CANADIAN INITIAL TRANSITION STRATEGY

FOR THE PHASE-OUT OF CHLOROFLUOROCARBON (CFC) USE

IN METERED DOSE INHALERS (MDIs)

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PATENTED MEDICINE PRICES REVIEW BOARD

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1. INTRODUCTION 2

2. BACKGROUND 2

2.1 QUANTITIES USED IN CANADA 2

2.2 ALTERNATIVES AVAILABLE 3

2.3 ORIGIN OF THE CFC MDIs SOLD IN CANADA 4

3. TRANSITION STRATEGY PRINCIPLES 4

4. STRATEGY OBJECTIVES 4

5. APPROVAL OF ALTERNATIVES 4

6. POST-MARKETING SURVEILLANCE 5

6.1 ADVERSE DRUG REACTION REPORTING 5

6.2 SAFETY AND EFFECTIVENESS IN SPECIFIC PATIENTS GROUPS 5

7. REMOVAL OF CFC-CONTAINING PRODUCTS 6

7.1 TIMEFRAME FOR PHASE-OUT OF CFC-CONTAINING PRODUCTS 6

7.2 MECHANISMS TO PHASE-OUT CFC MDIs 7

7.3 PRODUCTS FOR WHICH NO ALTERNATIVE WILL BE DEVELOPED 7

8. EDUCATION, INFORMATION, AWARENESS AND ACCEPTANCE 8

8.1 EDUCATION AND AWARENESS STEERING COMMITTEE 8

8.2 STEERING COMMITTEE MEMBERSHIP AND TERMS OF REFERENCE 8

8.3 DELIVERY OF MESSAGES 9

8.4 FUNDING OF INITIATIVES 9

8.5 PATIENT ACCEPTANCE 9

9. PRICING ISSUES 9

10. PRODUCT LABELLING 10

11. CONTROL ON ADVERTISING 10

12. IMPACT OF CANADIAN STRATEGY ON OTHER COUNTRIES 10

13. IMPACT OF NATIONAL TRANSITION STRATEGIES OF OTHER COUNTRIES ON CANADA 10

Appendix 1 12

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1. INTRODUCTION

Decision IX/19 adopted in Montreal in September 1997 by the meeting of the Parties to the Montreal Protocol calls for Parties submitting essential use nominations for CFCs for the manufacture of metered dose inhalers (MDIs) for the treatment of asthma and chronic obstructive pulmonary diseases (COPD) to present to the Ozone Secretariat an initial national transition strategy by January 1998, if possible, but no later than January 31, 1999. Canada is a Party to the Montreal Protocol and this document is Canada's draft initial transition strategy prepared in accordance with Decision IX/19. Its purpose is to describe how Canadians intend to manage the phase-out of CFC MDIs and their replacement with CFC-free treatments.

In 1996, Canada and the other developed countries stopped producing and importing new CFCs subject to limited exceptions. One such exception is for uses deemed "essential" by an international committee of experts established under the Montreal Protocol. Approvals of "essential use exemptions" are based upon substantive criteria established under Decision IV/25 of the Montreal Protocol. One of these essential use exemptions allows for the production and import of CFCs to manufacture MDIs for the treatment of asthma and other COPD.

The principle of essential use exemption was agreed on the basis that these exemptions would be temporary. Alternatives to the use of CFC MDIs are now becoming available and countries are required to abide by the principles they have set for themselves under the Protocol.

Environment Canada and Health Canada jointly held two consultations in 1997 to receive comments and feedback from stakeholders on the issues related to a transition to non-CFC treatment of asthma and COPD and on possible approaches to address these issues. In general, stakeholders agree on the need for a transition strategy and are willing to cooperate in order to ensure a smooth transition to non-CFC treatments. They requested that the strategy be as simple and clear as possible. Many stakeholders saw this exercise as an opportunity to refocus attention on the proper diagnosis and management of asthma and COPD and to revitalize the relationship between health care providers and their patients.

This document contains Canada's initial transition strategy to phase out the use of CFCs in MDIs. The strategy may be revisited from time to time as the transition evolves.

This initial transition strategy is the result of consultations with many stakeholders representing health professionals, patient groups, pharmaceutical manufacturers, government agencies and environmental groups. Environment Canada and Health Canada are most grateful for the invaluable assistance, comments and cooperation of these individuals and organizations in preparing this strategy.

2. BACKGROUND

2.1 QUANTITIES USED IN CANADA

More than 1.5 million Canadians suffer from asthma and COPD. It is estimated, based on the responses to the August 1997 questionnaire sent to Canadian MDI manufacturers and importers, that 214 000 kilograms of CFCs were emitted in 1996 from the use of 10.7 million inhalers.

Appendix 1 lists the different active ingredients sold in CFC MDIs in Canada. Fourteen active ingredients are marketed in Canada. The following tables present the most significant active ingredients and categories of CFC MDIs sold in 1996.

Active drug	total	
Beclomethasone diproprionate	2,329,793	21.9 %
Salbutamol sulfate	5,900,334	55.4 %
others	2,427,054	22.8 %
total	10,657,181	

Drug category	total	
beta-agonist	6,127,370	57.5 %
corticosteroid	2,754,790	25.8 %
other	1,775,021	16.7 %
total	10,657,181	

source: Environment Canada survey (1988, 1997).

As indicated in the above table, 55 per cent of the CFC MDIs sold in Canada contain salbutamol and another 22 per cent contain beclomethasone. The "other drugs" group is formed of twelve active ingredients and represents 23 per cent of the Canadian market.

2.2 ALTERNATIVES AVAILABLE

CFC-Free MDIs About 79 percent of all inhaled medicines are delivered through MDIs (Data for 1996, IMS Canada, Compuscript, September 1997). Pharmaceutical companies have undertaken extensive research and development in order to commercialize alternatives to most of the commonly used CFC MDIs. The first CFC-free MDI was approved in Canada in August 1997. The product which dispenses the drug salbutamol (also known as albuterol sulphate), uses HFC-134a as the propellant (also referred to as "HFA-134a"). As shown earlier, CFC MDIs containing salbutamol represent 55 per cent of the Canadian MDI market. This new CFC-free MDI has now been approved for use in more than thirty-five countries.

Development of an alternative to beclomethasone, the second most used active ingredient in MDI formulations in Canada (22 per cent of the total) and to the inhaled steroid fluticasone are well advanced. It is expected that submission for approval of CFC-free alternative to these products will soon occur in Canada.

Dry Powder Inhalers (DPIs) Although the Canadian market for inhaled therapy is dominated by MDIs, many drugs are also available in DPI formulations (see Appendix 1). The use of DPIs in Canada was estimated to cover 13 percent of the Canadian therapy. This use has not progressed in recent years in Canada. Penetration of DPIs into the market depends on their acceptance by health professionals and patients as well as on their cost. In some countries (i.e., Scandinavian countries), DPIs and MDIs have similar costs and DPIs dominate the market. In Canada, DPIs are much more expensive than CFC MDIs and that certainly hinders their penetration into the market. DPIs could be an appropriate alternative for CFC MDIs for some patients. This should be taken into account in future patient and physician education efforts.

Nebulised Drugs These are solutions which are delivered with nebuliser devices. They are generally used for young or elderly patients, patients with severe disease or those requiring higher doses of medication. They currently represent about 8 percent of the Canadian market.

Oral Therapy An new class of drugs (leukotriene receptor antagonist) is now available for asthma sufferers. The role of these drugs in the treatment of asthma is not clear yet. It is therefore impossible at this point to establish their significance for the Canadian transition strategy.

2.3 ORIGIN OF THE CFC MDIs SOLD IN CANADA

Only a small percentage of the domestically marketed CFC MDIs are manufactured in Canada.

Country of origin	total	
European Union (EU)	5,262,983	49.4 %
USA	5,311,790	49.8 %
others (including Canada)	82,438	0.8 %
total	10,657,181	

source: Environment Canada survey (1996 data)

The origin of the CFC MDIs on the Canadian market is equally divided between the United States and the European Union (United Kingdom, Germany and Ireland). It is expected that, in the future, manufacturing taking place in Canada will primarily be for export purposes.

3. TRANSITION STRATEGY PRINCIPLES

It is important to establish principles on which to base the Canadian transition strategy. All elements of the strategy and actions undertaken must be in accordance with these principles. There is a consensus among stakeholders and regulatory authorities on the following principles:

1. The health of patients and their access to supplies of medicine will be safeguarded.
2. All those involved must work towards a smooth and efficient transition towards CFC-free treatments of asthma and COPD.
3. The transition strategy will be developed and implemented in consultation with stakeholders, in a transparent and consistent manner.
4. Health care professional and patient education and voluntary acceptance of CFC-free treatments will form the basis of the strategy.

4. STRATEGY OBJECTIVES

During the first consultations (July and December 1997), stakeholders indicated their support for the adoption of a sunset date for the use of CFC MDIs in Canada. Moreover, they noted that the Aerosol Technical Options Committee established under the Montreal Protocol had indicated it did not foresee a need for essential use exemptions for MDIs after 2005.

The 1996 use survey showed that salbutamol currently represents 55 per cent of the Canadian use of CFC MDIs. As indicated above, the first CFC-free salbutamol MDI has been approved by Health Canada. Alternatives to beclomethasone and fluticasone (which are both used in significant quantities in Canada) are expected to be submitted for approval in the next few years.

It is therefore realistic to expect that a 60 per cent reduction of CFC-MDI use can be achieved by 2001 with a complete phase-out in 2005. These objectives will be reviewed as the situation evolves

5. APPROVAL OF ALTERNATIVES

The pre-market approval and the sale of replacement and alternative products to CFC MDIs are subject to the requirements of the Food and Drug Act and Regulations. Under these regulations, the manufacturer of a drug product must file with the Department of Health, Therapeutic Products Directorate (TPD), a drug submission containing evidence that the product meets established safety, efficacy and manufacturing quality requirements before the drug product can be marketed in Canada. There are national and international guidelines to aid

the manufacturer to meet these requirements during product development.

The current Health Canada performance standard for review of a new drug submission is 300 days. The TPD may grant priority review status, with 180 day review time, to a drug that provides significantly improved efficacy or diminished risk over existing therapies for serious, life-threatening or severely debilitating condition that is not adequately managed by marketed drugs or for which no drug is approved in Canada. Drug submissions for alternatives to CFC MDIs are not considered to meet priority review requirements. The granting of fast-tracking review to all or even a select few CFC-free MDI products may delay approval times for other submissions.

The time required to review CFC-free MDI submissions may be shortened by using assessment reports from external experts and other regulatory agencies, when available, to support a timely evaluation of certain parts of a submission provided the content and evaluation practices meet Canadian requirements.

Health Canada will make every effort to promptly review the submissions for CFC-free MDI products to ensure that asthma and COPD patients in Canada have an orderly and timely access to alternatives to CFC MDIs. The first CFC-free MDI was approved within the expected 300 days performance standard.

Regarding possible overload problems if too many alternatives are submitted to Health Canada at the same time, responses to the August 1997 survey indicate that only a few companies plan to present submissions to Health Canada for a few products in 1998 and 1999. Other companies cannot or do not want to indicate when they expect to present submissions for their products. It is therefore expected that the processing of submissions will not cause any overload to the existing approval process in the near future. The situation will be monitored to ensure appropriate planning of submission review activities.

6. POST-MARKETING SURVEILLANCE

Once CFC-free products begin to be prescribed, they will reach all patient groups, some of which may differ in various aspects from those represented in clinical trials performed for gathering data for product approval. How products are prescribed and how patients use them will also differ from the clinical trial situation. These clinical trials may not have been large enough to demonstrate rare side effects. Data from comparison studies between the CFC-free MDIs with the CFC MDIs may be needed. It is therefore important to consider post-marketing surveillance aspects in the transition strategy.

6.1 ADVERSE DRUG REACTION REPORTING

Spontaneous adverse drug reaction reporting is considered a critical on-going source of drug safety information available to regulatory agencies as part of the post-marketing surveillance. In Canada, adverse reaction reporting is mandatory for pharmaceutical manufacturers and voluntary for health care practitioners. Health care practitioners will be encouraged to report any adverse effect reactions. The education and awareness activities to be undertaken should promote such reporting.

6.2 SAFETY AND EFFECTIVENESS IN SPECIFIC PATIENTS GROUPS

Effectiveness is distinguished from efficacy in that efficacy deals with the performance of a drug product as measured by clinical trials before a new drug is approved. Effectiveness concerns the performance of the drug product under real life conditions and has a post-market focus. Real life conditions such as the patient's characteristics and the adherence to the physician's recommendations may affect drug safety and benefits.

The efficacy and immediate safety concerns are normally addressed by the pre-marketing studies. Post-marketing efforts should therefore focus on possible long term effects which will not appear until the drug product has been on the market for a period of time.

Two post-marketing strategies can be considered. The first strategy can be called "surveillance". Its purpose is to keep track of the use of the product and any associated adverse effect signals. It is a fact finding approach. The second strategy involves pharmaco-epidemiologic studies. Signals derived from the pre-marketing studies, adverse effect reporting and surveillance studies would identify potential concerns. Pharmaco-epidemiologic studies are initiated to investigate these concerns.

Pharmaceutical companies will be asked to submit a minimum of 12 months of Canadian post-marketing data. Substitution of Canadian data with international data will be possible if the manufacturer can establish the comparability of the patient populations, the similarity of drug utilization patterns, and of manufacturing and quality control. Pharmaceutical companies should seek the advice of regulatory authorities and medical associations to ensure that the studies to be undertaken will address any potential concerns and provide useful data.

The results of the post-marketing surveillance will be part of the information required to determine when the phase-out of a given CFC MDI product can begin.

7. REMOVAL OF CFC-CONTAINING PRODUCTS

Canadian stakeholders agree that it is necessary to establish a mechanism to eliminate the supply of CFC MDIs on the market as alternatives become available. This creates a strong incentive for manufacturers to develop alternatives. Stakeholders are made aware of the time horizon leading to this phase-out and can therefore prepare accordingly.

Stakeholders showed a preference for a "drug-by-drug" approach. Under this approach, once an inhaler containing the specific active ingredient(s) has been reformulated to a CFC-free MDI and is available on the market, the production and import of the CFC version of this active ingredient would no longer be allowed after a transition period during which both types of products will be on the market. As previously indicated, stakeholders also support a final sunset date for the use of CFC MDIs in Canada. Important features of such an approach are described in the following paragraphs.

7.1 TIMEFRAME FOR PHASE-OUT OF CFC-CONTAINING PRODUCTS

The following criteria must be met before the phase-out of a CFC MDI for which a CFC-free alternative exists:

1) There should be sufficient quantities of the alternative(s) available to assure an uninterrupted supply of medication;

2) Post-marketing surveillance data must confirm the safety of the alternative product(s);

3) There should be sufficient types of alternatives available to meet the needs of different patient sub-groups;

Manufacturers of the alternative(s) will be requested to confirm that they can adequately supply the Canadian market and to provide information on the production capacity of their manufacturing facilities and on the measures they intend to put in place to ensure the supply of the Canadian market

As indicated in Section 6.2, post-marketing surveillance data covering an initial period of at least 12 months will be needed in order for Health Canada to evaluate the safety of the alternative product(s). The type of data required and the size and the length of the studies will vary depending on the drug involved. The manufacturer of the alternative will need to submit the necessary post-marketing data and relevant analysis to Health Canada which will review them for any indication of significant adverse effects.

Once Health Canada is satisfied with the data submitted, Environment Canada and Health Canada will propose a phase-out decision for the CFC product(s). The proposed decision will be circulated to stakeholders. They will have a period of 60 days to comment on the proposed decision. Once the comment period is over, Environment Canada and Health Canada will make a final decision regarding the phase-out of the product(s). This phase-out may be partial or complete. For instance, the phase-out may allow the importation of CFC MDIs for a sub-population for which a significant adverse effect has been found

7.2 MECHANISMS TO PHASE-OUT CFC MDIs

Two approaches will be proposed to manufacturers. Initially, manufacturers of the CFC MDI to be phased-out will be asked to voluntary stop marketing this product at a given date upon notification by Environment Canada that conditions to start the phase-out have been met. Such voluntary agreement would reduce the cost and administrative burden created by regulations and would provide greater flexibility regarding potential exemptions to the phase-out for specific sub-groups or applications for which CFC MDIs still need to be used.

If there is no unanimity among manufacturers to sign the voluntary agreement described above, Environment Canada will mandate the phase-out of the CFC MDI product. This will be done through a manufacturing and importation prohibition under the Ozone-Depleting Substances Regulations or by Canada asking the producing countries to readjust CFC quantities obtained under the Essential Use Exemption Process (Montreal Protocol) for the manufacturing of these MDIs so that no quantities are given to manufacturers for production destined to Canada. Further work is necessary to determine which option will be most advantageous.

The approach selected will allow for exemptions if there are compelling reasons.

7.3 PRODUCTS FOR WHICH NO ALTERNATIVE WILL BE DEVELOPED

Many inhalation drugs have only one manufacturer supplying the Canadian market at the moment. Companies may not have an interest in finding an alternative for each product. Fortunately, these drugs do not represent a large portion of the Canadian CFC MDI use. The proposed sunset date of 2005 will avoid having an endless transition for these drugs.

However, health care professionals, patients and regulatory authorities need to be informed of these cases in advance in order to allow for a smooth transition towards other drugs. Companies are requested to give as much advance warning as possible to Canadian patients for products they do not intend to reformulate before the 2005 phase-out date.

A very limited number of products may require on-going exemptions. There may be some drugs for which acceptable alternatives cannot be found. The safety mechanism to allow for certain exemptions to the phase-out of a given product will also allow for these exceptions to the sunset date.

8. EDUCATION, INFORMATION, AWARENESS AND ACCEPTANCE

A number of factors may influence acceptance of alternative products to treat asthma and COPD: lack of awareness of new products or alternative treatments; general caution by physicians and patients in adopting a new product; and, lack of perceived incremental benefits to the patient. Thus, in order to ensure a smooth and efficient transition, without compromising the health of patients, it is essential that education and awareness campaigns be developed. These campaigns will form a central component of a national transition strategy.

Recognizing that a global transition is currently taking place from CFC-based to CFC-free treatments for asthma and COPD, the transition to CFC-free treatments will present unique challenges and opportunities for Canadians. The main challenge will be to ensure that alternative products are accepted by health care professionals and their patients. This is however an opportunity to refocus the attention on the proper diagnosis and management of asthma and COPD and revitalize the relationship between physicians and other health care providers and their patients with asthma and COPD.

Addressing these challenges and opportunities can be best accomplished in cooperation with wider education and information programs on the management and care of asthma and COPD, including the existing Canadian Consensus Guidelines on Asthma and the Canadian Thoracic Society Guidelines on the Management of COPD.

8.1 EDUCATION AND AWARENESS STEERING COMMITTEE

Education, information and awareness efforts will be undertaken through a collaborative approach among governments, the pharmaceutical industry and established health care organizations and patient groups. A steering committee will be established to coordinate education efforts aimed at health care professionals, patients and the general public. This committee will aim at ensuring that a unified message is delivered to physicians, pharmacists, nurses and other health care professionals, as well as patients and the general public. The steering committee will also act as a clearinghouse for information dissemination to the groups or organizations in charge of delivering this information.

8.2 STEERING COMMITTEE MEMBERSHIP AND TERMS OF REFERENCE

An initial call for nominations of representatives will be forwarded to a cross section of all the major professional, voluntary, governmental and industry stakeholders interested in the CFC phase-out, including established health care organizations and patient groups, industry associations, federal and provincial governments and environmental non-governmental organizations.

The Steering Committee will be tasked as follows:

Near Term:

- prepare a list of education and information initiatives on the transition from CFC MDIs which are on-going or in development;
- conduct a needs assessment and gap analysis;
- establish priorities for action;
- address issues such as:
    - how to ensure acceptance by health care professionals and their patients of alternative treatments for asthma and COPD;
    - how to use transition from CFC MDIs as an opportunity to refocus attention on the proper diagnosis and management of asthma and COPD and revitalize the relationship between physicians and other health care providers and their patients;
    - how to tie in with existing asthma and COPD education efforts targeted to assist

asthma and COPD health care providers (e.g., Canadian Consensus Guidelines on Asthma and the Canadian Thoracic Society Guidelines on the Management of COPD).

Long Term:

- Develop clear and concise messages;
- Identify and engage representatives of all interested organizations;
- Prepare or input in education, information and training materials, including consensus statements, key messages and information pamphlets for health care providers, their patients and the general public;
- Ensure dissemination of information, education and awareness material through professional associations, pharmaceutical industry, support groups, input into treatment guidelines, medical symposia, promotional and media material and medical literature.
- Assess success of education and information campaigns, through patient and health care professional surveys and respond accordingly.

8.3 DELIVERY OF MESSAGES

Established organizations such as the Canadian Thoracic Society, the Canadian Lung Association, the Canadian Network for Asthma Care, provincial asthma and COPD education networks and Continuing Medical Education (CME) initiatives from the different Universities will be approached to act as the delivery mechanisms for education campaigns.

8.4 FUNDING OF INITIATIVES

Organizations involved in the transition will be approached early in the process to determine the type of support they will be able to provide to the initiatives. Activities will have to be scaled according to the funds available.

8.5 PATIENT ACCEPTANCE

An important aspect to consider in monitoring the results of education and awareness activities is how patients accept the new products. This will influence their behavior (i.e. if they follow their physician's recommendations, their reaction in distress situations, etc.). Patient acceptance will be part of the feed-back needed on these activities. For instance, surveys can be distributed with the new products to patients who will have used them for six months.

9. PRICING ISSUES

Stakeholders have expressed concern on the price of alternatives. It is expected that higher priced alternatives will have difficulty entering the market. As the pricing of drugs is proposed by manufacturers, only a few actions can be undertaken to address this issue. Manufacturers will strongly be encouraged to establish the price of alternatives at the same level as the equivalent products they replace on the market.

There are indications that, in Canada, the first CFC-free MDI products to enter the market will be priced similarly to the generic version of the products they will replace. Pricing is therefore not considered an issue in the near term. Nevertheless, provincial and private formulary authorities will be approached in order to inform them of the reasons and associated benefits of replacing CFC MDIs.

Manufacturers introducing alternatives will be encouraged to discuss their proposed pricing structures with federal and provincial pricing authorities and public and private formulary

authorities well before their product is launched. Manufacturers should ensure that pricing structures do not negatively impact the penetration of alternatives in the market.

10. PRODUCT LABELLING

Decision VIII/10 (3) of the Parties to the Montreal Protocol calls for a differentiation of packaging between CFC and CFC-free MDIs. There are various means of differentiating the CFC MDIs from their alternatives such as changing the name of the product, adding "HFA" or "HFC" to the end of the current names or adding a "CFC-Free" logo on the product.

This differentiation presents many advantages. It allows consumers to be aware of the change, it can be used to gain patient acceptance in marketing campaigns and it will be useful for differentiating products in post-marketing surveillance. It is in everyone's interest that new CFC-free MDIs be easily identifiable so that any reported adverse effect be correctly attributed to the right product. For all these reasons. manufacturers will be asked to use differentiated labeling for CFC-free MDIs.

11. CONTROL ON ADVERTISING

Decision VIII/10 (4) of the Parties to the Montreal Protocol requests that countries encourage companies not to engage in false or misleading advertising targeted at either CFC-free alternatives or CFC MDIs. Companies will be asked to abide by this decision.

Moreover, in Canada, the Pharmaceutical Advertising Advisory Board (PAAB), an independent review agency, is responsible for ensuring that prescription drugs advertising is accurate, balanced and evidence-based. The PAAB maintains a Code of Advertising Acceptance and pre-clears advertising to health professionals prior to publication based on this code. The PAAB has been made aware of the transition to CFC-free treatments and potential issues related to advertising. The PAAB will be kept informed and consulted if advertising issues arise.

12. IMPACT OF CANADIAN STRATEGY ON OTHER COUNTRIES

A country's transition strategy may have a significant impact on another country's MDI supply. Canada is not a major MDI manufacturer. However, most of the Canadian production is exported. It is therefore necessary to address this aspect in this strategy. The consequences of Canada reducing the MDI supply of other countries could be significant: This could result in adverse health impacts in these countries which is something to be avoided. On the other hand, Canada does not want to encourage the use of CFC MDIs at the expense of the CFC-free alternatives.

Canada will adjust its yearly essential use nomination to reflect the phase-out decisions taken in other countries. Canada will not request CFC quantities to produce MDIs for countries that have indicated they do not want to receive them anymore.

Canada will also encourage Canadian companies to invest in the conversion of their facilities in developing countries and to obtain regulatory approval for CFC-free products in these countries.

13. IMPACT OF NATIONAL TRANSITION STRATEGIES OF OTHER COUNTRIES ON CANADA

As noted earlier, the vast majority of CFC MDIs sold in Canada are imported from other

countries. Thus, domestic policies currently being developed in these countries, particularly in the European Community and the United States, may have a direct or indirect impact on Canadian access to MDI products. Canada will monitor the transition strategies in order to identify any measures that could negatively impact the supply of CFC MDI products that are still needed in Canada. Concern about any potential negative impact will be raised with the relevant country(ies).

Appendix 1

Active ingredients sold in Canada

Active ingredient	Beta-Agonist	Corticosteroid	Other
Beclomethasone dipropionate		DPI, MDI	
Budesonide		DPI, Neb	
Di-sodium cromoglycate (Cromolyn)			DPI, MDI, Neb
Epinephrine			MDI
Fenoterol hydrobromide	MDI, Neb		
Flunisolide		MDI	
Fluticasone propionate		DPI, MDI	
Ipratropium bromide			MDI, Neb
Ipratropium bromide + Salbutamol sulfate			MDI, Neb
Isoproterenol hydrochloride	MDI, Neb		
Metaproterenol (orciprenaline) sulfate	MDI, Neb		
Nedocromil sodium			MDI
Pirbuterol acetate	MDI		
Salbutamol sulfate	DPI, MDI, Neb		
Salmeterol xinafoate	DPI, MDI		
Terbutaline sulfate	DPI		
Triamcinolone acetonide		MDI	

note: DPI: Dry Powder Inhaler
MDI: CFC Metered-Dose Inhaler
Neb: Nebuliser

Of the 17 active ingredients sold in Canada,

- 7 are formulated in DPI format,
- 14 are formulated in MDI format,
- 7 are formulated in Nebuliser format

- 4 are packaged in only one format (MDI)
- 8 are packaged in two formats (DPI +MDI, DPI + Neb, MDI + Neb,)
- 2 are packaged in all three formats (DPI + MDI + Neb)