UNITED NATIONS

EP

United Nations Environment Programme

Distr.
GENERAL

UNEP/OzL.Pro/ExCom/56/22
15 October 2008

ORIGINAL: ENGLISH

EXECUTIVE COMMITTEE OF
THE MULTILATERAL FUND FOR THE
IMPLEMENTATION OF THE MONTREAL PROTOCOL
Fifty-sixth Meeting
Doha, 8-12 November 2008

PROJECT PROPOSAL: ARGENTINA

This document consists of the comments and recommendation of the Fund Secretariat on the following project proposal:

Aerosol

- Phase-out of CFC consumption in the manufacture of aerosol MDIs IBRD

PROJECT EVALUATION SHEET – NON-MULTI-YEAR PROJECT
ARGENTINA

PROJECT TITLE(S)	BILATERAL/IMPLEMENTING AGENCY
(a) Phase-out of CFC consumption in the manufacture of aerosol MDIs	IBRD

NATIONAL CO-ORDINATING AGENCY	Secretariat of Industry, OPROZ

LATEST REPORTED CONSUMPTION DATA FOR ODS ADDRESSED IN PROJECT

A: ARTICLE-7 DATA (ODP TONNES, 2007, AS OF OCTOBER 2008)

CFCs	529		

B: COUNTRY PROGRAMME SECTORAL DATA (ODP TONNES, 2007, AS OF OCTOBER 2008)

ODS	Aerosol	MDI		
CFC-11	0.0	60.0		
CFC-12	0.0	133.6		
CFC-13	0.0	1.7		
Total	0.0	195.3		

CFC consumption remaining eligible for funding (ODP tonnes)	160.0

CURRENT YEAR BUSINESS PLAN ALLOCATIONS		Funding US $ million	Phase-out ODP tonnes
	(a)	4,203	115.0

PROJECT TITLE:	
ODS use at enterprise (ODP tonnes):	n/a
ODS to be phased out (ODP tonnes):	109.1
ODS to be phased in (ODP tonnes):	0
Project duration (months):	38
Initial amount requested (US $):	5,605,425
Final project costs (US $):	
Incremental Capital Cost:	
Technical assistance (product development)	
Incremental Operating Cost:	
National transition strategy	
Total Project Cost:	
Local ownership (%):	
Export component (%):	
Requested grant (US $):	
Cost-effectiveness (US $/kg):	
Implementing agency support cost (US $):	
Total cost of project to Multilateral Fund (US $):	
Status of counterpart funding (Y/N):	Y
Project monitoring milestones included (Y/N):	Y

SECRETARIAT'S RECOMMENDATION	For Individual Consideration

PROJECT DESCRIPTION

1. On behalf of the Government of Argentina, the World Bank has submitted a project proposal for the phase-out of CFC consumption in the manufacture of aerosol metered-dose inhalers (MDIs) in Argentina for consideration by the Executive Committee at its 56th Meeting. The total funding requested in the project, as originally submitted, is US $5,605,425 plus support costs of US $420,407 for the World Bank and includes a request for an MDI transition strategy.

Sector background

2. CFC-MDIs are manufactured in Argentina by the following enterprises: Laboratorio Pablo Cassará (100 per cent local ownership), which consumes approximately 80 per cent of the pharma-grade CFCs imported into the country for the manufacturing of MDIs with different active ingredients; 3M, a multinational enterprise that fills MDIs for a group of 15 laboratories, five of which are nationally owned; and Denver Farma, a local laboratory (100 per cent local ownership) that used to fill its MDIs through 3M but established its own CFC-MDI production line in 2007. IVAX, another multinational enterprise established in Argentina, stopped production of CFC-MDIs during 2007.

3. The level of CFC consumption used for the manufacturing of MDIs in Argentina by locally-owned and multinational enterprises increased from 187.0 to 195.9 ODP tonnes between 2005 and 2007. CFC consumption used by locally-owned enterprises only increased from 99.9 to 118.4 ODP tonnes over the same period, as shown in Table 1 below.

Table 1 Total CFC consumption for the manufacturing of MDIs in Argentina

Description	ODP tonnes		
	2005	2006	2007
Consumption for domestic use	135.7	123.6	136.4
Export to Article 5 countries	51.3	49.5	59.5
Total consumption	187.0	173.1	195.9
Consumption eligible for funding			
Pablo Cassará	83.5	85.0	106.4
Denver Farma(*)	2.0	2.0	3.1
Phoenix(*)	10.9	10.9	4.4
Dallas(*)	0.1	0.1	0.1
Raffo(*)	2.7	3.1	3.6
Roux(*)	0.7	0.6	0.8
Sub-total eligible enterprises	99.9	101.7	118.4
Consumption by multinational			
3M(**)	51.2	49.5	59.5
IVAX(***)	35.9	21.9	18.0
Sub-total multinationals	87.1	71.4	77.5

(*) CFF-MDIs filled through 3M. Denver Farma established its own CFC-MDI production line in 2007.
(**) Excluding CFC consumption used for filling CFC-MDIs for locally-owned enterprises.
(***) Stopped production of CFC-MDIs during 2007.

4. As of 2007 (the base year chosen to establish baseline consumption), CFC-MDIs with the following seven different active ingredients were registered and sold in Argentina: salbutamol, budesonide, fenoterol, ipratropium, fluticasone, fluticasone/salmeterol, ipratropium/fenoterol, ipratropium/salbutamol and salmeterol/beclomethasone.

Project description

5. The objectives of the project are: to eliminate the use of CFCs at Laboratorio Pablo Cassará for the production of salbutamol CFC-MDIs; to eliminate the use of CFCs at Laboratorio Denver Farma for the production of salbutamol and budesonide CFC-MDIs; to provide technical support for alternative formulations for four locally-owned laboratories filling their own MDIs through third parties; and to support the MDI transition strategy.

Laboratorio Pablo Cassará

6. The project proposes the phase-out of 97.1 ODP tonnes of CFCs used in the manufacturing of salbutamol MDIs at Cassará, using isobutane as a propellant. The project includes feasibility studies for the selection of isobutane sources; development of an MDI formulation and packaging; long-term stability studies and bioequivalence studies in patients; registration of the newly developed isobutane-MDI with relevant health authorities; and scaling up the MDI production line to industrial-scale equipment.

7. Isobutane technology has been selected for the following reasons:

(a) Isobutane is already in use in marketed rectal foams and oral aerosols in some countries;

(b) High purity grades of isobutane have a similar cost to CFCs and would make it possible to keep operating costs unchanged. There are also several different potential suppliers of isobutane, whereas there are only a few for HFAs;

(c) Isobutane has a very low GWP value (100-year GWP is 3); it is not a consumer product and therefore not regulated by any government because of the relatively small consumption volume; it is a definitive solution to the environmental problems associated with ODS emissions by aerosols for both ozone depletion and greenhouse effects;

(d) The transition cost of having a one-step change from CFC to isobutane would be lower than having a two-step change, i.e. from CFC to HFA, and from HFA to hydrocarbons;

(e) Flammability is not considered a significant drawback because hydrocarbons are extensively used as propellants in the aerosol industry for domestic and cosmetic use and both consumers and industry are already used to taking cautionary measures in this regard. Furthermore, in the case of MDIs, the unit only delivers the metered dose, which is less than 50 mg per shot.

8. The total cost of the project has been estimated at US $3,800,720 and includes laboratory equipment and a small filing line for manufacturing pilot batches to test trial formulations (US $699,333); installation of additional equipment items within the existing production line, installation of a hydrocarbon storage and distribution system, modifications to the production facility to allow for the use of hydrocarbons (US $2,980,717); and product development (US $120,670). Counterpart funding by Cassará to cover part of the product development costs and modifications to the production facilities has bee estimated at over US $1.8 million.

9. The project will be completed by 2012. The transition from CFC-MDIs to both isobutane- and HFA-MDIs requires the production of both CFC- and non-CFC MDIs for a period of time. As a result, completely new non-CFC-MDI manufacturing facilities of equivalent capacity are required or Argentina will have to engage in campaign production to supply patients during this period.

Laboratorio Denver Farma

10. Denver Farma, a locally-owned pharmaceutical company founded in 1989, specializes in the production of generic medicines, including MDIs. Since 1998, Denver Farma has been producing some 15,000 salbutamol and budesonide CFC-MDIs a year, filled by 3M, for the local market. In 2007, Denver Farma established its own CFC-MDI production line with a total CFC consumption of 3.1 ODP tonnes.

11. The project proposes to replace CFCs by HFA propellant. This technology has been selected by Denver Farma given that it has been fully developed commercially. The benefit of using HFAs is that MDI format is maintained which is an advantage to the patients since they are used to this format; offers the most cost-effective method for inhalation delivery, minimizing the potential incremental operating costs that will be realized in the transition from CFC MDIs; and the company's commercial strategy.

12. Replacement to HFA technology requires the installation of a small pilot plant for batch production of HFA-MDIs (US $65,000); retrofitting the existing CFC production line (US $270,000); and developing two new formulations based on HFA for salbutamol and budesonide (US $122,400).

13. Denver Farma is committed to completely phase out CFC consumption for manufacturing of salbutamol and budesonide MDI, 2 years after the project is initiated.

Technical support for laboratories

14. The objective of this project component is to provide technical assistance for the development of HFA formulations of MDIs for the following locally-owned laboratories: Dallas, Phoenix, Raffo, and Roux-Ocefa. In 2007, these laboratories consumed approximately 8.9 ODP tonnes of CFCs, as shown in Table 2:

Table 2. MDIs manufactured for locally-owned laboratories (2007)

Laboratory	Formulation	CFC (ODP tonnes)	Date	Ownership(%)
Phoenix	Budesonide	4.4	Oct-99	51
	Fluticasone	-	May-06	
	Fluticasone/salmeterol	-	Aug-06	
Raffo	Salbutamol/beclomethasone	3.6	Prior-03	100
Roux-Ocefa	Salbutamol	0.8	Mar-03	100
Dallas	Budesonide	0.1	Mar-01	100
Total		8.9		

15. In total, US $531,822 is being requested for the development of HFA formulations, technology transfer, and development of new primary bottles; manufacturing of 3 pilot batches of 3,000 MDIs for each product, stability tests, pharmaceutical equivalence studies and product registration. The four laboratories have selected HFA as the replacement technology given the cost, environmental concerns, and each company's commercial strategy.

16. The four laboratories are committed to completely phasing out CFC consumption for manufacturing of MDIs, 2 years after the project is initiated.

Transition strategy

17. The total cost of the transition strategy has been estimated at US $600,000 and includes the following activities:

(a) Dissemination strategy (radio, television, newspaper) to create awareness of the benefits of using CFC-free MDIs; letters to pharmacists to communicate the phase-out of

salbutamol CFC MDIs, its rationale and the environmental advantages of CFC-free alternatives; promotional material to be distributed to doctors, patients and the general public.

(b) Distribution of information to all physicians to instruct patients on the change away from CFC-based MDIs.

(c) Mail distribution of user manuals to physicians, for handing out to patients;

(d) Clinical symposium (or roundtable) organized within a major national or international Congress to discuss the characteristics of CFC-free MDIs;

(e) Publication of articles in local newspapers and magazines about the advantages of changing to CFC-free MDIs; and

(f) Presentations on television on the environmental advantages, as well as the effectiveness, safety and different taste of CFC-free MDIs.

SECRETARIAT'S COMMENTS AND RECOMMENDATION

COMMENTS

18. The Secretariat reviewed the project proposal for the phase-out of CFCs in the manufacture of aerosol MDIs in Argentina in light of the policy papers on the MDI sub-sector submitted to the 37th, 49th and 51st Meetings; MDI phase-out projects that have been approved for Bangladesh, Cuba, Egypt, Iran, and Mexico; and relevant decisions on MDIs.

Eligible CFC consumption and manufacturing lines

19. At the 42nd Meeting, the Executive Committee approved the national plan for the phase-out of ODS in Argentina covering all remaining CFC consumption eligible for funding, excluding CFCs used in the manufacturing of MDIs. The phase-out plan was based on the level of CFC consumption in 2003. The agreement between the Government of Argentina and the Executive Committee for the phase-out of ODS stipulates that Argentina reserves the right to request funding for the MDI sector in the future in accordance with the prevailing eligibility and funding criteria of the Multilateral Fund (decision 42/25). The amount of CFCs used for MDI production that were excluded from the national phase-out plan was estimated at 160 ODP tonnes.

20. The historical consumption of CFCs used for the manufacturing of MDIs as submitted by the Government of Argentina is as follows:

Year	2000	2001	2002	2003	2004	2005	2006	2007
CFC consumption	128.5	135.1	141.0	84.5	141.0	187.7	173.1	195.6

21. Through the World Bank, the Government of Argentina indicated that 2003 consumption did not reflect the real situation in the sector. Due to the severe economic crisis experienced in Argentina at the end of 2002, industrial activity (including pharmaceutical production) declined sharply. As a result, consumption of CFCs for MDI production decreased significantly during 2003, and returned to normal levels by 2004. On this basis, the level of CFC consumption for MDI production eligible for funding has been established at 109.1 ODP tonnes. The remaining CFC consumption of 86.5 ODP tonnes will be phased out without assistance from the Fund.

22. As reported in the project proposal, Denver Farma established a new CFC-MDI production line only in 2007, and Phoenix started manufacturing fluticasone CFC-MDIs in May 2006 and fluticasone/salmeterol CFC-MDIs in August 2006. Given this framework, the Secretariat pointed out that the conversion of the MDI production line at Denver Farma and for the reformulation of the MDIs manufactured for Phoenix after 2003 was not eligible for funding. The project proposal was subsequently revised as follows:

(a) Funding will only be provided for the development of HFA-MDIs for salbutamol and budesodine that were filled by 3M for Denver Farma. Funding for the conversion of the current MDI production line, estimated at US $335,000, will be covered by the laboratory;

(b) No funding will be provided for development of fluticasone and fluticasone/salmeterol by Phoenix.

Essential use exemptions for CFCs

23. Through its decision 51/34, the Executive Committee requested, *inter alia*, that those countries with MDI manufacturing plants should be advised of the timing for beginning to consider the need for essential use exemptions beyond the 2010 phase-out date. According to the proposal, it is estimated that the conversion to non-CFC MDIs will be completed by December 2014, i.e., five years after the mandatory date for the complete phase-out of CFCs. However, the need for essential use exemptions for CFCs or for stockpiling pharmaceutical grade CFCs has not been fully considered in the project proposal. Based on consultations with the Government of Argentina, the World Bank reported that the post 2010 amounts of CFCs that would be needed for the production of MDIs would be as follows:

Year	2010	2011	2012	2013	2014	2015
CFCs (ODP tonnes)	164.0	222.0	289.0	311.0	193.0	73.0

Issues related to isobutane technology

24. The project proposes the conversion of CFC-MDI salbutamol to isobutane-MDIs. This will represent the first MDI project submitted for consideration by the Executive Committee requesting the replacement of CFCs with isobutane instead of HFA-134a. The Secretariat therefore raised a number of issues, which have been addressed by the World Bank as follows:

(a) According to information received from the TEAP Medical Options Technical Committee, an isobutane-MDI has been developed in Germany;

The Bank pointed out that the technology for the use of isobutane as an MDI propellant was patented in Germany and Europe by IG Sprühtechnik GmbH on 27 September 1991. The patent law of Argentina makes international patents valid from 1 January 1995 (i.e., only innovations internationally patented after 1 January 1995 would be valid in Argentina); therefore the patent of the isobutane technology is not valid in Argentina. Furthermore, as the European patent will have expired by 2012 and the launch of the product in Argentina is expected by the end of 2012-beginning of 2013, it guarantees free access to isobutane technology for MDIs in Argentina and elsewhere.

(b) One of the reasons justifying the use of isobutane as the replacement technology is that it "is already in use in marketed rectal foams and oral aerosols in the US". However, these applications are not the same as MDIs, where the propellant reaches the patient's lungs;

The World Bank reported that even though there are no inhalation products on the market

containing isobutane as a propellant, there is a long history of human exposure to hydrocarbon propellants in cosmetics (including deodorants) and medicinal products. The medicinal rectal aerosols containing isobutane are cited as a safety reference given the high rectal absorption rate and the large quantity of isobutane in the foam. In the cosmetic segment, butane is used as a propellant in personal aerosol deodorants and ambient deodorants. The American Conference of Governmental Industrial Hygienists defines a chronic inhalation exposure limit of 800 ppm of isobutane during 8 continuous hours, 5 days per week, and 52 weeks per year as being safe. This limit is accepted and included in Argentinean regulations. It corresponds to a daily chronic inhalation of 43.7 grams of isobutane per day. An exaggerated delivery of 20 daily doses from an isobutane salbutamol MDI would provide 2.24 grams of isobutane per day. This amount is 94.5 per cent lower than the daily limit considered safe by the Argentinean law.

(c) Whether or not representatives from Cassará discussed their proposal for the development and commercialization of isobutane MDIs with relevant health authorities in Argentina, since currently all commercially available MDIs worldwide are based on CFCs or HFA;

On this issue, the World Bank indicated that the laboratory has already talked to Argentine health authorities regarding the pathway to register MDIs containing isobutane. This includes an analysis of the formulation's stability data and pharmaceutical equivalence to salbutamol MDIs containing CFC. The decision to register the product is taken by the health authorities after reviewing the data submitted by the company. This is standard procedure for all MDI formulations. These studies will be completed by Cassará during product development.

(d) In regard to the consequences if the isobutane MDI formulation is not approved by relevant authorities at any stage of project implementation; the World Bank stated that "Cassará has committed to stop CFC consumption for non-essential uses and convert to non-ODS substances at its own cost if the project is not approved by local health authorities".

(e) In regard to the availability of potential and reliable sources of supply of pharma-grade isobutane, the World Bank indicated that the company has already identified several sources for such supply;

(f) The expected time of completion of the conversion of the MDI production line;

The World Bank explained that salbutamol CFC-MDIs cannot be phased out immediately after introduction of salbutamol HFA-MDI into the market because patients should be allowed to get used to the new formulations gradually. The company plans to continue offering salbutamol CFC-MDI for three years after the first introduction of salbutamol isobutane MDI. The level of CFC consumption forecast in the 2010 – 2015 period remains high because of essential uses of CFC MDIs containing not only salbutamol (up until 2014), but also other active ingredients, and the company's estimated growth on the basis of expected local and international business.

25. The Secretariat also notes that the technical reviewer of the project indicated that the successful use of isobutane as a propellant in MDIs has not been practically established. All of the major pharmaceutical companies have elected to use HFC-227ea and 134a. The reasons for these selections over isobutane are possibly perceived liabilities concerning flammability. Technically and toxicologically, isobutane should be a good replacement for CFCs in MDIs. Spraying 50 to100 micro-l into the buccal cavity using isobutane would not constitute a significant risk. The reviewer was, however, ambivalent

about the project. He further indicated that technically, isobutane can be used as a propellant in MDIs; Cassará is to be commended for seriously trying to make the conversion in this manner, however, it faces many obstacles before a successful conversion is assured.

Cost related issues

26. The Secretariat raised a number of issues on the eligibility and the level of funding being requested for some of the equipment items for the conversion of the MDI manufacturing line at Cassará, the adjustments to the costs associated with MDI formulations that were introduced in the market post-2003 (including the manufacturing line at Denver Farma), and the high costs of the transition strategy. The cost of the project as proposed by the Secretariat is US $2,806,874 with the following breakdown:

(a) US $2,090,000 as the total funding for the development of salbutamol isobutane MDIs and the full conversion of the MDI production line to isobutane technology in Laboratorio Pablo Cassará;

(b) US $646,874 as technical assistance for the development of HFA-MDIs that were on the market before 2004 by the following laboratories: Denver Farma, Phoenix, Raffo, Roux-Ocefa and Dallas;

(c) US $70,000 for the transition strategy.

27. Subsequently, the World Bank communicated the Secretariat's comments and recommendation on the funding level for the MDI project to the Government of Argentina. However, at the time of the preparation of this document, the agreement of the Government on the recommended funding level could not be reached.

28. The Secretariat notes that, on the basis of decisions 20/15 and 41/80, the MDI project proposal for Argentina should not have been submitted for consideration by the Executive Committee since no agreement has been reached on the level of funding. The Secretariat, however, decided to forward this project for consideration by the Executive Committee, pending an agreement on cost, in view of decision 54/5 requesting all MDI investment projects to be submitted no later than the 56th Meeting. Furthermore, implementation of this project will achieve the complete phase out of CFCs in Argentina.

RECOMMENDATION

29. Pending.

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