quite general options reflect this uncertainty.

1. Do Nothing: - This option involves no expenditure on the part of purchasing authorities in the short term, but carries the risk of significant additional expenditure in two years time. It also forgoes the opportunity to improve the quality of prescribing in the management of the affected group of diseases. This option also carries the risk of the industry managing the change throughout the transition period, to meet its own agenda.
2. Independent local guidance on reviewing and switching patients between products using an evidence based approach: - This option addresses the issue but will carry the cost of significant duplication of activity at different purchasing authorities. It also carries the risk of conflicting guidance between different authorities impairing the ability of purchasers to influence the behaviour of prescribers.
3. Co-ordinated regional/national guidance on reviewing and switching patients between products using an evidence based approach: - This option addresses the issue of directing care to optimise the effectiveness of prescribing and manage the scale of additional expenditure. It also avoids the problem of duplication and the risk of conflicting recommendations.

The area is changing very rapidly, and as a consequence there are clearly risks of NHS expenditure being increased with little or no benefit for patients. It is difficult to give clear-cut guidelines to Health Authorities on appropriate purchasing which will be valid for very long. The evidence, therefore, should be reviewed again one year after the switch to CFC-free products has taken place.

REFERENCES

1. *IMS Medical Data Index* 1995; 3 (4).

2. Gerald Malone MP, Secretary of State for Health. Hansard: Written Answers; 8 July 1996.

3. United Nations Environment Programme Technology and Economic Assessment Panel of the Montreal Protocol on Substances that Deplete the Ozone Layer. *Part III: Update of the 1994 TOC Aerosols Report and the MDI Transition Strategy*. TEAP, 1996.

4. The British Asthma Guidelines Co-ordinating Committee. British Guidelines on Asthma Management. 1995 Review and Position Statement - Introduction. *Thorax* 1997; 52: S1-24.

5. NHS Executive. *Burdens of Disease* : a discussion document. Department of Health, 1996.

6. Office for National Statistics. *Mortality Statistics, Series DH2 (22) Cause, England and Wales*. London: HMSO, 1995.

7. Levy ML Metered Dose Inhalers: Current and Future Uses. *British Journal of Clinical Practice* 1995; Supplement 79: 10-12.

8. Department of Health. *Asthma: An Epidemiological Overview*. London: HMSO, 1995.

9. McGuigan S. *Compendium of Health Statistics.* 10th edition. London: Office of Health Economics, 1997

10. Kleerup EC, Tashkin DP, Cline A, Ekholm BP . Cumulative dose-response study of non-CFC propellant HFA-134a Salbutamol sulfate metered dose inhaler in patients with asthma. *Chest* 1996; 109: 702-707.

11. Bleeker ER. Twelve week efficacy and safety comparison of AiromirTM and CFC Salbutamol. *British Journal of Clinical Practice* 1995; Supplement 79: 35-36.

12. Harrison LI, Donnell D, Simmons JL, Ekholm BP, Cooper KM, Wyld PJ. Twenty-eight day double-blind safety study of an HFA-134a inhalation aerosol system in healthy subjects. *Journal of Pharmacy and Pharmacology* 1996; 48: 596-600.

13. Dockhorn R, van den Burght JA, Ekholm BP, Donnell D, Cullen MT. Clinical equivalence of a novel non-chlorofluorocarbon-containg Salbutamol sulfate metered-dose inhaler and a conventional chlorofluorocarbon inhaler in patients with asthma. *Journal of Allergy and Clinical Immunology* 1995; 96: 50-56.

14. British National Formulary. Number 33 (March 1997).

15. British Pharmaceutical Index. December 1996. International Medical Statistics Ltd

16. Monthly index of Medical Specialties (March 1997)

Appendix 1: Published results of Clinical Studies of Airomir™ inhaler versus a CFC-Salbutamol inhaler or placebo.

Details of the Study	Findings
Randomised, double-blind, four week comparative study of HFA-134a and CFC propellant systems in 16 healthy male volunteers (age range 18-55 years). Subjects randomly allocated to receive one of two treatments, either HFA-134a or CFC. In the HFA-134a group, four subjects received 16 inhalations per day for two weeks followed by 32 inhalations per day for two weeks and four subjects received 32 inhalations per day for two weeks followed by 16 inhalations per day for two weeks. In the CFC group the number of subjects were four and four respectively for 16/32 inhalations and 32/16 inhalations. **Harrison L I et al. Safety and tolerability of HFA-134a in healthy volunteers. J Pharm Pharmacol 1996, 48:596-600.**	No clinically significant abnormalities or trends in safety parameters or adverse events were observed between groups. The study demonstrated that both propellant systems were well tolerated in all subjects.
Designed to determine the dose of Airomir™ inhaler which produces efficacy comparable with two puffs of CFC-Salbutamol in asthmatic patients. Twenty-six patients were entered into a randomised, double-blind, double-dummy, placebo-controlled, six-period crossover study. During each of the six study periods patients received a total of four inhalations comprising one, two or three inhalations of Salbutamol sulphate in the HFA-134a propellant system plus placebo, or one of two inhalations of Salbutamol CFC inhaler plus placebo or four inhalations of placebo. **Dockhorn R et al., Clinical equivalence of a novel non-chlorofluorocarbon-containg Salbutamol sulfate metered-dose inhaler and a conventional chlorofluorocarbon inhaler in patients with asthma. J Allergy Clin Immunol 1995, 96:50-56**	There were no clinically or statistically significant differences between two puffs of either Airomir inhaler or CFC-Salbutamol as measured by FEV_1. Insufficient power to test the relevant potencies of the active drugs at the different doses, but based on mean FEV_1 data, the effect of the two inhalations of Airomir inhaler most closely matched the effect of two inhalations of CFC-Salbutamol.
Randomised, single blind, two-period crossover study to compare the safety and efficacy of Airomir™ inhaler and a CFC-Salbutamol inhaler in a cumulative dose response design. Twenty-four patients with a history of asthma received consecutive doses of 1, 1, 2, 4 and 8 inhalations (total 16 inhalations) of Airomir inhaler or CFC-Salbutamol at 30 minute intervals during each study period. **Kleerup E C et al. Cumulative dose-response study of non-CFC propellant HFA-134a Salbutamol sulfate metered-dose inhaler in patients with asthma. Chest 1996, 109:702-707**	Safety and efficacy data indicate that Airomir™ inhaler is clinically and statistically equivalent to a CFC-Salbutamol inhaler in this cumulative dose-response design. These results suggest that Airomir inhaler would be an accepTable substitute for CFC-Salbutamol inhaler.

Appendix 2: Unpublished results of Clinical Studies of Airomir™ inhaler versus a CFC-Salbutamol inhaler or placebo.

Details of the Study	Findings
Randomised, double-blind, three period crossover study in 12 healthy male volunteers. On each of the three consecutive study days subjects received cumulative rising doses of 1, 1, 2, 4, and 8 puffs (total of 16 inhalations) separated by 30 minutes, allocated to three treatments; HFA-134a propellant system; HFA-134a + Salbutamol sulphate and; CFC propellant system. Parameters assessed included; pulmonary function tests, biochemistry, 12 lead ECGs, blood pressure, heart rate, tremor (by accelerometer) and serum potassium. **Data on file, SL34-PB-01-91-GB-1. Safety and tolerability of the HFA-134a propellant system, Airomir™ inhaler and CFC propellant system in healthy volunteers.**	The administration of HFA-134a propellant was as safe as the administration of the commonly used CFC propellants in healthy volunteers. Airomir inhaler caused no unexpected safety concerns in these subjects.
Randomised, multicentre, single-blind, four period, crossover study designed to compare the safety and efficacy of Airomir inhaler, HFA-134a placebo and CFC-Salbutamol sulphate in 24 patients with asthma. Inhaled steroids were allowed as concomitant medication. During each study period, patients received consecutive doses of 1, 1, 2, 4 and 8 inhalations of Airomir inhaler, CFC-Salbutamol sulphate, or HFA-134a placebo 30 minutes apart for cumulative dose levels of 1, 2, 4,8 and 16 inhalations. There was a 1 to 8/day washout between each study period. CFC-Salbutamol sulphate was given in 2 periods to test the within subject variability of response. **Data on file, 1044-SILV. Cumulative dose response study of Airomir™ inhaler, CFC-Salbutamol sulphate versus HFA-134a placebo in patients with asthma.**	Safety and efficacy data indicate that Airomir™ inhaler is clinically and statistically equivalent to CFC-Salbutamol sulphate in this cumulative dose-response design. Results suggest that Airomir inhaler would be an accepTable substitute for CFC-Salbutamol sulphate.
Randomised, double-blind, double dummy, placebo controlled, parallel group, multicentre study designed to compare the long-term safety and efficacy of Airomir inhaler, CFC-Salbutamol and HFA-134a placebo in 565 patients with asthma. Study consisted of a 7 day run-in followed by a 12 week double blind treatment [period. Upon entry into this period, each patient was assigned to one of the three treatments (each treatment being 2 puffs from each inhaler four times daily) according to a stratified (user or non-user of inhaled steroids) randomisation schedule. **Data on file, 1012-SILV. 12 week safety and efficacy study of Airomir™ inhaler, CFC-Salbutamol and HFA-134a placebo in patients with asthma.**	Results of this 12-week study demonstrate that Airomir inhaler was clinically comparable with CFC-Salbutamol in the safety and efficacy parameters measured. In terms of efficacy, both active treatments were significantly better than HFA-134a placebo. No significant drug or propellant related adverse events were reported in the 12 weeks of exposure.

Randomised, open-label, parallel group, age stratified, multicentre study designed to compare the safety and efficacy of Airomir inhaler with a CFC-Salbutamol inhaler over a four week period in 63 children with asthma. patients all had a history of sTable reversible obstructive airways disease (asthma) for at least 6 months prior to entry to the study, with ages ranged between 4 and 11 years of age. Patients randomised to receive Airomir inhaler or CFC-Salbutamol inhaler at a dose of two inhalations four times each day (total 8 inhalations) over the four week study period. **Data on file, 1141-SILV. 4 week safety and efficacy study of Airomir™ inhaler and CFC-Salbutamol inhaler in children with asthma**.	No significant differences were observed between the Airomir inhaler group and the CFC-Salbutamol inhaler group for all efficacy variables analysed. In two well matched groups of paediatric asthma patients, Airomir inhaler, at a daily does of two inhalations, four times a day over a two week period demonstrated comparable safety and efficacy profiles as the CFC-Salbutamol inhaler at the same dosing schedule.
Three month non-interventional study to compare the safety of Airomir™ inhaler with CFC-Salbutamol pressurised metered dose inhaler in the general practice setting. Any patient (adult or child) who required treatment with inhaled Salbutamol was eligible for inclusion. **Data on file, 1178-SILV Three month, open label, non-randomised, non-interventional, observational cohort, post-marketing surveillance study to compare safety of Airomir Inhaler with CFC-Salbutamol pressurised metered dose inhaler in patients prescribed inhaled Salbutamol in the general practice setting.**	There was a tendency for patients prescribed Airomir inhaler to have less severe disease of shorter duration than the CFC-Salbutamol PMDI group. There was no statistically significant difference between the two treatment groups in terms of hospital admissions and other patient/doctor consultations or in the overall incidence of adverse events. Study demonstrates that the safety profile of Airomir inhaler is not significantly different fro that reported with CFC-Salbutamol pMDI products.

Appendix 3: Dose and Cost Assumptions Underlying the Transition Scenarios.

Scenario	Dose Assumptions	Cost Assumptions
Salbutamol CFC-free	1 CFC-free Salbutamol (3M) Unit 100mcg (200 dose) = 1 Salbutamol Unit 100 mcg (200 dose)	1 Unit CFC-free Salbutamol (3M) 100mcg (200 dose) = £2.06
Terbutaline DPI	250 mcg Terbutaline = 100mcg Salbutamol	1 Unit Terbutaline Dry Powder Turbo Device (Astra) 500mcg (100 dose) = 1 Unit Salbutamol 100mcg (200 dose) = £7.96
Fluticasone	25mcg Fluticasone Inhaler (Glaxo) = 50mcg Beclomethasone 50mcg Fluticasone Inhaler (Glaxo) = 100mcg Beclomethasone 125mcg Fluticasone Inhaler (Glaxo) = 250mcg Beclomethasone 50mcg Beclomethasone (200 dose unit) = 1.66 Units of 25mcg Fluticasone Inhaler (Glaxo) (120 dose units) 100mcg Beclomethasone (200 dose unit) = 1.66 Units of 50mcg Fluticasone Inhaler (Glaxo) (120 dose units) 250 mcg Beclomethasone (200 dose unit) = 1.66 Units of 125mcg Fluticasone Inhaler (Glaxo) (120 dose units)	In line with BTS Guidelines 2:1 Flix to Beclo 25mcg Fluticasone Inhaler (Glaxo) = £6.86 50mcg Fluticasone Inhaler (Glaxo) = £11.43 125mcg Fluticasone Inhaler (Glaxo) = £22.86
Budesonide (1:1)	Budesonide is as effective dose for dose as Beclomethasone when delivered from the 2 devices. 1 (200 dose) 100mcg Budesonide = 0.5 (200 dose) 50mcg Beclomethasone 1 (100 dose) 200mcg Budesonide = 1 (200 dose) 100mcg Beclomethasone 1 (50 dose) 400mcg Budesonide = 0.4 (200 dose) 250mcg Beclomethasone	Note: This is in line with recent clinical practice although studies have shown that Lung deposition from the Dry Powder device may be more effective than a MDI - "Lung deposition of Budesonide from a Turbohaler is twice that from a pressurised dose inhaler" (Thorsson et al. Eur Respir J. 1994: 7,1839 - 1844) 100mcg (200 dose) = £18.50 200mcg (200 dose) = £18.50 400mcg (50 dose) = £18.50

Budesonide (2:1)	1 Unit Budesonide Dry Powder Turbo Device = 2 Units Beclomethasone Inhaler 1 (200 dose) 100mcg Budesonide = 1 (200 dose) 50mcg Beclomethasone 1 (100 dose) 200mcg Budesonide = 2 (200 dose) 100mcg Beclomethasone 1 (50 dose) 400mcg Budesonide = 0.8 (200 dose) 250mcg Beclomethasone	Note: This is in line with recent clinical practice although studies have shown that Lung deposition from the Dry Powder device may be more effective than a MDI - "Lung deposition of Budesonide from a Turbohaler is twice that from a pressurised dose inhaler" (Thorsson et al. Eur Respir J. 1994: 7,1839 - 1844) 100mcg (200 dose) = £18.50 200mcg (200 dose) = £18.50 400mcg (50 dose) = £18.50
Beclomethasone extra-fine CFC-free	50mcg Beclomethasone extra fine aerosol CFC-Free (3M) = 100mcg Beclomethasone 100mcg Beclomethasone extra fine aerosol CFC-Free (3M)= 250mcg Beclomethasone	50mcg Beclomethasone extra fine aerosol CFC-Free (3M) (200 dose) = £8.24 100mcg Beclomethasone extra fine aerosol CFC-Free (3M) (200 dose) = £18.02

Appendix 4: Calculations from a Health Authority Perspective

A4.1 Salbutamol Options - Health Authority Perspective

Health Authority cost of moving to alternatives for Salbutamol users

Scenario	Minimum	Maximum
Salbutamol CFC-free	£1,453	£12,456
Terbutaline DPI	£32,074	£1,033,156
Cheapest Branded Alternative	£2,699	£53,976

A4.2 Beclomethasone Options - Health Authority Perspective

Health Authority cost of moving to alternatives for Beclomethasone users

Scenario	Minimum	Maximum
Beclomethasone extra-fine CFC-free	(£48)	(£82,358)
Budesonide (1:1)	£27,301	£1,285,102
Budesonide (2:1)	£6,026	£221,352
Fluticasone	£18,753	£864,516
Cheapest Branded Alternative	£2,665	£53,292

note: *brackets denote a saving*