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EXECUTIVE COMMITTEE OF
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DRAFT GUIDELINES FOR METERED DOSE INHALER (MDI) PROJECTS

I. INTRODUCTION

1. At their 12th Meeting (2000), the Parties to the Montreal Protocol discussed the issue regarding the transition to chlorofluorocarbon-free metered-dose inhaler products (MDIs) and decided, among others, to encourage each Article 5 Party to: (a) develop a national or regional transition strategy based on economically and technically feasible alternatives or substitutes that it deems acceptable from the standpoint of environment and health and that includes effective criteria and measures for determining when CFC MDIs can be replaced with CFC-free alternatives; (b) submit the text of any such a strategy to the Ozone Secretariat by 31 January 2005; and (c) report to the Ozone Secretariat by 31 January each year thereafter on progress made on its transition to CFC-free MDIs.

2. At the same Meeting, the Parties also requested the Executive Committee to consider providing technical, financial and other assistance to Article 5 Parties to facilitate the development of MDI transition strategies and the implementation of approved activities contained therein, and to invite the Global Environment Facility to consider providing the same assistance to those eligible countries with economies in transition (Decision XII/2).

3. Subsequently, the Parties at their 13th Meeting decided to request the Executive Committee to prepare guidelines for the presentation of MDI projects involving the preparation of strategies and investment projects that would enable the move to CFC-free production of MDIs in Article 5 countries, and enable them to meet their obligations under the Montreal Protocol (Decision XIII/9).

4. In response to Decisions XII/12 and XIII/9, the Executive Committee decided at its 35th Meeting, to request the Secretariat, in co-operation with the implementing agencies, to prepare a paper for the Executive Committee's consideration on the issues associated with developing projects for the CFC MDI sub-sector to give effect to Decision XIII/9 of the 13th Meeting of the Parties (Decision 35/4(c). At its 36th Meeting, the Executive Committee decided to consider draft guidelines for MDI projects at its 37th Meeting (Decision 36/9).

5. This paper is presented for the consideration by the Executive Committee in response to the above-mentioned decisions taken by the Parties and the Executive Committee.

Terms of reference

6. For the preparation of this paper, the Secretariat hired an international expert who has been actively involved in pharmaceutical and aerosol research and inhalation technology, and since 1996, has been a member of the UNEP Aerosol Technical Options Committee. The Fund Secretariat prepared draft terms of reference for the preparation of guidelines for developing projects for the CFC MDI sub-sector, and sent these to the implementing agencies for their comments.

Structure of the paper

7. This paper consists of the following three sections:

(a) Section I: Introduction;

(b) Section II: An overview of the MDI sub-sector;

(c) Section III: Draft guidelines for the preparation of transitional strategies and development of investment projects for phasing out CFCs in the MDI sub-sector.

II. OVERVIEW OF THE MDI SUB-SECTOR

A. Background

8. An MDI is a complex system designed to provide a fine mist of medicament, generally with an aerodynamic particle size less than 5 microns, for inhalation directly to the airways for the treatment of respiratory diseases such as asthma or chronic obstructive pulmonary disease (COPD).

9. The main components of all MDIs are:

(a) The active ingredient (the drug) may be either dissolved in the propellant or a co-solvent (e.g., ethanol) or suspended in the propellant. A surface-active agent may be included to ensure that the drug is well suspended and to help lubricate the metering valve;

(b) The propellant (a liquefied gas), usually CFCs (CFC-12 and CFC-11, and sometimes CFC-114), and more recently HFC-134a and HFC-227ea (in the pharmaceutical sub-sector, HFC is referred to as HFA). In addition, some preliminary work has been conducted using hydrocarbons as propellants;

(c) The metering valve is the key to measuring and presenting a consistent and accurate dose to the patient, and is made up of a number of precision-made plastic or metal components. The valve is crimped onto a canister;

(d) The canister, ordinarily made of aluminium;

(e) The actuator/mouthpiece holds the canister and through which the patient inhales the dose.

Propellant

10. HFC-134a and HFC-227ea are novel pharmaceutical excipients (inactive ingredients) developed for widespread and long-term use as replacements for CFCs in MDIs. As the propellants in MDIs comprise the large majority of the formulation (often in excess of 98 per cent), and the patients using these drugs are particularly vulnerable to airway irritation or

toxicity, extensive testing had to be conducted on these propellants. Thus, both these HFCs have undergone the same toxicological testing as any new chemical drug substance. Both are now widely approved as propellants suitable for MDI use.

11. All the HFA MDIs contain the same physical components as the CFC-based MDI products (e.g. drug, propellant, canister, metering valve and actuator). However, the very different physical properties of HFC propellants has meant that significant changes have had to be made to the technology for these components.

Dry powder inhaler (DPI)

12. "Not in kind" non-CFC alternatives are now becoming more widely available. The first dry powder inhaler (DPI) became available in 1968. Until the late 1980s, all DPIs consisted of single pre-measured doses stored in gelatine capsules (single dose products). These are still being used today. DPIs have been formulated successfully for most anti-asthma drugs and are now widely available in non-Article 5 countries and in some Article 5 countries.

13. DPIs are preferred by some patients because of their ease of use, but they do not represent a satisfactory therapeutic alternative to the pressurised MDI for all patients or for all drugs. DPI formulations either contain the active drug alone or have a carrier powder (e.g. lactose) mixed with the drug. The drug particles must be of sufficiently small aerodynamic diameter to make it to and deposit on the airways. Micronised dry powder can be inhaled and deposited in the airways effectively from DPIs by patients with adequate breathing capacity as they can pull sufficient air through the device. However, young children, some patients with severe asthma and elderly COPD patients, may not always be able to achieve adequate inspiratory flow to ensure optimal medication delivery from DPIs.

14. There are two types of DPIs:

(a) Single-dose powder inhalers are devices in which a powder-containing capsule is placed in a holder. The capsule is opened within the device and the powder is inhaled. The capsule must be discarded after use and a new capsule inserted for the next dose. Several introductions of single dose DPIs have occurred over the last few years, including in some Article 5 countries where these devices may have a role as they provide the opportunity to purchase a small number of doses at an affordable cost;

(b) Multi-dose powder inhalers can deliver many doses without a need to refill the device after each inhalation. They typically either have drug in a blister (as a discrete dose) or contain drug that is metered from a drug reservoir. Current products vary between four and two hundred doses. There is an increasing use of the multi-dose dry powder inhalers and this is likely to accelerate with the widespread availability of a range of drugs as multiple dose devices.

Availability of non-CFC MDIs

15. In 1994, the first HFA MDI was introduced in the United Kingdom for the widely prescribed short acting b-agonist salbutamol. Today, there are over 60 countries, including 30 Article 5 countries, with at least one salbutamol HFA MDI approved and marketed.

16. The Aerosol Technical Option Committee estimated that in 2001 there were over 100 million HFA MDIs produced globally, representing approximately 25 per cent of the world-wide MDI production, and over 70 million multi-dose DPIs. These alternative products are now being used in a number of countries around the world (TEAP report 2002). Another b-agonist (fenoterol, Boehringer-Ingleheim) is also available in a number of European countries. In Germany, there are no more CFC-based MDIs containing salbutamol.

17. In addition to the beta-agonist HFA MDIs, there are a growing number of controller medications available as HFA MDIs. These include (beclomethasone, fluticasone, di-sodium cromoglycate and nedocromil sodium). Further product introductions are anticipated in the coming years; however, it should be noted that some products cannot or will not be reformulated with HFCs as MDIs and as such alternatives (such as DPIs) are being developed.

18. There are a number of companies providing HFA MDIs and DPIs (3M Pharmaceuticals, USA; GlaxoSmithKline, UK; Boehringer Ingelheim, Germany; Aventis, France; Cipla, India; Asta-Medica, Germany; Ivax-Norton Healthcare, USA/UK; Chiesi, Italy; AstraZeneca, UK; and Norvartis, Switzerland). All of these companies have developed either a new HFA MDI technology or have a DPI with one or more drugs. Many of these products are the subject of intellectual property that cover either the drug molecule, the method of formulation, the device (in the case of DPI) or the filling process.

19. Table 1 below summarises the available formulations for the widely prescribed inhaled drugs salbutamol, beclomethasone and budesonide, which represent over 60 per cent of all MDIs used world wide. The rest of the formulations are made up of more recent or more narrowly prescribed pharmaceutical drugs, such as ipratropium bromide, salmeterol, fluticasone, formoterol and budesonide, either alone or as combinations.

Table 1

Available formulations for the salbutamol, beclomethasone and budesonide

Drug compound	Formulation	Company
Salbutamol	Ethanol/Surfactant/134a	3M Pharmaceuticals
		Ivax-Norton Healthcare
	134a alone	GlaxoSmithKline
		Cipla
	Surfactant/A31*	SprayTechnica
Beclomethasone	Ethanol/134a	3M Pharmaceuticals
		Ivax-Norton Healthcare
	Ethanol/134a/Glycerol	Chiesi

Drug compound	Formulation	Company
Budesonide	Ethanol/134a/Glycerol*	Chiesi
	134a alone	Cipla

*experimental formulation only

Use of MDIs in Article 5 countries

20. According to the most recent available information, CFC MDIs units used in Article 5 countries were estimated to number between 45 and 60 million in 2001 (Table 2). This equates to between 1,100 and 1,500 metric tonnes of CFCs used annually. It is anticipated that the vast majority of this use is for CFC MDIs that contain either salbutamol or beclomethasone (as was the case in non -Article 5 countries).

Table 2

Estimate of MDIs units used in selected Article 5 countries in 2001

Country	Total MDIs (million)	HFA MDIs (million)	% production by multinationals
Argentina	3.34	0	87
Brazil	6.13	0	99
China	12.89	0	12
Cuba	(*)	(*)	(*)
India	9.47	0.720	21
Malaysia	(*)	(*)	(*)
Mexico	1.88	0	98
Pakistan	1.98	0	85
Philippines	1.2	0.680	94
South Africa	1.95	0.025	53
Thailand	(*)	(*)	(*)
Turkey	2.47	0	95
Uruguay	1.27	0.047	(*)

*Data is currently not available

B. Transitional strategies

21. Over the past 5 years, various non-Article 5 countries have developed and published a range of transitional strategies to non-CFC MDIs depending on their market circumstances and the way asthma/COPD is treated. Initial strategies based on a therapeutic approach to CFC MDI phase out have given way to the phase out of individual drug substances (a detailed listing of the strategies available is provided on the TEAP web site www.teap.org).

22. The transitional strategies generally fall into three major categories:

(a) Molecule by molecule (brand by brand), is the replacement of a known brand (e.g. Ventolin with and HFA product);

(b) Targets and timetables; where countries have selected a reduction in CFC volume by a certain time (e.g., Australia); and

(c) Therapeutic category, where there is a determination of how many CFC free alternatives need to be available in that therapeutic class (e.g. beta-agonists) before all other products in that class that use CFC are banned from the market (e.g., European Union).

23. The transition period from CFC MDIs to non-CFC products has varied from country to country, depending on price considerations, differences in medical practice and patient preferences. Trends in the reduction of the use of CFC MDIs have been mirrored by the uptake of HFA MDIs and, in some countries, by the introduction of DPIs. However, the introduction of an HFA MDI does not necessarily lead to a successful transition. Experience in non-Article 5 countries indicates that transition can only be achieved by phasing out the corresponding CFC product once the alternative is widely available.

24. Since the price of the MDI is such an important factor in the use of inhaled therapy, the price of CFC alternatives will be a major barrier to transition, unless their price is no more expensive than comparable CFC products. In general, prices of DPIs and brand-name MDIs of the same drug are similar if compared on a cost per dose basis. However, in some countries there is a significant difference in price between DPIs and generic MDIs of the same drug. Since Government authorities will favour lower priced medicines, countries will need to address the means to have these constituents accept the non-CFC alternatives. In some cases this could mean a demand to return to lower priced oral medicines for the treatment of asthma and COPD. These are regarded as dangerous and not medically justified.

25. Despite widespread educational initiatives in non-Article 5 countries, transition to non-CFC MDIs does not appear to have a high priority amongst most healthcare providers who generally are the point of contact with patients who take these medicines. Thus, pharmaceutical companies' educational and marketing endeavours have, for the most part, been the driving force in the uptake of non-CFC alternatives and this is likely to be the case in many Article 5 countries.

26. The most effective management of the transition to non-CFC MDIs has been through the co-operation of industry and government in working towards a common goal of having target dates for the cessation of sale of certain CFC MDI products (this appears to have been successfully accomplished in Australia and Canada).

MDI transitions in Article 5 countries

27. It would appear that the transition to CFC-free alternatives in many Article 5 countries will happen smoothly as part of their overall phase out of CFC uses. In many cases, Government authorities (Health and Environment Ministries jointly) should encourage non-Article 5 pharmaceutical companies to switch their CFC MDI business as soon as is practical, consistent with the needs of patients and with the appropriate education efforts.

28. Since for many Article 5 countries the supply of MDIs is largely by imports, national transition approaches will be passive. Multinational pharmaceutical companies will switch their CFC products by introducing the HFA MDI, quickly evaluating their acceptance in the market place and then stop supply of the corresponding CFC product. In the absence of any Government driven legislation, this is an effective approach to achieve the transition to non-CFC MDIs. This transition will be driven by the desire of the pharmaceutical companies to introduce products globally once they have been developed.

29. In order to establish the need for technical assistance, Article 5 countries should develop a realistic evaluation of their current inhaler market: who manufactures these products and where they are produced. Data on the active ingredient of the product, marketing company, local ownership, country where the MDI is produced, and estimated amounts of MDI units used on a yearly basis should be collected.

30. Those Article 5 countries with CFC MDI manufactured by local companies will likely require support and guidance through the transition process. Not only will they require assistance with the development of alternative formulations, they may need help to modify their manufacturing plant and develop effective transition policies. The level of technical assistance will vary, depending on whether or not local manufacturing is undertaken independently, or under a licensing agreement with a non-Article 5 company that has a product already developed. As has been the case in non-Article 5 countries, an evaluation of whether reformulation of a specific drug is technically feasible may also be needed. This will require input by appropriate pharmaceutical and technical experts in order to ensure optimal use of any development funding.

31. Although expectations for the design of clinical trials may differ between regulatory authorities, there has been a need to fully characterise the re-formulated product, both from a clinical efficacy and safety perspective. Specific demands for regulatory studies will vary from country to country and some countries may rely on approvals from existing “competent” authorities to gain marketing authorisation (e.g. a product licence granted in the United Kingdom may allow a product to be sold in some countries without further local testing under a “free sales certificate” or Certificate of Pharmaceutical Product).

32. Based on an understanding of the range of inhalers available in a country this data can then be used to establish what would be the most effective transition strategy for that country. It is anticipated that in many cases there will be a limited number of inhaled products, with salbutamol and beclomethasone products being the majority. Simple time based targets to phase out these products consistent with local regulatory timetables for product authorisation would seem the most effective approach.

C. Investment project proposals

33. Given that there are now several non-Article 5 companies that have developed suitable salbutamol and beclomethasone HFA MDIs, it seems plausible that an Article 5 enterprise could seek, via its governmental agencies, the opportunity to gain access to the technology to develop and produce these products.

34. The first step in developing such proposals should be to establish the inhaler market statistics and evaluate where the needs are highest. As highlighted above, in many Article 5 countries, it will not be necessary to develop investment projects as the non-Article 5 companies will be effecting the transition. In those Article 5 MDI producing countries, project proposals to convert to non-CFC MDI should clearly describe:

(a) The product (drug molecule) that is being reformulated;

(b) The replacement technology available for the specific drug molecule to be reformulated (how and by what method will it be made);

(c) Data available to demonstrate comparability with CFC product including stability (e.g. dose delivery; particle size comparisons - cascade impaction or twin impinger);

(d) Regulatory and policy measures needed for marketing authorisation, including the needs for any additional clinical testing;

(e) Description of the equipment baseline (including installed production capacity and current production) and annual consumption of CFCs should also be provided;

(f) Time frame for the development of the re-formulated product;

(g) How the CFC phase out in the MDI sub-sector fits with the overall CFC phase-out plan proposed by the Government.

Incremental cost categories

35. Typical production of an HFC inhaler will involve similar steps to the corresponding CFC MDI. There are essentially two ways to manufacture MDIs.

(a) Pressure filled, where the gas or the gas plus the drug is driven in under pressure through the metering valve;

(b) Cold filled, where the formulation is chilled to a low temperature (-40 ^{o}C), filled as a liquid and then the value is crimped on the canister.

Capital costs

36. Depending on the existing baseline, the method of manufacturing and the production volume, the incremental cost of the conversion will vary. For example, the cost for a new high-speed filling line (i.e., 12 million canisters per year) varies between US $2 and US $3 million, while the cost for a lower speed lines (i.e., 6 million canisters per year) range between US $1.2 and US $1.5 million.

37. In many cases, where production volumes are small, (i.e., 1.0 million units or less) it may be possible to retrofit the production lines to HFCs. Estimates of cost are between US $200,000 to US $400,000, depending on the line configuration and the product to be filled. In these cases, there will be a need to evaluate the baseline equipment, type of products to be filled and annual production volume, in order to establish which pieces of the line(s) can be retrofitted. Direct discussions with MDI filling equipment suppliers would facilitate specific product manufacturing cost comparisons.

38. For DPIs, the most likely replacement product (e.g., for a salbutamol CFC MDI) would be a reservoir powder device (e.g., ClickHaler, Innovata Biomed, UK). This device also has a counter (to tell the patient how many doses are left) so direct comparisons are not truly representative. However, for production volumes of between 5 and 10 million per annum, typical capital investment costs are between US $2.8 and US $4.0 million. The capital costs for multi-dose individually metered dose DPIs would be even higher (estimated at between US $8 and US $10 million); however, as a strict replacement option they currently do not represent a viable alternative.

Operating costs

39. Ongoing production costs for HFA MDIs are likely to be dependent on volume. After initial familiarity with the operation of the lines (set up, trials and training), the basic principles of operation are similar between comparable CFC- and HFA MDI technologies and thus ongoing costs will be similar.

40. Therefore, assuming a production volume of at least ONE million UNITS per annum, and that the prices for CFC and HFA are roughly comparable, the costs of most of the MDI components will likely be very similar, except for the valves, as shown in Table 3 below:

Table 3

Estimate of operating costs for CFC and HFC based MDIs

Description	CFC MDI (US$/100)	HFA MDI (US$/100)	Difference (US$/100)
Active ingredient (e.g. salbutamol)	4	4	0
Canister	6	6	0
Valve	40-45	60-70	20-25
Propellant: CFC HFA	5	7	2
Formulation excipients	2-3	0-3	-2-0
Actuator	10	10	0

41. The major difference is in the valve costs (as much as US $0.25 per can assuming that all testing needs are the same). These costs depend on the specifications of the MDI product and filling procedure (e.g. cold filled or pressure filled; compatible with ethanol, etc.). However, as the volumes of CFC MDIs decrease, it is likely that CFC valve costs will increase and thus will drive down the differences further. Conversely, as HFA MDI volumes increase, valve costs will decrease. Canister costs may vary depending on whether or not they need to be coated.

42. In any case, on an initial basis the net increase of annual operating costs for a production of one million canisters will be on the order of US $250,000.

D. Access to HFA MDI and DPI technology

43. In addition to capital costs (either for the establishment of a new filling line or for the retrofit of an existing line) and operating costs (mainly costs for replacement valves), costs associated with product development and stability/clinical study (up to 2 years) may be required to achieve registration. These costs could range between US $1 and US $3 million.

44. One alternative for Article 5 countries could be a license arrangement with pharmaceutical companies that currently have the products developed and can achieve efficiencies in terms of component supply and thus reduce production costs. Thus, they might be able to achieve access sooner and less expensively through the provision of a royalty payment.

45. Cross licensing arrangements with major pharmaceutical companies have been made with the HFC technology (e.g., 3M Pharmaceuticals and Ivax/Norton Healthcare recently made an agreement for their Beclomethasone technology, although the terms are not publicly disclosed). It could be anticipated that small royalty payments (typically up front payments on signing the agreement (US $2-US $4 million) or payments of a few cents per canister) would be made where such technology is covered by patents.

46. In countries where no patent coverage exists or the patents are not enforceable, it is possible that access to technology could be granted in exchange for a greater market presence (i.e. by establishing a joint venture in that country) would provide a sufficient incentive to the pharmaceutical company with developed products to find such arrangements attractive.

47. Specific discussions on how technology could be transferred will need to be between the Article 5 government agency and the pharmaceutical companies directly.

48. The magnitude of payments for this type of technology is usually on the order of a few percent of sales or it could come in the form of a share of revenue from sales of an already developed product.

III. GUIDELINES FOR THE PREPARATION OF TRANSITIONAL STRATEGIES AND DEVELOPMENT OF INVESTMENT PROJECTS FOR PHASING OUT CFCs IN THE MDI SUB-SECTOR

1. The purpose of this guidelines is to assist implementing and bilateral agencies in the preparation of investment projects for the replacement of CFCs used in MDI applications.

Transitional strategies

2. In developing transitional strategies (action plan), Article 5 countries can be broadly classified according to the number of MDI units used per year in the country and whether these are produced locally or imported. The following will serve as broad classification for the purposes of defining funding support from the Multilateral Fund for transitional strategies:

(a) Low consumers of MDIs, with an annual usage of less than one million MDIs (equating to less than 25 tonnes of ODS per annum), and who are totally supplied by imports, will need minimal assistance. Experience in developed countries, where supply of CFC MDIs comes primarily from multi-national companies, is that CFC free alternatives can be introduced promptly within the regulatory framework of the country, and the corresponding CFC MDIs phased out;

(b) Large consumers of MDIs, with an annual use of more than one million MDIs, and who are totally supplied by imports. They will need more assistance in developing an understanding of the currently available range of products in their country, drafting an action plan for transition and communicating this to doctors and asthma/ COPD patients; and

(c) MDI producer countries, where the production could be from nationally-owned companies, joint ventures between Article 5 and non-Article 5 companies, partially-owned companies (partially owned by a non-Article 5 company), and/or a non-Article 5 enterprise. This is where most of the financial support will be focussed and could cover both the development and dissemination of transition action plans, as well as access to non-CFC alternate products.

Information requirements

3. Basic information on the CFC MDI sector within the country has to be gathered and will be a pre-requisite to the development of any transition strategy.

4. For the development of a transition strategy in any Article 5 country, the information should include:

(a) The volume of CFC MDIs used, by type of molecule, and therapeutic class and the availability of non-CFC alternatives (including DPIs);

(b) A list of companies manufacturing and/or marketing CFC MDIs, the extent of local ownership and production/marketing volumes (units per year); and

(c) A description of the legislation/regulations in place regarding testing and approval requirements of new drugs, in particular new MDIs or DPIs.

5. For major MDI user countries (more than one million MDIs per annum), in addition to the information required for all countries, the following should also be provided:

(a) A description of the anticipated availability of non-CFC MDIs and the feasibility of replacing MDIs by other alternatives (i.e., DPIs);

(b) A summary of the most likely source of the alternative products (e.g. local development; licence of technology; establishment of joint ventures);

(c) The proposed time frame for the introduction of non-CFC MDIs and the proposed duration of the transitional period where both CFC and non-CFC MDIs will be available in the market concurrently;

(d) A description of the planned awareness programmes addressed to health care professionals and patients to explain the need for changes to their inhalers; and

(e) A description of the proposed monitoring requirements during the transitional period and what remedial action will be taken if the initial target reductions in CFC volumes are not met.

6. For MDI producer countries, in addition to the information required for major MDI user countries, baseline information on existing CFC MDI production facilities will be required. This should include:

(a) A brief description of the production process, by type of drug, including installed capacity and current capacity;

(b) A listing of all of the CFC MDIs produced by active ingredient; annual volumes of CFCs, valves and canisters used during the past 3 years;

(c) A description of the type of equipment used in each production line and the number of lines within the facility;

(d) A description of any licensing agreements, or technology transfer agreements in place for the CFC MDI product; and

(e) A statement of the extent of local ownership.

7. The process should be consultative and include major stakeholders involved in the MDI sub-sector. This would likely include the Ministries of Health and Environment, as well as Customs, patient associations, and other interested NGOs.

8. The cost for the development of transition strategies ranges from up to US $30,000 for low consumers of MDIs to up to US $50,000 for large consumers of MDIs including MDI producers.

Guidelines for investment projects

9. Those countries with CFC MDI manufacture by local companies will require assistance with the development of alternative formulations, modification of manufacturing line and fulfilling all regulatory obligations for product license. This assistance will vary, depending on whether local manufacture is undertaken independently, or under a licensing agreement.

10. Project proposals should be consistent with all relevant rules and policies of the Multilateral Fund as decided by the Executive Committee.

Description of the baseline

11. To ensure the effective use of available funding, extensive baseline information on the existing CFC MDI production facility will be required. This should include:

(a) A description of the production process, by type of drug, including installed capacity and current capacity, as well as annual volumes of CFCs, valves and canisters used during the past 3 years;

(b) A listing of all of the CFC MDIs produced, by active ingredient;

(c) A description of the type of equipment used in each production line and the number of lines within the facility;

(d) A description of any licensing agreements, or technology transfer agreements in place for the CFC MDI product; and

(e) A statement of the extent of local ownership.

12. As a general principle any project for the manufacture of a new, non-CFC alternative will relate to that product only. It will not cover retrofitting for new valve or canister supplies should they be needed.

Retrofit

13. It may be possible to convert the existing equipment to the manufacture of non-CFC products. This will depend on the type of equipment currently in use and the non-CFC product planned to be produced. Typically existing rotary filling (high volume) equipment cannot be upgraded effectively and will need to be replaced.

14. Retrofitting may be possible and would typically cost US $200,000 to US $400,000 depending on the production line and its capacity. Any request for funding should fully outline the steps needed to retrofit the line and include:

(a) A detailed technical and economic feasibility analysis for the retrofit of the existing production line;

(b) A description of the product(s) and volumes planned to be produced by the modified equipment, including details of the formulation if feasible, canister and valves;

(c) A description of the major pieces of equipment that can be retrofitted and by whom;

(d) The proposed time frame for the conversion to the non-CFC MDI manufacturing process;

(e) An outline of the testing/trials and time frame needed to achieve a new pharmaceutical MDI product registration; and

(f) An estimate of the ongoing operating costs of the new production facility versus the current production.

New production line

15. It may be necessary to install a new production line to manufacture the HFA MDI. This would require a similar analysis to the above. New line installation may cost between US $1 million to US $4 million and therefore will need a strong justification. A project request will need to include:

(a) A detailed technical and economic feasibility analysis for the installation of a new filling line for the alternate product (be this HFA MDI or DPI);

(b) A description of the alternate product(s) and volumes planned to be produced on the modified equipment, including details of the formulation, if feasible;

(c) A description of the major pieces of equipment essential for the installation and manufacture of the alternate product;

(d) A proposed time frame for the conversion to the alternate product;

(e) An outline of the testing/trials and time frame needed for a new pharmaceutical product and new installation registration;

(f) A comparative operational cost analysis between the existing CFC MDI and the alternate product.

Technology transfer

16. A final source of an alternate product could be for an Article 5 enterprise (or the country) to discuss with relevant international pharmaceutical companies (including those owned by some Article 5 countries) an agreement under which access would be gained to products that are already developed and produced in non-Article 5 countries. Possible arrangements for access to these products could include:

(a) Supply of the finished product;

(b) Transfer of the technology to the Article 5 enterprise for local production;

(c) A joint venture established to produce the alternate products locally.

17. The cost of access to the technology will depend on whether there are existing patents that cover the product being contemplated and whether these are enforceable in the Article 5 country.

18. Cross licensing agreements have been established in this technology field and are depending on the products and countries in question. Payments will typically include an up-front payment on signing the agreement and then license fees (typically a low percentage of sales or as a royalty per canister) where these are due.

19. Discussions with international pharmaceutical companies (including those owned by some Article 5 countries) are encouraged to establish whether there is a willingness on the part of certain companies to assist in making their products more widely available. These could be developed to establish project proposals but will need sound economic justification. They may offer a better economic alternative to the retrofitting of existing equipment or establishing new production lines.

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