Review of therapeutically equivalent alternatives to short acting β_2 adrenoceptor agonists delivered via chlorofluorocarbon-containing inhalers

D A Hughes, A Woodcock, T Walley

Abstract

***Background*—To study the transition from metered dose inhalers using chlorofluorocarbons as propellants (CFC-MDIs) to non-CFC containing devices, a systematic review was conducted of clinical trials which compared the delivery of salbutamol and terbutaline via CFC-MDIs and non-CFC devices.**

***Methods*—Papers were selected by searching electronic databases (Medline, Cochrane, and BIDS) and further information and studies were sought from pharmaceutical companies. The studies were assessed for their methodological quality.**

***Results*—Fifty three relevant trials were identified. Most were scientifically flawed in terms of study design, comparison of inappropriate doses, and insufficient power for the determination of therapeutic equivalence. Differences between inhaler devices were categorised according to efficacy and potency. Most trials claimed to show therapeutic equivalence, usually for the same doses from the different devices. Two commercially available salbutamol metered dose inhalers using a novel hydrofluorocarbon HFC-134a as propellant were equally as potent and efficacious as conventional CFC-MDIs, as were the Rotahaler and Clickhaler dry powder inhalers (DPIs). Evidence suggests that a dose of 200 μg salbutamol via CFC-MDI may be substituted with 200 μg and 400 μg of salbutamol via Accuhaler and Diskhaler DPIs, respectively. Terbutaline delivered via a Turbohaler DPI is equally as potent and efficacious as terbutaline delivered via a conventional CFC-MDI.**

***Conclusions*—When substituting non-CFC containing inhalers for CFC-MDIs, attention must be given to differences in inhaler characteristics which may result in variations in pulmonary function.**

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Keywords: inhaled bronchodilators; salbutamol; terbutaline; chlorofluorocarbons (CFCs); metered dose inhalers; CFC-free; hydrofluorocarbons; therapeutic equivalence

Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool L69 3GF, UK
D A Hughes
T Walley

North West Lung Centre, Wythenshawe Hospital, Manchester M23 9LT, UK
A Woodcock

Correspondence to:
Professor T Walley.

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The forthcoming conversion from metered dose inhalers using chlorofluorocarbons as propellants (CFC-MDIs) to non CFC-containing inhalers[1] will affect millions of patients with respiratory diseases in the UK alone. A part of the conversion will be the selection of appropriate alternative inhaler devices, which is dependent upon several factors such as the determination of therapeutically equivalent alternatives, their handling and acceptability by patients, and their cost. Doctors and patients in Europe will be faced with a choice of up to 30 different metered dose inhalers using a novel hydrofluorocarbon HFC-134a as propellant (HFC-MDIs) by the year 2000.[2] At the same time many doctors may take the opportunity to increase their use of dry powder inhalers (DPIs).

It is necessary to define the clinical effectiveness of the newer HFC-MDIs compared with the existing CFC-MDIs. This should be based on properly conducted trials with relevant clinical end points in preference to surrogate markers of efficacy such as drug deposition or pharmacokinetic parameters. This point is reinforced by a previous review[3] which considered the relationship between clinical efficacy and lung deposition, and concluded that differences in drug deposition alone did not always explain corresponding differences in bronchodilatory responses among inhaler devices.

Important clinical differences might therefore be missed by studies with such end points. To investigate the comparability of CFC-containing and CFC-free devices we undertook a systematic review of the evidence from trials which compared the bronchodilator effects of the short acting β_2 adrenoceptor agonists salbutamol and terbutaline delivered via CFC-free inhalers (DPIs and HFC-MDIs) and CFC-MDIs.

Methods

Studies for inclusion in the review were selected by searching the Medline, BIDS, and Cochrane databases. The search strategy included the use of the following "free text" terms: {*salbutamol* **or** *albuterol* **or** *terbutaline*} **and** {*inhaler device(s)*} **and** {*clinical trial**} **and** {*compar** **or** *equivalen** **or** *bioequivalen** **or** *versus*} **and** {*English language*}. Additional clinical trials, published or unpublished, were obtained from the medical information departments of 3M Health Care, Glaxo-Wellcome, Astra Pharmaceuticals, and Medeva pharmaceutical companies.

Of the studies identified, only those which compared two or more inhaler devices and evaluated clinical (bronchodilator) end points were included. Some studies which described the transfer from CFC-MDIs for both inhaled

Table 1 Summary of trials comparing salbutamol delivered via CFC-free devices and via CFC-MDI

Ref. no.	Patient numbers and characteristics	Study design	Intervention[a]	Dose of salbutamol via CFC-MDI	Dose of salbutamol via CFC-free device	Outcome measures	Interpretation of result: Efficacy[b]	Interpretation of result: Potency
(a) Trials comparing salbutamol delivered via Airomir (HFC-MDI) and CFC-MDI								
8	25 moderately asthmatic adults	DB crossover R, PC	Single dose on separate days	100 or 200 μg	100, 200 or 300 μg	FEV_1	HFC-MDI = CFC-MDI	HFC-MDI = CFC-MDI
9	44 mild to moderately asthmatic children	DB crossover R	Single dose	200 μg (Volumatic® spacer device)	200 μg (Volumatic® spacer device)	FEV_1, VC	HFC-MDI = CFC-MDI	
10	24 moderately asthmatic adults	SB crossover R, PC	Cumulative dosing	100–1600 μg	100–1600 μg	FEV_1	HFC-MDI = CFC-MDI	HFC-MDI = CFC-MDI
11	24 mild to moderately asthmatic adults	SB crossover R	Cumulative dosing	100–1600 μg	100–1600 μg	FEV_1, FVC, $FEF_{25–75\%}$	HFC-MDI = CFC-MDI	HFC-MDI = CFC-MDI
12	565 moderately asthmatic adults	DB parallel R, PC	12 weeks	200 μg qid	200 μg qid	FEV_1	HFC-MDI = CFC-MDI	
13	63 asthmatic children	Open parallel R	4 weeks	200 μg qid	200 μg qid	FEV_1	HFC-MDI = CFC-MDI	
(b) Trials comparing salbutamol delivered via Evohaler (HFC-MDI) and CFC-MDI								
14	20 mild to moderately asthmatic adults	DB crossover R, PC	Single dose on separate days	100 μg, 200 μg	100 μg, 200 μg	FEV_1	HFC-MDI = CFC-MDI	
15	24 asthmatic adults	DB crossover R, PC	Single dose	200 μg (spacer device)	200 μg (spacer device)	Histamine PD_{20}, FEV_1	HFC-MDI = CFC-MDI	
16	25 asthmatic children	DB crossover R, PC	Single dose	200 μg (spacer device)	200 μg (spacer device)	Histamine PD_{20}, FEV_1	HFC-MDI = CFC-MDI	
17	423 mild to moderately asthmatic adults	DB parallel R	4 weeks	400 μg per day	400 μg per day	Total daily dose, PEFR, FEV_1	HFC-MDI = CFC-MDI	
(c) Trials comparing salbutamol delivered via Rotahaler (ROT) and CFC-MDI								
18	20 adults	DB crossover R, PC	Single dose on separate days	200 μg	200, 400, 600 μg	FEV_1, FVC	ROT = CFC-MDI	
19	10 acutely asthmatic adults	DB crossover R	Single dose on separate days	200 μg	50, 100, 200, 400 μg	PEFR	ROT = CFC-MDI	
20	10 moderately asthmatic adults	DB crossover R, PC	Single dose on separate days	200 μg	200, 400 μg	FEV_1, VC	ROT = CFC-MDI	
21	22 moderate to severely asthmatic adults	DB crossover PC	Single dose on separate days	200 μg	400 μg	PEFR	ROT = CFC-MDI	
22	9 moderate to severely asthmatic adults	crossover R	Single dose on separate days	400 μg	400 μg	FEV_1, PEFR, FVC	ROT < CFC-MDI (FEV_1)	ROT < CFC-MDI
23	44 mildly asthmatic adults	DB crossover R, PC	Single dose on separate days	200 μg	200 μg	FEV_1	ROT = CFC-MDI	
24	14 adults	crossover R	Cumulative dosing	100–1500 μg	100–1500 μg	FEV_1, FVC	ROT = CFC-MDI	ROT = CFC-MDI
25	7 adults	open crossover R	Cumulative dosing	100–4400 μg	200–9000 μg	FEV_1, FVC	ROT = CFC-MDI	ROT = CFC-MDI
26	25 children	DB crossover R, PC	Cumulative dosing	100–200 μg	100–400 μg	FEV_1, FVC, $FEF_{25–75\%}$	ROT = CFC-MDI	ROT = CFC-MDI
27	27 severely asthmatic adults	Open parallel R	Cumulative dosing	3600 μg total (spacer device)	3600 μg total	FEV_1	ROT = CFC-MDI	ROT = CFC-MDI
24	12 adults	Open crossover R	1 month	674 μg/day	790 μg/day	Total daily dose, PEFR	ROT = CFC-MDI	
26	185 mild to moderately asthmatic children	DB parallel R	3 months	200 μg qid	200 μg qid	FEV_1, FVC, $FEF_{25–75\%}$	ROT = CFC-MDI	
28	38 adults	DB sequential	3 months	720 μg/day	660 μg/day	Total daily dose, PEFR, FEV_1	ROT = CFC-MDI	
29	43 moderately asthmatic children	DB crossover R	1 month	320 μg/day	660 μg/day	Total daily dose, PEFR	ROT > CFC-MDI (PEFR)	
(d) Trials comparing salbutamol delivered via Diskhaler (DISK) and CFC-MDI								
30	41 adults	DB crossover R, PC	Single dose on separate days	200 μg	400 μg	FEV_1	DISK = CFC-MDI	
31	11 mildly asthmatic adults	DB crossover	Single dose on separate days	200 μg	400 μg	FEV_1, VC, FRC, FEV_1PC_{20}	DISK = CFC-MDI	
32	9 moderately asthmatic adults	Open crossover R	Single dose on separate days	400 μg	400 μg	FEV_1, urinary salbutamol	DISK = CFC-MDI (FEV_1) DISK > CFC-MDI (urinary excretion)	DISK = CFC-MDI
(e) Trials comparing salbutamol delivered via Accuhaler and CFC-MDI								
33	24 mild to moderately asthmatic adults	DB crossover R, PC	Single dose on separate days	200 μg	200 μg	FEV_1, PEFR	Accuhaler = CFC-MDI	
34	30 mild to moderately asthmatic	DB crossover	Single dose on separate days	200 μg	200 μg	FEV_1, PC_{20}	Accuhaler = CFC-MDI	
(f) Trials comparing salbutamol delivered via Clickhaler (CLICK) and CFC-MDI								
35	16 mild, moderate and severely asthmatic adults	DB crossover R, PC	Single dose on separate days	200 μg	200 μg	FEV_1	CLICK = CFC-MDI	
36	85 mild to moderately asthmatic children	Crossover	Single dose on separate days	100 μg (spacer device)	100 μg	FEV_1, FVC, PEFR	CLICK = CFC-MDI	
37	62 mild to moderately asthmatics	DB crossover R	Cumulative dosing	100–400 μg	100–400 μg	FEV_1, FVC, PEFR	CLICK = CFC-MDI	CLICK = CFC-MDI

[a]Time refers to duration of treatment per group.
[b]Comparative efficacy at the doses used in each study.
SB = single blind; DB = double blind; R = randomised; PC = placebo controlled; VC = vital capacity; FVC = forced vital capacity; $FEF_{25–75\%}$ = forced expiratory flow between 25% and 75% of FVC; $Vmax_{50}$ = 50% maximum instantaneous forced expiratory flow; FRC = functional residual capacity; VTG = volume of trapped gas; Rrs = respiratory system resistance; sGaw = specific airway resistance; (=) = equieffective (or potent); more (>) and less (<) effective (potent); tending to be more (=) or less (=) effective (potent).

Table 2 Summary of trials comparing terbutaline delivered via Turbohaler (TBH) and via CFC-MDI

Ref. no.	Patient numbers and characteristics	Study design	Intervention[a]	Dose of terbutaline via CFC-MDI	Dose of terbutaline via Turbohaler	Outcome measures	Interpretation of result	
							Efficacy[b]	Potency
38	10 "stable" asthmatics	Open crossover R	Single dose	500 µg	500 µg	FEV_1, VC	TBH = CFC-MDI	
39	46 asthmatic adults	Open crossover R	Single dose on separate days	250 µg, 500 µg	250 µg, 500 µg	FEV_1, FVC	TBH = CFC-MDI	TBH = CFC-MDI
40	10 highly reactive asthmatic adults	SB crossover R, PC	Single dose on separate days	250 µg	250 µg	sGaw	TBH = CFC-MDI	
41	13 moderately asthmatic adults	DB crossover R	Single dose on separate days	250 µg, 500 µg	250 µg, 500 µg	FEV_1, FVC, PEFR, $FEF_{25-75\%}$, sGaw	TBH = CFC-MDI	TBH = CFC-MDI
42	22 moderately asthmatic children	Open parallel R	Single dose	500 µg (spacer device)	500 µg	FEV_1, PEFR, sGaw	TBH = CFC-MDI	
43	12 children (exercise-induced asthma)	DB crossover R, PC	Single dose on separate days	500 µg	500 µg	FEV_1, VTG, VC	TBH = CFC-MDI	
44	118 mildly asthmatic children	DB parallel R, PC	Single dose on separate days	500 µg	500 µg	FEV_1, $Vmax_{50\%}$	TBH = CFC-MDI (FEV_1) TBH > CFC-MDI (V_{max})	TBH = CFC-MDI
45	12 moderately asthmatic adults	DB	Single dose	?? (spacer device)	??	FVC, FEV_1, PEFR, $FEF_{25-75\%}$	TBH = CFC-MDI	
46	10 mildly asthmatic adults	DB crossover R, PC	Single dose on separate days	1000 µg (spacer device)	1000 µg	FEV_1	TBH = CFC-MDI	
47	15 severe COPD adults	DB crossover R, PC	Single dose on separate days	1.0 mg, 2.5 mg (spacer device)	1.0 mg, 2.5 mg	FEV_1, FVC, RV, sGaw	TBH = CFC-MDI	
48	15 mild to moderately asthmatic adults	DB crossover R, PC	Single dose on separate days	2 mg (spacer device)	1 mg	FEV_1	Not comparable	
49	62 severely asthmatic children	Open parallel R	Single dose	5 mg (spacer device)	5 mg	PEFR, FEV_1	TBH = CFC-MDI	
50	12 moderately asthmatic adults	Open crossover R	Cumulative dosing	250–4000 µg	250–4000 µg	FEV_1, FVC	TBH = CFC-MDI	TBH = CFC-MDI
51	9 moderately asthmatic adults	Open crossover R	Cumulative dosing	250–4000 µg	250–4000 µg	FEV_1, FVC	TBH = CFC-MDI	TBH = CFC-MDI
52	31 moderately asthmatic adults	Open crossover R	Cumulative dosing	125–4000 µg	125–4000 µg	FEV_1, PEFR, FVC, $FEF_{25-75\%}$	TBH = CFC-MDI TBH > CFC-MDI (FEV_1)	TBH = CFC-MDI
53	13 moderate to severely asthmatic children	SB crossover R	Cumulative dosing	125–1875 µg	250–2000 µg	FEV_1, FVC, $FEF_{25-75\%}$	TBH = CFC-MDI	TBH = CFC-MDI
54	10 asthmatic children	DB crossover R, PC	Cumulative dosing	250–2000 µg (spacer device)	250–2000 µg	Rrs	TBH = CFC-MDI	TBH = CFC-MDI
55	57 children	DB crossover R	2 weeks	500 µg tid + prn	500 µg tid+ prn	PEFR	TBH = CFC-MDI	
56	19 moderately asthmatic adults	Open crossover R	2 weeks	500 µg qid	500 µg qid	PEFR	TBH = CFC-MDI	
57	231 moderately asthmatic adults	Open parallel R	6 weeks	500 µg qid	500 µg qid	PEFR	TBH = CFC-MDI	
58	21 children	Open crossover R	2 weeks	500 µg tid (spacer device)	500 µg tid	PEFR (am and pm)	TBH > CFC-MDI (am) TBH = CFC-MDI (pm)	TBH ⩾ CFC-MDI

[a]Time refers to duration of treatment per group.
[b]Comparative efficacy at the doses used in each study.
SB = single blind; DB = double blind; R = randomised; PC = placebo controlled; VC = vital capacity; FVC = forced vital capacity; $FEF_{25-75\%}$ = forced expiratory flow between 25% and 75% of FVC; $Vmax_{50}$ = 50% maximum instantaneous forced expiratory flow; FRC = functional residual capacity; VTG = volume of trapped gas; Rrs = respiratory system resistance; sGaw = specific airway resistance; (=) = equieffective (or potent); more (>) and less (<) effective (potent); tending to be more (=) or less (=) effective (potent).

bronchodilators and steroids were not considered eligible for inclusion.

EVALUATION OF METHODOLOGICAL QUALITY

Studies were evaluated for methodological quality by considering the following factors: subjects, study design, treatment interventions, and clinical outcomes. Trials in healthy volunteers were excluded because of the influence of the disease state upon the response to inhaled therapy. Most studies evaluated compared the effects of drug/inhaler combinations in asthmatic patients, which enabled the severity of lung disease to be classified as mild, moderate, severe, or life threatening according to the British Thoracic Society guidelines for the management of asthma.[4]

With regard to study design, patient and sequence (in crossover studies) randomisation was considered essential for unbiased trial conduct. Those which were double blind and included a placebo control group were considered superior to single blind or open studies. Most trials conformed to one of three study designs: single doses taken on separate days, cumulative dosing, and chronic treatment. Some single dose studies determined changes in PD_{20} FEV_1 values (logarithm of the dose of bronchoconstrictor required to reduce the forced expiratory volume in one second (FEV_1) by 20%) following the administration of bronchoprovocative agents such as histamine.

Various pulmonary function tests were used to assess the comparative efficacy of inhaler devices. Most studies measured FEV_1 and/or peak expiratory flow rate (PEFR) as primary outcome measures. PEFR, however, is not only associated with a greater degree of variability than FEV_1 (an observation independent of the measuring device), but is also not generally regarded as the most sensitive indicator of airflow obstruction.[5]

To show that the test product is of comparable efficacy to a standard therapy requires that trialists validate the statistical power of the study to reduce the likelihood of falsely concluding that two inhaler devices are therapeutically equivalent. For studies where details of sample size calculations were absent, estimations of power were made according to standard methods.[6 7] In addition, studies were scrutinised to ensure that the effect of treatment was greater than the predefined therapeutic limit (maximally tolerated clinical differences) in order to exclude trials which reported two treatments as equivalent when both were ineffective.

Results

SALBUTAMOL DELIVERING DEVICES

Six studies comparing one HFC-MDI (Airomir®, 3M) with a CFC-MDI[8–13] and four comparing another (Evohaler®, Allen and Hanbury) with a CFC-MDI[14–17] were found and are presented in table 1(a) and (b), respectively. More studies comparing dry powder devices with CFC-MDIs were found: 14 studies used a Rotahaler® (Allen and Hanburys),[18–29] three used a Diskhaler® (Allen and Hanburys),[30–32] two used an Accuhaler®

Table 3 Therapeutically equivalent alternatives to short acting β_2 adrenoceptor agonists delivered via CFC-MDIs

Alternatives to salbutamol CFC-MDI
(1) Evidence for equal potency and efficacy:
Salbutamol HFC-MDI (Airomir)
Salbutamol HFC-MDI (Ventolin Evohaler)
Salbutamol Rotahaler
Salbutamol Clickhaler
(2) Evidence for single doses being equally efficacious:
Salbutamol 200 μg via CFC-MDI
Salbutamol Accuhaler, 200 μg
Salbutamol Diskhaler, 400 μg
Alternatives to terbutaline CFC-MDI
(1) Evidence for equal potency and efficacy:
Terbutaline Turbohaler

(Allen and Hanburys),[33 34] and three a Clickhaler® (Medeva).[35–37] The results of these studies are presented in table 1(c)–(f).

TERBUTALINE DELIVERING DEVICES

Twenty one studies were found which compared a dry powder device (Turbohaler®, Astra) with a CFC-MDI[38–58] and the results are presented in table 2.

QUALITY OF STUDIES

Most studies identified were of inferior methodological quality, mainly because of inadequate blinding, absence of a placebo control group, and failure to randomise. Many trials were reported as abstracts or not published at all and so were devoid of substantial details for critical appraisal. This may partly be due to the reluctance of many journals to publish such evaluations. The most frequently encountered flaw was that many were designed as comparative or (superiority) trials with null hypotheses of equal efficacy and were therefore underpowered to detect inequivalence, the real concern of equivalence studies. The absence of high quality evidence and substantial variation in the nature of many of the studies prevented any attempt at more formal statistical analysis.

The summary of evidence for alternatives to CFC-MDIs has been divided into two categories: (1) those which, when administered at the same dose, are interchangeable and (2) those where there is only sufficient evidence for substitution at given dose combinations. These are presented in table 3.

Discussion

Salbutamol and terbutaline are the most widely used short acting β_2 agonist bronchodilators with CFC-based MDIs of these drugs accounting for 83% of all bronchodilator delivery devices sold in the UK. Most patients will change device but not drug, and it is important that it should be clear which CFC-free devices are clinically equivalent. Other issues important in ensuring a smooth transition such as patient acceptability, patient education, and cost are not addressed here.

The practitioner of evidence based medicine will have considerable difficulty in identifying studies of adequate quality to assist in the choice of device and will be forced to depend on the often unpublished evidence presented to national licensing agencies, and on the interpretation of these studies by the licensing agencies. In the UK the Medicines Control Agency requires new non-CFC containing products to show therapeutic equivalence to existing products containing CFC. The guidance[59] states that this is best obtained from pharmacodynamic, single dose, short term studies by, for example, demonstrating equivalent dose and time-dependent increases in pulmonary function following single inhaled doses in asthmatic patients. Doses used in the trial should ensure that clinically relevant differences are shown. If therapeutic equivalence is not demonstrated, dose ranging studies are required. A final concern for the evidence based practitioner will be that the only widely available source of information about the outcome of the licensing procedures is indirect in the form of pharmaceutical industry advertising.

A key issue in the studies presented here is that they are often not capable of demonstrating the equivalence which they claim to address. If there appeared to be no differences between treatment groups, for instance, the null hypothesis was not rejected and the investigators interpreted the data as showing that the two treatments were equivalent. In properly designed equivalence trials, however, the conventional significance test has little relevance: failure to detect a difference does not imply equivalence. The null hypothesis should not be "equivalence"—that is, that there is no difference between the treatments—but rather "inequivalence"—that is, that there is a difference. Rejecting this hypothesis then leads to a correct interpretation of both treatments being statistically and clinically equivalent.[6]

Such trials require an increased sample size to provide appropriate statistical power and many of the trials evaluated in this review were underpowered. As an example, one study claimed that the Turbohaler was an effective alternative to CFC-MDI for the delivery of an identical dosage of terbutaline.[43] Twelve subjects completed the crossover trial. To estimate the true sample size required for 80% statistical power to deem that both inhalers were therapeutically equivalent, however, a total of 138 subjects were required. This is based upon a sample size formula for a one sided interval[7] with the therapeutic equivalence limit for FEV_1 taken as ±0.3 l (a maximally tolerated clinical difference) and the intra-subject standard deviation in FEV_1 as 1.0 l (taken from the study). The inadequacy of including only 12 subjects is clear.

Therapeutic equivalence is determined by the observation of equal effects with two inhaler/drug combinations independent of dose, drug (except for pharmacological class), or inhaler type. If two combinations show therapeutic equivalence at whatever dose of each, this result applies strictly to those doses and cannot be extrapolated to all doses. A common misinterpretation by authors in the studies reviewed was to claim equal potency of two drug/device combinations on the basis of these studies looking at therapeutic equivalence.

A further issue is the use of non-comparable doses. If, for example, subjects were given salbutamol via inhaler A at a higher dose than

actually required (on the plateau of the dose-response curve), then a smaller dose administered via inhaler B may appear to be equally efficacious and the interpretation of equivalence of potency will be erroneous.[60] To this end, dose ranging studies are more informative for establishing potency differences between drug/inhaler combinations than chronic treatment studies, even though the latter may be a better reflection of the therapeutic use of these drugs.

Dose recommendations derived from the comparative clinical trial data differ somewhat from those in current practice. Recommendations in the British National Formulary[61] suggest that, for salbutamol, the doses of DPIs should be twice those of CFC-MDIs. This does not seem to be the case for the Rotahaler or the Accuhaler, although there is a shortage of evidence for the latter.

For the purpose of substituting non-CFC containing inhalers for current CFC-MDIs, we found no evidence to suggest that HFC-MDIs are inappropriate. The quantity of evidence in favour of substituting HFC-MDIs, however, is rather limited compared with the more established dry powder devices. In addition to establishing therapeutically equivalent alternatives, the other factors identified above which are beyond the scope of this review must also be considered when deciding on alternatives.

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