CUBA

Phase-out of CFC consumption in the Manufacture of Aerosol Metered Dose Inhalers (MDIs) in Cuba

United Nations Development Programme

(Revised)
November 2003

MULTILATERAL FUND FOR THE IMPLEMENTATION OF THE MONTREAL PROTOCOL ON SUBSTANCES THAT DEPLETE THE OZONE LAYER

PROJECT COVER SHEET

COUNTRY:	CUBA
IMPLEMENTING AGENCY:	UNDP
PROJECT TITLE:	Phase-out of CFC consumption in the Manufacture of Aerosol Metered Dose Inhalers (MDIs) in Cuba
PROJECT IN CURRENT BUSINESS PLAN:	Yes (project submitted in 2002)
SECTOR/ Sub-sector:	AEROSOL/ **Pharmaceutical Aerosols**
CONSUMPTION:	
ODS Consumption in SECTOR (2001):	137.3 ODP tons (28.2 ODP tons to be phased-out from ongoing project)
ODS Consumption in Sub-Sector (2001):	**109.1 ODP tons**
BASELINE (1995-1997 average):	625 ODP tons
CURRENT CONSUMPTION (2001):	504 ODP tons
PROJECT IMPACT:	**109.1 ODP tons**
PROJECT DURATION:	32 months after MLF Approval
Costs of Conversion:	
National MDI Transition Strategy (Annex 7)	**US$ 190,000**
Incremental Capital Cost Conversion Project:	**US$ 1,830,000**
Incremental Operating Cost (2 years):	**US$ 2,900,000**
Total Project Cost: (Excluding Technology Transfer fees for conversion project/license)	**US$ 4,920,000,**
Technology Transfer Fees	**US$ 1,040,000**
Total Cost	**US$ 5,960,000**
LOCAL OWNERSHIP:	**100%**
EXPORT COMPONENT:	**0%**
REQUESTED GRANT:	**US$ 5,960,000 (US$ 3.759,800 from 2002 and 2003 BP; the remaining from 2004)**
AGENCY SUPPORT COSTS:	**US$ 447,000**
TOTAL COST TO THE MLF:	**US$ 6,407,000**
COST-EFFECTIVENESS:	(No Sector CE Threshold)
STATUS OF COUNTERPART FUNDING:	Enterprise Commitment Received
PROJECT MONITORING MILESTONES:	Included in Project Document
NATIONAL COORDINATING BODY:	Oficina Tecnica de Ozono

PROJECT SUMMARY

The objectives of this project are (a) to phase-out the consumption of 109.1 ODP tonnes of CFC 11 and CFC 12 used in the manufacture of Aerosol Metered Dose Inhalers (MDIs) in Cuba, and (b) to manage the transition from CFC based MDIs to CFC-free MDIs in the country.

This involves conversion to CFC free MDI manufacturing technology at Laboratorio Farmaceutico "Julio Trigo Lopez", the only manufacturer of aerosol MDIs in Cuba, and the dissemination of a National MDI transition strategy based on an awareness campaign to educate doctors prescribing MDIs on the timing and reasons for the transition from CFC MDIs to CFC-free MDIs.

To implement the selected replacement technologies, Laboratorio Farmacéutico "Julio Trigo López" will require technology transfer from one, or more, established multinational enterprises that have experience in the development and manufacture of MDIs using CFC free technologies, and who has the right to transfer such technology without infringement of any intellectual property related to either the drug molecule, the method of formulation, the design of the metering valve or actuator, or the filling process. This proposal addresses the conversion to a manufacturing facility of MDI using HFC 134a. The proposal is presented with the corresponding incremental capital costs; incremental operational costs and technology transfer costs.

As far as the HFC 134a technology, the transition process from CFC MDIs to HFC MDIs in Cuba requires that for a period of some time there will need to be production of both CFC MDIs, and HFC MDIs. As a result, completely new HFC MDI manufacturing facilities of equivalent capacity are required or Cuba will have to run campaign production to supply patients during this period. The project covers an HFC MDI Manufacturing Facility of similar production capacity to the baseline facility (>6 million units per annum). Funds are also required for materials that will be consumed in, Equipment Proving Trials, Pilot Scale Production, Clinical Trials, Product Stability, as well as for Product Stability Testing, Clinical Trials, Testing, and Product Registration and Overall Project Supervision. The total cost of this is US$ 1,830,000. The technology transfer fees are being requested by the provider at a level of US$ 1,040,000.

For the technology transition the funding requested for implementation of the National MDI transition strategy, necessary as a support measure to ensure a successful transition is US$190,000.

Capital costs had been discussed and agreed with the Secretariat before the 38th Executive Committee Meeting based on an analysis of possible equipment needs for HFC 134a technology current available, without going into specific providers and their equipment requirements, as at that time none had been identified. Therefore, in deepening the discussions with identified providers, UNDP has found out that specific needs are different for each technology provider. This is reflected in the change in capital cost from the previous project document. The period used for the calculation of the Incremental Operational Cost was 2 years. The total IOC for the project are US$ 2,900,000.

It must be noted that MLF funding of the CFC-free MDI technology transfer costs is essential to successful project completion. Flexibility in the use of the allocated funds is also required.

IMPACT OF THE PROJECT ON THE COUNTRY'S MONTREAL PROTOCOL OBLIGATIONS

While Cuba has approved projects that are still ongoing as of August 2002, these will phase-out only 32.6 ODP tonnes of CFCs. To meet the Montreal Protocol compliance level of 313 ODP tonnes of annual CFC consumption in 2005, Cuba must then eliminate a further 155 ODP tonnes from the 2001 level of

consumption of 504 ODP tonnes. This project will eliminate the use of 109.1 ODP tons, and as such it is critical to helping Cuba to comply with Montreal Protocol Annex A Group I measures.

TABLE OF CONTENTS

PROJECT OF THE GOVERNMENT OF CUBA

PHASE-OUT OF CFC CONSUMPTION IN THE MANUFACTURE OF AEROSOL METERED DOSE INHALERS (MDIs) IN CUBA BY CONVERSION TO CFC FREE TECHNOLOGY AT *LABORATORIO FARMACEUTICA "JULIO TRIGO LOPEZ"*:TO MANAGE THE RESULTING TRANSITION TO CFC FREE MDI TECHNOLOGY IN THE COUNTRY

1. PROJECT OBJECTIVES

The joint objectives of this project are (a) to phase-out the use of CFC 11 and CFC 12 in the manufacture of salbutamol Aerosol Metered Dose Inhalers (MDIs) in Cuba, which represent 80% of the consumption in the MDI sector, and (b) to manage the transition from CFC based MDIs to CFC Free MDIs in the country. This involves conversion of Laboratorio Farmaceutica "Julio Trigo Lopez", the only manufacturer of aerosol MDIs in Cuba, and a dissemination of the National MDI transition strategy based on an awareness campaign to educate doctors prescribing MDIs on the timing and reasons for the transition from CFC MDIs to CFC-free MDIs.

2. SECTOR BACKGROUND

Cuba ratified both the Vienna Convention for the Protection of the Ozone Layer and the Montreal Protocol on Substances that Deplete the Ozone Layer in July 1992. Subsequently in October 1998, it ratified both the 1990 London Amendment, and the 1992 Copenhagen Amendment, to the Montreal Protocol.

The Country Programme (CP), based on the 1991 ODS consumption data, was approved in July 1993. Under the CP the Government proposed to eliminate 35% of CFC consumption between 1993 and 1996 by implementing training programmes for service technicians in the refrigeration sector. The remaining consumption was to be phased out by other activities by the year 2010.

Cuba does not produce CFCs, and total demand is met through imports. CFC consumption during the period 1990 – 2001 was as illustrated in the following table:

Annex A Group I CFC Consumption (ODP tonnes)											
1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
778	324	122	122	150	546	664	663	531	571	534	504

As the data in the table shows, in practice CFC consumption declined by 84% between 1990 and 1993, but then increased more than 4-fold between 1993 and 1996. This pattern of consumption is unrelated to activities in the Country Programme; it simply reflects the difficult economic situation in the country.

According to the CP, in 1991 some 307 ODP tonnes (95%) of the 324 ODP tonnes of CFC consumption in Cuba was in the refrigeration and air-conditioning sector, and the majority of this was for service and repair activities. The balance of 17 ODP tonnes was in the aerosol sector. There was no other CFC consumption for foam, or solvent, applications.

In 2001, the reported total CFC consumption was 504 ODP tons, of which 372 ODP tons (74%) was in the refrigeration service sector, with the balance of some 132 ODP tonnes for aerosols.

Cuba's average consumption level of Annex A Group I CFCs for the three years 1995 – 1997, the "Baseline Consumption" on which the Montreal Protocol (MP) consumption compliance levels are based, was 625 ODP tonnes. In 1999, in order to ensure compliance with the first MP control step, Cuba froze the imports of Annex A Group 1 substances at the baseline level. However, differences in consumption levels between 1997 and 2001 continue to be strongly influenced by the economic situation rather more than actions to eliminate CFC consumption.

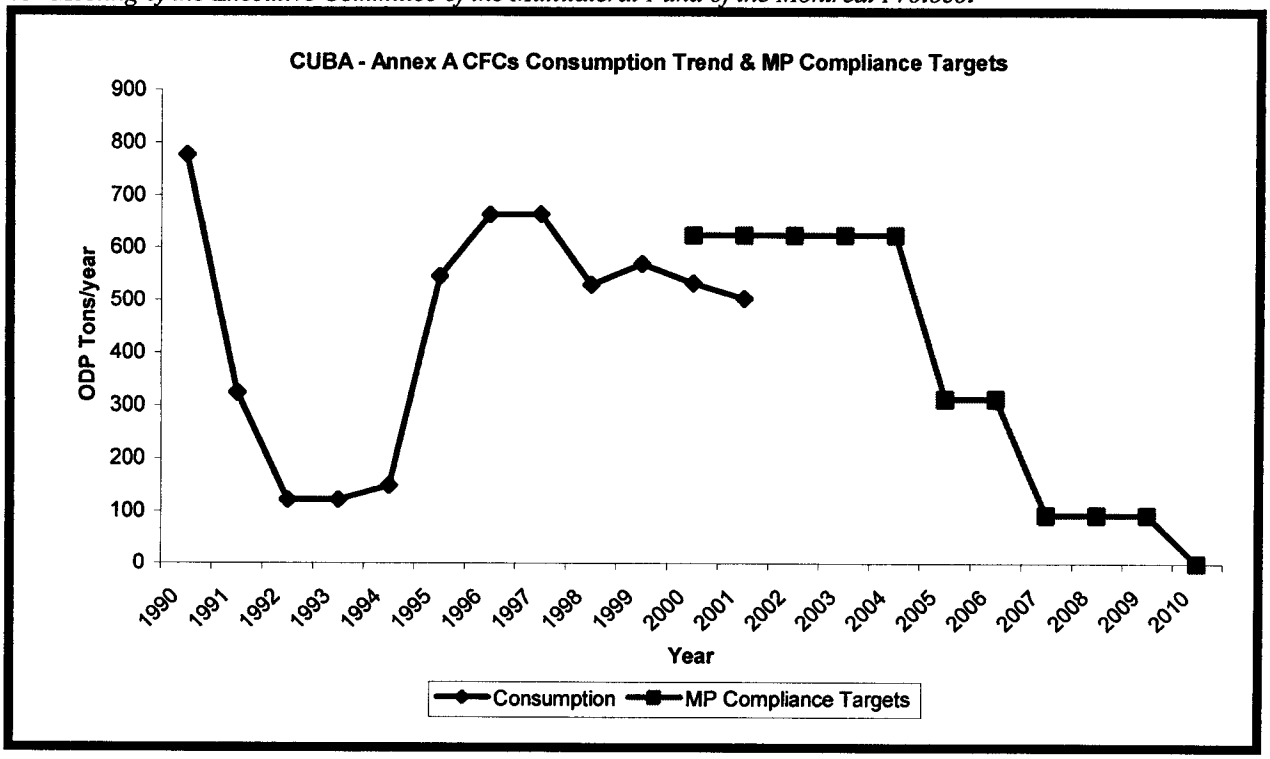
To meet its obligations under the Montreal Protocol, Cuba must now ensure that the annual consumption of Annex A Group I substances (CFCs 11, 12, 113, 114, and 115) does not exceed the "Baseline Consumption" of 625 ODP tonnes for each of the years 2000 through 2004. Thereafter, the maximum permitted levels of annual CFC consumption for compliance with the Montreal Protocol are as follows:

2005 – 2006 (50% of the "Baseline Consumption") – **313 ODP tonnes**.

2007 – 2010 (15% of the "Baseline Consumption") – **94 ODP tonnes**.

2010 Zero consumption.

While the historical levels of consumption have been dictated by the economic situation in the country, the following graph serves to illustrate the trend of consumption in ODP tonnes of Annex A Group I CFCs in Cuba, and the consumption control levels for compliance with the Montreal Protocol;



Graph 1. CFC Consumption Trend: Actual and MP Compliance Levels

While Cuba has approved projects that are still ongoing as of June 2002, these will phase-out only 32.6 ODP tonnes of CFCs. To meet the MP compliance level of 313 ODP tonnes of annual CFC consumption in 2005, Cuba must then eliminate a further 155 ODP tonnes from the 2001 level of consumption of 504 ODP tonnes.

Pursuant to ExCom Decision 35/57, Cuba has selected Option 1 for determining the starting point for implementation of it's national aggregate CFC consumption (Montreal Protocol Compliance Baseline minus CFC projects approved but not yet implemented as of 31 December 1997, and minus CFC projects approved for phase-out between 1998 and 2001). The remaining CFC consumption eligible for funding resulting from Cuba's selection of Option 1 under ExCom Decision 35/57 is then 585.7 ODP tonnes.

Cuba is then eligible to receive additional MLF assistance, and such assistance appears essential if Cuba is to meet the 2005 CFC consumption compliance level of 313 ODP tonnes.

Aerosol Sector Background

Two distinct sub-sectors make up the aerosol sector in Cuba:

- The Industrial/Technical Aerosol Manufacturing Sector – This is comprised of a single production facility founded in 1983 and located in the *Centro de Investigaciones y Desarrollo Tecnico (CIDT)* under the jurisdiction of the Ministry of Interior. A project to eliminate 28.2 ODP tonnes of CFC 12 at this facility by conversion to the use of

hydrocarbon propellant was approved at the 34th ExCom Meeting in July 2001. This project is ongoing.

- The Pharmaceutical Aerosol Manufacturing Sector – This again is a State controlled activity under the Ministry of Public Health (MINSAP). It is concerned solely with the manufacture of metered dose inhalers, predominately bronchodilator products for the treatment of asthma, allergic respiratory diseases, and chronic obstructive pulmonary disease (COPD).

  Production of MDIs in Cuba began in 1993 because of the high incidence of asthma and COPD in the population, coupled with the need to both substitute imports, and introduce new medications. According to data from the *Ministerio de Salud Publica (MINSAP)* the incidence of these diseases in the Cuban population is as follows:

Asthma	-	10%
Allergic Respiratory Disease	-	8%
COPD	-	5%

  The first MDI manufacturing facility with a capacity of 8,500 units/day was installed at Laboratorio Farmacéutico "Andrés Berro" belonging to the enterprise "Reinaldo Gutiérrez". Manufacturing capacity was increased to 24,242 units/day in 1994 by the installation of additional MDI manufacturing facilities at Laboratorio Farmacéutico "Julio Trigo López", also belonging to the enterprise "Reinaldo Gutiérrez".

  In 2000, the aforementioned MDI manufacturing facilities were combined into a single operation at Laboratorio Farmacéutico "Julio Trigo López" with a resultant increase in MDI production capacity to 30,000 units/day.

  MDI production in 2001 totalled 6 million MDIs, made up of 4.8 million (80%) Salbutamol 200 dose bronchodilator MDIs, and 1.2 million (20%) Beclomethasone 50 μg controller medication MDIs.

  CFC consumption for the manufacture of aerosol MDIs has increased steadily since 1993, while consumption of CFCs for the production of industrial, technical, and consumer aerosol products such as insecticides, has been erratic due to influence by the state of the Cuban economy. Recent CFC consumption is more meaningful than historic consumption, and the data obtained for preparation of the CIDT aerosol conversion project in 2001, and the data obtained for preparation of this aerosol MDI conversion project proposal are summarized in the following table:

Aerosol Sector CFC Consumption (ODP tonnes)

Sub-sector	1999	2000	2001	2002 (Estimate)
Industrial/Technical Aerosols	3.5	15.0	25.0	25.0
Aerosols MDIs	74.3	84.7	109.1	109.1

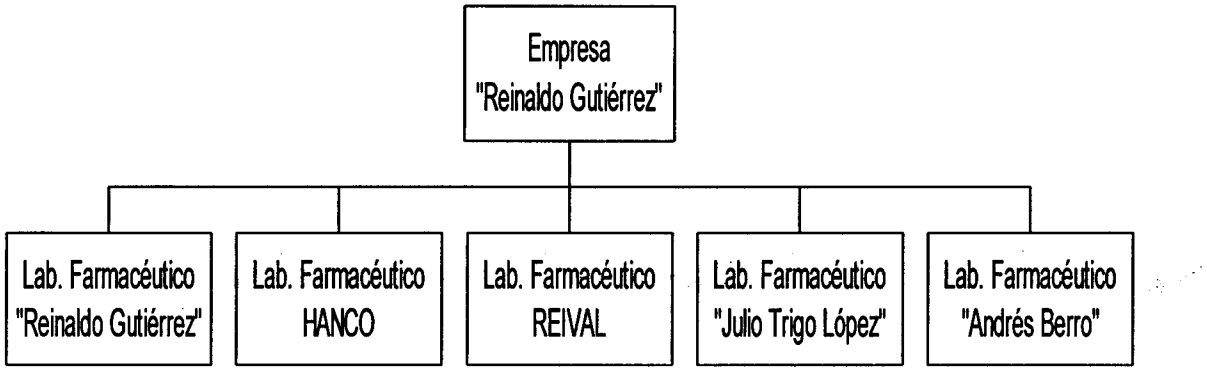
Total	**77.8**	**99.7**	**134.1**	**134.1**

Considering that all of the remaining CFC consumption in the refrigeration and air-conditioning sector is for repair and service activities where reduction in consumption is difficult to achieve without equipment replacement or retrofit, this growth trend in CFC consumption in the aerosol MDI manufacturing sector further emphasises the need for MLF assistance for a conversion project for the MDI sector to enable Cuba to meet the MP CFC consumption compliance target in 2005.

3. ENTERPRISE BASELINE DATA

Aerosol MDI manufacturing activities began in Cuba in 1993 at the Laboratorio Farmacéutico "Andrés Berro" belonging to the enterprise "Reinaldo Gutiérrez". Additional manufacturing capacity was installed in 1994 at the Laboratorio Farmacéutico "Julio Trigo López", also belonging to the enterprise "Reinaldo Gutiérrez". These separate MDI production facilities were amalgamated in 2000 into a single MDI manufacturing operation based in the Laboratorio Farmacéutico "Julio Trigo López" in Havana.

The enterprise "Reinaldo Gutiérrez" is 100% Cuban owned, and is comprised of several laboratorios farmacéuticos as illustrated in the following enterprise structural organisation chart.



Initially, only a 200 dose aerosol MDI based on the short acting b-agonist Salbutamol was produced, but a second, controller medication product, a 50 μg MDI based on Beclomethasone was introduced in 1999. In 2001, the 200 dose Salbutamol MDI accounted for 80% of the total production of 6 million units.

Laboratorio Farmacéutico "Julio Trigo López" currently consumes both CFC-11 and CFC-12 in the manufacture of aerosol MDIs. The CFC-11 is used for the preparation of a "suspension slurry" of the active ingredient to facilitate filling the precise quantity into the open aerosol MDI container, after which the MDI aerosol container is closed with the aerosol metering valve, and

the CFC-12 that acts as the aerosol "propellant" is injected into the aerosol container under pressure through the metering valve. This production process applies for both the existing 200 dose Salbutamol and the 50 µg Beclomethasone CFC MDI products.

Presently there are no licensing, technical assistance, or technology transfer agreements relating to MDI manufacture. The MDI formulation technology is based on the enterprises own research work, and the aerosol filling technology was obtained from the well known aerosol filling equipment supplier, Pamasol Willi Mader AG of Switzerland.

All production is sold within Cuba. Current CFC MDI production capacity at the Laboratorio Farmacéutico "Julio Trigo López" is 30,000 units/day, around 6.9 million units/year, is based on a single production line. Remodelling of the production area, and incorporation of the second production line based on the equipment from Laboratorio Farmacéutico "Andrés Berro", is almost complete and this will increase production capacity to around 8 million units/year. This is necessary to satisfy National demand; as well as to be able to introduce new MDI based medication products into the Cuban market. It must be emphasized that the production of CFC MDIs at Laboratorio Farmacéutico "Julio Trigo López" is intended to, and does, satisfy total demand for MDIs in Cuba, and there are no imports of MDIs.

The MDI manufacturing facilities at Laboratorio Farmacéutico "Julio Trigo López" are well managed and all production complies with the "Buenas Prácticas de Producción de Medicamentos".

More detailed baseline data on Laboratorio Farmacéutico "Julio Trigo López" and the MDI manufacturing facilities is provided in **ANNEX 1**.

4. PROJECT DESCRIPTION

The requested MLF funding is to address two distinct needs, conversion of CFC MDI production in Cuba to CFC Free MDI filling technology, and separately the development, implementation, and management of a National transition strategy related to the phase-out of CFC MDIs, and the introduction of the replacement technology.

4.1 NATIONAL CFC MDI MANUFACTURING SECTOR CONVERSION PROJECT

4.1.1 Overview & Selection Of Replacement Technologies For CFC MDIs

Metered dose inhalers, which were introduced in the 1950's, have been a safe, efficient and reliable device to treat respiratory diseases such as asthma and COPD. No other inhalation therapy has been so widely used for the treatment of reversible diseases of human airways, and the MDI is used in approximately 80% of the patients with asthma.

Metered-dose inhaler products contain therapeutically active ingredients dissolved or suspended in a propellant, a mixture of propellants, or a mixture of solvents, propellants, and/or other excipients in compact pressurized aerosol dispensers. An MDI product may discharge up to several hundred metered doses of one or more drug substances. Depending on the product,

each actuation may contain from a few micrograms (mcg) up to milligrams (mg) of the active ingredients delivered in a volume typically between 25 and 100 microliters.

Although similar in many features to other drug products, MDIs have unique differences with respect to formulation, container, closure, manufacturing, in-process and final controls, and stability. These differences need to be considered during product development because they can affect the ability of the product to deliver reproducible doses to patients over the life of the product as well as the product's efficacy. Some of the unique features of MDIs are listed below:

- The container, the valve, the actuator, the formulation, any associated accessories (e.g., spacers), and protective packaging collectively constitute the drug product. Unlike most other drug products, the dosing and performance and, therefore, the clinical efficacy of a MDI are dependent on the design of these components.

- The fraction of the formulation delivered to the patient consists of a mixture of micronized (or solubilized) drug substance in the desired physical form, which may be within a residual matrix of oily excipient material, propellant, and/or solvent.

- The aerosolization of materials from a pressurized container is a complex and rapid sequence of events. When the content of the metering chamber is released, it undergoes volume expansion and forms a mixture of gas and liquid before being discharged as a jet through the orifice of the actuator. Within the expanding jet, the droplets undergo a series of processes. Subsequent to the aerosolization and dispersion of the drug product into a multitude of droplets, and during the propulsion of these droplets from the actuator to the biological target, the drug substance particles in the droplets become progressively more concentrated due to rapid evaporation of the volatile propellant components.

MDIs possess numerous characteristics that, taken together, set them apart from other inhalation delivery systems, such as dry power inhalers and nebulisers. The table below provides a comparison between these three types of inhalers.

Type of inhaler	Advantages	Disadvantages
Metered Dose Inhalers (MDI)	• Simple actuation system • Reliable accurate dose regardless of the patient's breathing capacity • Compact and portable • Easy use • Economical • The stability of the medication is not affected by ambient temperature or humidity	• Mostly use CFCs as propellants • The method of pressing and breathing requires coordination between actuation and breathing (breath-actuated systems do not have this drawback)
Dry Power Inhalers (DPI)	• No propellant used	• Drug release depends on the patients breathing capacity • The inhaled fraction is reduced if the patient breath is directed into the

		system • Relatively expensive
Nebulisers	• No special breathing coordination required • Works with patients using mechanical ventilation • Useful to administer new or less used drugs.	• Not portable • Dependent on an electric supply • Expensive • Operation takes a long time • Requires the use of preservatives to reduce risk of bacteria contamination

MDIs are 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 other chronic obstructive pulmonary disease (COPD).

The important features of MDIs is that they represent a cost-effective, tamper-proof, packaging form for safe and easy administration of the required dosage of medicament to dependent patients of all ages who, particularly in the case of asthma sufferers, generally need to achieve fast relieve from the disease symptoms.

CFC MDI manufacturing technology was developed based on a marriage of typical aerosol filling techniques and the established practices and standards of the pharmaceutical industry. While the selection and development of active ingredients and the design of metering valves for accurate dosage represented the difficult part in the development of the technology, the physical, chemical, and toxicological properties of CFC-11 and CFC-12 coupled with almost standard aerosol filling equipment and techniques, enabled the manufacture of MDI products that met all of the design requirements for effective medication delivery, and ease of use by patients.

The most common CFC MDI formulation based on Salbutamol is manufactured by using a typical aerosol filling method. The Salbutamol powder is mixed with a special surfactant (sorbitan triolate) and CFC-11 in stirred mixing vessel designed to produce and maintain a homogeneous suspension of the Salbutamol powder in the surfactant/CFC-11. This suspension is then accurately dosed in an aluminium monobloc aerosol container. After this the metering valve is crimped on the monobloc container, and CFC-12 to act as the propellant for delivery of the drug suspension in the required particle size, is introduced into the monobloc container through the metering valve.

While the manufacturing process is relatively simple, it must be noted that the CFC-11 and CFC-12 employed must manufactured to recognised pharmaceutical standards, and strict quality control of all stages of the procurement and storage of materials and components, as well as the manufacturing process, is required. Normally immediately after the addition of the CFC-12 propellant the MDIs are then pressure tested, production batches are clearly identified and quarantined for 1-3 months, before further testing, and finally release into the market.

The foregoing represents the basic CFC MDI manufacturing process employed by Laboratorio Farmacéutico "Julio Trigo López" in Havana, Cuba.

Ideally then, the conversion of CFC MDIs to a CFC-free formulation would require zero-ODP replacements for both CFC-11 and CFC-12 that possess similar physical, chemical, and

toxicological properties. However, replacements with such properties are not available. The CFC MDI conversion process led by the established multinational pharmaceutical companies has spawned new formulations, new manufacturing processes, as well as non-aerosol dry powder inhalers (DPIs). 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.

Both HFC-134a and HFC-227ea have been developed as zero-ODP replacements for CFC-12 to serve as the propellant function in CFC-free MDIs, and in some products also as the CFC-11 replacement. However, differences in the physical (e.g. boiling point) and chemical (e.g. solubility) properties of these substances and the CFCs they replace, require changes to the manufacturing process and equipment, as well as to seal materials used in both MDI valves and manufacturing equipment.

HFC-134a and HFC-227ea, again manufactured to recognised pharmaceutical standards, are commercially available and are now widely used throughout non-Article 5 countries.

The options for CFC MDI conversion to CFC-free formulations (not in any order of importance as applied globally) can be briefly summarised as follows:

A. **HFC/Ethanol MDIs (Pressure Filled)** - The medicament drug suspension is manufactured basically by similar technology as used for the CFC MDI version, but the CFC-11 used as the liquid phase of the suspension and to solubilise the surfactant, as well as to modify the final vapour pressure of the MDI formulation, is replaced by ethyl alcohol (ethanol). However, due to the different solubility properties of ethanol and CFC-11 the surfactant has to be replaced by a new surfactant chemical. This suspension is then, as previously described metered in the aluminium monobloc container. The propellant CFC-12 is replaced by HFC-134a. As the spray/particle size characteristics of the ethanol/HFC-134a MDI formulation are different to those of the CFC MDI version, the valve and actuator have to be redesigned to achieve the required spray and particle size characteristics for efficacious dosage. Some products use HFC-227ea as the propellant instead of HFC-134a.

B. **HFC MDIs (Pressure Filled)** - The MDI is manufactured in such a way that HFC-134a serves as the replacement for both CFC-11 and CFC-12. The medicament drug suspension is manufactured only with HFC-134a, but since HFC-134a has a boiling point of -26.2 °C and it is gaseous at normal pressure, the drug/HFC-134a suspension must be prepared under pressure of about 6 bar in a special mixing vessel. The prepared drug suspension in HFC-134a is then directly metered under pressure through a special design valve into the aluminium monobloc container by means of a diaphragm filler. In some cases part of the required amount of HFC 134a may be pressure filled through the valve after the drug/HFC134a suspension has filled in order to clear the valve of suspension.

C. **HFC MDIs (Cold Filled)** The HFC MDI is again manufactured in such a way that HFC-134a serves as the replacement for CFC-12. In some cases CFC-11 is replaced with ethanol. In this process the complete CFC-free MDI formulation is prepared in a special mixing vessel, chilled to a temperature of around -40 °C, then filled as a liquid suspension into the open

aluminium monobloc container, followed immediately by the metering valve being crimped in place to close the container.

D. **Single-Dose DPI** - One form of Dry-Powder Inhaler (DPI) developed as a replacement for CFC aerosol MDIs is the single-dose powder inhaler. In this type of device 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.

E. **Multi-Dose DPI** - Another form of DPI is the multi-dose powder inhaler. This can deliver many doses without a need to refill the device after each inhalation. The multi-dose DPI typically either have the drug in a blister (as a discrete dose) or they contain drug that is metered from a drug reservoir. Current products vary between four and two hundred doses.

F. **Nebulisers** - These devices produce aerosols by agitation of solutions of the medication, and they account for 1-2% of the global market. They are generally reserved for patients with special needs, such as very young babies or patients with severe disease, who need much higher doses of active substance.

G. **Oral treatment** - This type of oral therapy is generally use as preventive treatment and may reduce the use of inhalers. Although the use of tablets for asthma patients may be of some value, it is highly unlikely that it will become a significant substitute for the current inhaled preventive therapy.

The first CFC-free MDI based on Salbutamol/HFC-134a was introduced in the UK in 1994. Today, Salbutamol/HFC-134a MDIs are approved and marketed in over 60 countries, including 30 Article 5 countries. It has been estimated that in 2001 global production of HFC based MDIs was over 100 million units, representing approximately 25% of total global MDI production, while multi-dose DPI production was over 70 million units.

Both HFC-134a MDI technology, and DPI technology, can therefore be considered as fully developed commercially, even though the technology may not be in the public domain.

The HFC based MDIs have a different taste and a different cooling effect from the traditional CFC MDIs. While physicians and patients need to be aware of these changes (and the reasons for them) and be well prepared to accept them, experience indicates that properly managed the change can be effected with minimal patient concerns.

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.

Selection of CFC MDI Replacement Technology

Laboratorio Farmacéutico "Julio Trigo López" has based the selection of the replacement technology for it's current CFC MDI products on an evaluation of the following criteria:

- The specific needs of the Cuban population;
- The current CFC MDI products manufactured by Laboratorio Farmacéutico "Julio Trigo López" in Havana, Cuba;
- The existing experience and skills of the Laboratorio Farmacéutico "Julio Trigo López" personnel;
- The high incidence of asthma, allergic respiratory diseases, and chronic obstructive pulmonary disease (COPD) in all ages of the Cuban population;
- The familiarity of existing Cuban patients with the MDI design as a device for delivery of the required medication;
- The maturity and established commercialisation of HFC-134a based MDI technology;
- The established "Patient Acceptance" of CFC-free MDIs;
- HFC-134a price, product availability, and cost-effectiveness of the HFC-134a MDI formulation;
- The present, and short to medium term future, economic situation in Cuba.

Laboratorio Farmacéutico "Julio Trigo López" wishes to stay with the MDI as the drug delivery system, and the selected replacement technologies are as follows:

200 Dose Salbutamol CFC MDI - Laboratorio Farmacéutico "Julio Trigo López" wishes to be able to offer patients in Cuba a Salbutamol bronchodilator formulation developed commercially in Article 2 countries, based a formulation of Salbutamol in HFC-134a alone.

50 µg Beclomethasone CFC MDI - Laboratorio Farmacéutico "Julio Trigo López" wishes to convert this product to a CFC-free MDI based on a solution of Beclomethasone in ethyl alcohol (ethanol), and HFC-134a.

The total baseline consumption, including losses, in the year 2001, and the ODP tonnes that will be eliminated by this project, are shown in the following table:

Enterprise	CFC-11 ODP tonnes eliminated	CFC-12 ODP tonnes eliminated	Total ODP tonnes eliminated
Laboratorio Farmacéutico "Julio Trigo López"	37.6	71.5	109.1

Technology Transfer

To implement the selected replacement technologies, Laboratorio Farmacéutico "Julio Trigo López" will require technology transfer from one, or more, established multinational enterprises that have experience in the manufacture of CFC-Free MDIs using alternative technologies and that have the right to transfer such technology without infringement of any intellectual property related to either the drug molecule, the method of formulation, the design of the metering valve or actuator, or the filling process.

It must be recognised that without such transfer of technology it would likely take Laboratorio Farmacéutico "Julio Trigo López" between 6 – 10 years to develop and obtain approval for CFC-free replacements for their current CFC MDIs. This timescale will likely result in Cuba's non-compliance with its 2005 CFC consumption limits under the Montreal Protocol, but more seriously, it is likely to impact the production and availability of CFC MDIs in Cuba, with resultant adverse health consequences for the large numbers of the Cuban population that suffer from asthma, chronic obstructive pulmonary disease (COPD), and other lung diseases characterized by obstruction of airflow and shortness of breath. (See ANNEX 8).

The present project proposal therefore includes the analysis of one technology transfer option based on the offer received from a recognised laboratory of the sector. The alternative and its corresponding cost is described in the project document and is presented for consideration as the most appropriate for the Cuban case.

It is anticipated that an Independent Expert MDI Consultant will also be required to assist in project implementation and monitoring activities.

4.1.2 Process Implications Of The Selected Replacement Technologies

The selected replacement technologies require different production processes than those used at present for the existing CFC MDI products.

- The conversion of the 200 dose Salbutamol CFC MDI to an HFC MDI based on a suspension of Salbutamol in HFC-134a requires completely different production equipment. The HFC-134a will replace both the CFC-11 and CFC-12 in the CFC MDI formulation, but because HFC-134a is a gas at atmospheric pressure this will involve preparation of a "suspension slurry" of the Salbutamol in HFC-134a in a pressure vessel. Precisely measured amounts of the Salbutamol/HFC-134a "suspension slurry" will then be injected under pressure through a modified metering valve into the already closed aerosol MDI container. A further injection of HFC-134a will be made into the aerosol container through the metering valve to clear any of the Salbutamol/HFC-134a "suspension slurry" from the valve.
- The 50 μg Beclomethasone CFC MDI will be converted to a HFC MDI based on ethyl alcohol (ethanol) and HFC-134a. The process has similarities with the existing process in that precisely measured amounts of the Beclomethasone/ethanol mixture will be filled into the open aerosol MDI container, after which the MDI aerosol container will be closed with the aerosol metering valve, and the HFC-134a that acts as the aerosol "propellant" will be injected into the aerosol container under pressure through the metering valve.

While in other requests for MLF assistance for CFC conversion projects the retrofit of existing CFC using manufacturing equipment to be able to use the CFC replacement technology is always considered, in the case of this MDI project in Cuba, retrofit is not possible because of the poor compatibility of the 134a with existing seals and because of the new indexing method of filling.

As stated previously, the Cuban situation is unique as there are no imports of MDIs, and all MDI demand is met by local production. This is because of the economic situation in the country, and replacing local MDI production with imported MDI products while the existing manufacturing facilities are converted for use with CFC-Free technology (including retrofit of any parts that might be possible to retrofit) is not an option. The transition process from CFC MDIs to CFC-free MDIs in Cuba requires that for a period of some time there will need to be production of both CFC MDIs, and CFC-free MDIs. As a result, completely new CFC-free MDI manufacturing facilities of equivalent capacity are required. (Please refer also to **Section 4.2 - CUBAN TRANSITION STRATEGY FOR THE ELIMINATION MDIs WITH CFC, AND THE INTRODUCTION OF THE REPLACEMENT CFC-FREE MDIs**).

Details of the baseline equipment related to the manufacture of CFC MDIs at Laboratorio Farmacéutico "Julio Trigo López" are provided in **ANNEX 1**. This equipment will be dismantled and destroyed, or otherwise rendered unusable with CFCs, once the conversion to CFC-free MDI products has been successfully completed.

4.2 CUBAN TRANSITION STRATEGY FOR THE ELIMINATION MDIs WITH CFC, AND THE INTRODUCTION OF THE REPLACEMENT CFC-FREE MDIs.

Important Note: The detailed Cuban National Strategy for the phase-out of CFC MDIs, and the introduction of the replacement CFC-free MDIs is appended as **ANNEX 7**. The following is a summary of key points provided for convenience.

4.2.1 Principles, Objectives, & Approach Of The Cuban National Transition Strategy

Principles - There is consensus amongst all the stakeholders that the National transition strategy for the phase-out of CFC use in MDIs in Cuba should be based on the following principles:

- Patients' health should be the first priority in the transition period. The patient is at the core of the transition.
- All interested parties should actively manage the transition to ensure the patient's access to needed treatments is not interrupted.
- There must be transparency and efficacy in the authorization and follow-up of new products in the market.
- The strategy will focus on the development and implementation of an education programme with the active participation of all sectors, health professionals, Ministries, pharmaceutical companies, and the community.

In addition to these principles, the strategy may and should be able to encourage the elaboration and execution of a National programme to control Asthma and COPD, two diseases that due to their prevalence represent a key health concern in Cuba.

Objectives - The objective of this strategy is the phase out of the use of CFC MDIs according to a timetable and criteria previously agreed by all the stakeholders, and this implies the acceptance of these new products by both health professionals and patients.

The Cuban situation is unique with 100% of the National demand for MDIs being met by local manufacture by a State-owned enterprise. There are no imports of MDIs, and the intention is that this scenario should continue during, and after, the implementation of a CFC MDI conversion project to enable the local manufacture of CFC-free MDIs.

Both the National CFC MDI conversion project and the National transition strategy for the phase-out of CFC use in MDIs in Cuba are then inextricably linked. While the objective of the conversion project is also related to reducing CFC consumption and Cuba's compliance with the obligations of the Montreal Protocol, the National transition strategy for the phase-out of CFC use in MDIs in Cuba cannot be implemented without implementation of the National CFC MDI conversion project, and vice versa. Because of the economic situation in Cuba, the implementation of **both** these projects is also dependent on MLF assistance.

Approach - The report of the Aerosol Technical Option Committee of the Montreal Protocol recognizes that there is no single strategy applicable to all countries for the phase-out of CFC MDIs. The process of transition to non-CFC alternatives is complex and involves the need for dialogue between health authorities, environmental agencies and other interested groups.

The Cuban situation is distinctly different from other countries and much simpler. There is only a single , State controlled, CFC MDI manufacturer that satisfies all National demand, and there are no imports of MDIs. The product range consists of only two MDI products, a Salbutamol bronchodilator product which accounts for 80% of production, with a Beclomethasone controller product making up the balance. This situation exists because of the Cuban economy, and is likely to continue for the foreseeable future. While new products are being examined, their introduction is not considered imminent.

The transition strategy has then been formulated based on the unique Cuban situation, and a timetable for CFC phase-out agreed with all stakeholders, and on a time scale compatible with the expected date for the local manufacture of CFC-free MDIs. This timetable will be monitored periodically and modifications will be made as necessary in the light of its effective application and the introduction of the CFC-free products.

CFC MDIs will be withdrawn from the market as soon as is feasible following the introduction of the CFC-free MDIs, and the period in which both CFC-free MDIs and CFC MDIs co-exist in the market should be limited.

The following factors have to be taken into consideration in setting the timetable for the phase-out CFC MDIs:

- Sufficient time for post-marketing surveillance data collection. Awareness and education activities should promote the practice amongst health professionals of reporting adverse reactions to the drug surveillance centres.

- Market acceptance of the new products. Awareness and education activities should promote the use of CFC-free MDIs amongst health professionals and patients.

- The time necessary for the approval, the level of funds approved, and implementation of the National CFC MDI conversion project.

Other factors that impact the approach to CFC MDI phase-out in Cuba are as follows:

- The only significant production of the high quality CFCs needed for MDI use is in the Netherlands (European Union);

- Several non-Article 5 Countries have already phased-out CFC MDIs, in particular salbutamol CFC MDIs, and the target date for the completing the transition to CFC-free MDIs generally adopted by non-Article 5 Countries is 2005;

- CFC production has been phased-out in non-Article 5 Countries, except for the basic domestic needs of Article 5 countries, and for agreed "essential uses". There is Governmental pressure on European Union producers to cease supply even for these uses, and the production of high quality CFCs for MDIs in the Netherlands is expected to end in 2004, with some stockpiling to meet demand in 2005/6.

Roles & Responsibilities – The following is a non-exhaustive list of Government Agencies and other interested parties that will play a role in the development and implementation of the National transition strategy for the phase-out of CFC MDIs, and their responsibilities:

Ministry of Science, Technology, and Environment (CITMA) (through the Ozone Technical Office - OTOZ):

- Coordinate the various activities resulting from this transition strategy: national education campaign, conversion of the national industry, formulation of the necessary legal provisions together with the Ministry of Public Health (MINSAP).
- Apply via UNDP to the Multilateral Fund for the Implementation of the Montreal Protocol to provide technical and financial assistance for the application of this National transition strategy.

Ministry of Public Health (MINSAP):

- Carry out the national education campaign in coordination with all other stakeholders, MINSAP, State pharmaceutical company, and Ministry of Science, Technology, and Environment (CITMA).
- Grant marketing authorizations for CFC-free MDIs.
- Withdraw CFC MDIs from the market in compliance with the agreed timetable and criteria.

- Formulate the necessary legal provisions together with the Ministry of Environment.
- Support the national education campaign.

State Pharmaceutical Company:

- Support to the national education and sensitisation campaign.
- Provide CFC-free products within the terms agreed in this strategy.
- Withdraw CFC products within the terms agreed.

4.2.2 Costs of the Cuban National Transition Strategy

At its 37th Meeting in July 2002 the MLF Executive Committee considered draft guidelines for MDI projects (Ref. UNEP/OzL.Pro/ExCom/37/58) and decided (Decision 37/61):

- To take note of the draft guidelines;

- To request members of the Executive Committee to submit comments on the issue to the Secretariat in time for a further discussion at the 40th Meeting of the Executive Committee;

- In the meantime, to allow consideration of some projects on a case-by-case basis, taking into account the relative need of the country to have an MDI project to ensure compliance, the relative cost-effectiveness of the project and the possibility that essential use applications for MDIs might be considered by the Parties as early as 2008.

The draft guidelines in Document UNEP/OzL.Pro/ExCom/37/58 cover both the preparation of National transition strategies and investment projects for phasing out CFCs in the MDI sub-sector. On "Transition Strategies" the guidelines state:

"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:

- 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;
- 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
- 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.

Cuba clearly falls into the "MDI producer Countries" category.

The guidelines contain an extensive list of information requirements that are provided either in the body of this project document, or its Annexes. The detailed calculations of the cost of implementing the Transition Strategy are presented in Annex 7, and are estimated at US$ 190,000.00.

Conclusions - Considering all of the foregoing, and the unique situation relating to CFC MDI manufacture and consumption in Cuba, Cuba needs to be looking aggressively at ways to achieve the phase-out of CFC MDIs in 2005. This will require immediate commitment from all stakeholders, and the approval of MLF funding in 2002 for:

- Implementation of the proposed National CFC MDI conversion project, including provision for the transfer of the CFC-free MDI technology required for the CFC MDI products presently manufactured in Cuba; and,
- The development and implementation of a National transition strategy.

This must be followed by immediate action by all parties to progress the implementation of both the MDI conversion project and transition strategy.

5 PROJECT COSTS

5.1 INCREMENTAL CAPITAL COSTS - CFC MDI CONVERSION PROJECT

The following represents a summary of the budget costs for a flexible aerosol MDI manufacturing facility that is designed for use with the technology provider MDI formulation. This aerosol MDI manufacturing facility can operate at approximately 60 cans per minute giving an annual output of over 6 million cans/year based on 230 working days/single shift operation. This was used to determine the level of capital cost that Cuba would need taking into consideration specific requirements of the identified provider.

The filling machines comprise the following filling heads:

- **5cc capacity suspension/solution filler.**
  This filler is capable of filling either HFC or Ethanol product suspensions or solutions into the open can.
- **Valve crimper with vacuum capability.**
  This machine is capable of crimping 20mm metering valves without vacuum for CFC or HFA two stage formulations and with vacuum for HFA single stage formulations.
- **20ml capacity diaphragm suspension/propellant filler.**
  This machine is capable of filling CFC or HFA propellant only or HFA product suspensions under pressure through the aerosol valve.

The filling line comprises automatic can and valve feeders, an automatic checkweigher and a trayloader. It is complete with an electrical control system and a comprehensive validation documentation package, and the budget costs include installation and commissioning by the suppliers engineers. (Please refer to **ANNEX 2** for a more detailed explanation of the costs).

Equipment Required: The final list of equipment to produce HFA MDI, including the one currently used for CFC MDI is as follows:

Item	Cost (US$)
Additional Equipment Required for HFA	
1. Mixing Vessel	659,899
2. Macromat Line for Filling MDI with HFA Suspensions/Solutions	507,169
Equipment in place or not needed	
3. Spray Checking Machine	0
4. Weighing Balances	0
5. Air Filters	0
6. Labelling Machines	0
7. Laser Particle Counter	0
8. Ink jet Printer	0
9. Socoge Gauge	0
Sub-total for equipment for CFC-free MDI Manufacturing Facility	
Packing, Freight, & Insurance	116,709

Contingencies (10%)	116,223
TOTAL FOR EQUIPMENT FOR CFC-free MDI MANUFACTURING FACILITY	1,400,490

TOTAL FOR EQUIPMENT FOR HFA MDI MANUFACTURING FACILITY	
Materials Consumed in Equipment Proving Trials, Pilot Scale Production, Clinical Trials, Product Stability (10 batches at 25K per batch)	250,000
Costs of New Product Testing, Clinical Trial Testing, Product Registration and Approval	140,000
Overall Project Technical Supervision, Inspections, Certification of Completion	40,000
TOTAL CAPITAL COST FOR GENERAL HFA MDI MANUFACTURING FACILITY *	1,830,000

Notes:

* Excluding CFC-free MDI Technology Transfer Costs

3. Lab Testing Equipment Required: In addition to the equipment listed above, the laboratory will need to have a list of testing equipment to undertake the quality control in process and final product. This equipment will depend on the particular standard of quality determined by Cuba to produce HFA MDIs. This standard is a number (a percentage) that results from the cascade impactor test used by the USP. This equipment is not listed in the present project document as it is not eligible for funding under the Multilateral Fund.

5.2 TECHNOLOGY TRANSFER COSTS – CFC MDI CONVERSION PROJECT

The technology provider should be able to provide support to the Cuban laboratory to provide an alternative manufacturing capability to the existing CFC-propelled metered dose inhaler facility. The technology provider should have access to salbutamol HFA and BDP HFA or an alternative product with similar characteristics that can be used in replacement.

The technology provider should be able to provide assistance in the following ways:

- Access to data in support of regulatory approval
- Dossier compilation
- Facility design and equipment installation qualification
- Sourcing of components
- Clinical Trial management/execution
- Facility and equipment validation
- Production of a determined number of batches of each one of the products in presence of the Cuban technicians.
- Control checks to comply with the established quality standard.
- Handover the plant producing with HFA technology.

Details of the above will be subject to discussions between the parties upon award of the project. The technology provider would also be able to collaborate with other parties (for example equipment suppliers) to ensure that project timeframes are achieved within approved budgets.

The table below provides an outline of costs for the technology provider during the project timescale, estimated at 2-3 years.

Activity	Costs (US$)
Regulatory filer access, compilation of data as required by Cuban Regulatory Authorities	240,000
Technical/Engineering support • Travel • Accommodation • Subsistence Allowance • Equipment Hire charges Etc.	
Validation for facility & equipment	
Clinical trial planning, management & execution	(Included in ICC)
Payment to dossier holder ($400,000 pa)	800,000*
Total project cost	**1,040,000**

*capped based upon two years projected volumes of 5 million units each year.

It is proposed that the technology provider engineering personnel provide detailed specifications to ensure equipment is fit for its intended purpose. Equipment will be sourced from recognized suppliers or agents and will be fully inspected and tested prior to transport and installation at the manufacturing site.

Equipment suppliers will provide technical support during the build, testing and installation of the equipment and will provide formal documented training at the manufacturing site. Service contracts will be negotiated prior to placement of any order to ensure on-going technical after sales support.

The technology provider will assume responsibility for all engineering and validation activities during the project and will liase directly with the manufacturing site to ensure a seamless transition of technologies.

The technology provider will provide project support in the form of technical assistance, project management, layouts, installation qualification etc.

The above table of costs exclude any equipment (formulation tanks, filling equipment, water baths, etc.) and ancillary building costs (e.g. building shell, cleanrooms, electrical, mechanicals etc.) that are to be provided by either equipment suppliers or the Cuban authorities.

Please note that it is anticipated that the layout/footprint for the installation would be in the region of 400 square metres, the design layout and other details of which would be dependent upon the footprint of the outer shell provided by the authorities in Cuba.

In order to access the files of the technology provider alliance partners, it will be necessary to pay a fee of US$800,000 during the project life. This will be payable as two annual fees.

Furthermore, as previously noted, should it be deemed prudent, the technology provider will be willing to help support the retrofitting of HFA capability for the existing CFC filling lines, once the new facility is up and running.

The Laboratorio Julio Trigo Lopez will be responsible for all the engineering works required to adapt the plant to suitable standards requirements of the HFA filling line. The Government of Cuba is committed to ensure in a period no longer than 6 months the preparation of a plant complying with all the specifications of space, temperature, humidity and others required by the technology provider to produce HFA MDI.

In order to expedite registration process, provisional license can be provided by CECMED based on information of the product produced in the technology provider plant. However, it is required to do all the tests with the product produced in the Cuban lab.

5.3 INCREMENTAL COSTS – NATIONAL MDI TRANSITION STRATEGY

For both of the alternatives the development and implementation of the National MDI Transition Strategy is the same: **US$ 190,000.00**

5.4 INCREMENTAL OPERATING COSTS - CFC MDI CONVERSION PROJECT

Incremental operating costs are requested for four years and are based on the current production of CFC MDIs. Details of the calculations are provided in **ANNEX 3**.

TOTAL ANNUAL INCREMENTAL OPERATING COST (Including both drugs)	US$ 1,670,976
TOTAL FOR TWO YEARS AT NPV	**US$ 2,900,000**

5.5 INCREMENTAL OPERATING BENEFITS - CFC MDI CONVERSION PROJECT

There are no incremental operating benefits arising from the conversion to the CFC replacement technology.

5.6. TOTAL PROJECT INCREMENTAL COSTS (excluding MDI Technology Transfer)

% Article 5.1 Country Ownership	100%

- **TOTAL COST** (Capital + Operating Costs – Operating Benefits) **US$ 4,730,000**

5.7. PROJECT COST EFFECTIVENESS & FUNDING REQUESTED FROM THE MLF

TOTAL PROJECT COST (Transition Strategy not included) = **US$ 5,770,000**
TOTAL ODS ELIMINATED = **109.1 ODP Kg**
INCLUDING THE TECHNOLOGY TRANSFER FEE (US$ 1,040,000) THE COST EFFECTIVENESS OF THE PROJECT IS 52.88 US$/Kg

6. FINANCING PLAN

Initial approval from the Multilateral Fund will include the funds necessary to cover the incremental capital costs, the incremental operational costs and the first half of the technology transfer.

Once the plant is handed over to produce MDI with HFA technology a second disbursement including the second half of the technology transfer fees will be released.

7. PROJECT IMPACT

This project will eliminate the use of 109.1 ODP tons per year. This is based on the actual ODS consumption during the calendar year 2001.

8. PROJECT IMPLEMENTATION

8.1 MANAGEMENT

While the CFC MDI replacement technology will be sourced from appropriate centres of expertise using funds requested under the project, UNDP will oversee the successful implementation of this project, and will provide additional technical assistance during project execution.

Because of the specialist nature of the CFC-free MDI manufacturing equipment, this equipment will be built and test run at the equipment supplier's factory before being dismantled, parts labelled to facilitate reassembly, and shipped to the beneficiary enterprise. In addition, the equipment supplier will also install and commission the equipment at the beneficiary enterprise's factory, and conduct "Factory Acceptance Test Trials".

Any construction work and services required to accommodate and operate the equipment for the new CFC Free MDI aerosol technology will be carried out by the counterpart (Laboratorio Farmacéutico "Julio Trigo López"). The relevant details are not reflected in the project document. The specifications for any construction work will be coordinated by Laboratorio Farmacéutico "Julio Trigo López" and elaborated by a local construction company after project

approval and as an outcome of the necessary site inspection and related discussions between plant staff, the selected international contractor (technology and equipment supplier) and UNDP project staff.

8.2 TENTATIVE PROJECT SCHEDULE

- Adaptation of plant and installation of the equipment: 9 months
- Starting production at commercial level: 2 months
- Obtaining registration to produce in Cuba: 6 months

Detailed tentative project schedule is presented in next page:

TASK	2003				2004				2005				2006			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Submission of Project Proposal to MLF			x													
ExCom Approval of Project Proposal				x												
Project Document submitted to beneficiary				x												
Project Document Signature					x											
Implementation Appraisal					xxx											
Preparation/Agreement of Equipment Specs. etc.					xxx											
Bid Documents Prepared and Bids Requested					xxx											
Signature of Contract for CFC-free MDI Technology Transfer					xxx											
Bid Analysis & Vendor Selection					xx											
Equipment Supply Contracts Awarded						xxx										
CFC-free MDI Manufacturing Equipment Delivered							xxx									
Installation & Commissioning of CFC-free MDI Manufacturing Equipment							xxx	xxx	xx							
CFC-free MDI Formulation, Stability Testing & Clinical Trials								xxx	xxx							
Production of CFC-free MDIs on manufacturing equipment for Stability Testing, Clinical Trials, Registration, & Approval								xxx	xxx							
CFC-free MDI Approval									x	xxx						
Full Scale CFC-free MDI Manufacture											xxx	xxx	xxx			
Post Market Surveillance Data Collection												xxx	xxx			
Major Transition Strategy Implementation Activities						xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx			
Verification & Certification of Project Completion													X			
Submission of Project Completion Report													X			

8.3 MILESTONES FOR MONITORING PROJECT IMPLEMENTATION

TASK	MONTH*
(1) Project document submitted to beneficiary	1-2
(2) Project document signature	2-3
(3) Implementation Appraisal	3
(4) Signature of Contract for CFC-free MDI Technology Transfer	4
(5) Equipment Bid Documents prepared and Bids requested	4
(6) Bids Analysis, Vendor Selection, & Contracts Awarded	5-6
(7) MDI Manufacturing Equipment Delivered, Installed, & Commissioned	7-17
(8) Commence Production of CFC-free MDIs on manufacturing equipment for Stability Testing, Clinical Trials, Registration, & Approval	13-18
(9) CFC-free MDI Approval	18-21
(10) Start of Commercial CFC-free MDI manufacture	21->
(11) Post Market Surveillance Data Collection	25 ->
(12) Verification & Certification of Project Completion	28
(13) Confirmation of Destruction/Disablement of baseline CFC MDI equipment replaced with MLF funding	29
(14) Submission of Project Completion Report	30
Commence MDI Transition Strategy Activities	10

* As measured from project approval

- **ANNEXES**

ANNEX 1: Laboratorio Farmacéutico "Julio Trigo López" - Baseline Data.

ANNEX 2: Replacement Equipment Incremental Capital Costs.

ANNEX 3: Incremental Operating Costs.

ANNEX 4: List of Equipment to be Retrofitted, Destroyed, or Rendered Unusable, During Project Implementation, or Following Successful Project Completion.

ANNEX 5: Enterprise "Letter of Commitment" to Project Completion.

ANNEX 6: Asthma and Chronic Obstructive Pulmonary Disease (COPD) – Definitions etc.

ANNEX 7: Cuban National Strategy for the phase-out of CFC MDIs, and the introduction of the replacement CFC-free MDIs.

ANNEX 8: Pharmaceutical Quality CFC & HFC Propellants, Availability & Specifications for use in MDIs.

ANNEX 1 - ENTERPRISE BASELINE DATA

FULL NAME:	Empresa Laboratorio Farmacéutico "Julio Trigo López" (MDI Plant of Empresa"Reinaldo Gutiérrez")	
ADDRESS:	Avenida Independencia Km 5 ½, Boyeros, Ciudad del la Habana, Cuba.	
CONTACT PERSONS:	Lic. Fidel Montiel Curbelo Lic. Dignora Berrio Fleites	Director Plant Manager
TEL / FAX:	Tel: (537) 578807, 444498	Fax: (537) 547270
E-mail:	rgut1@infomed.sld.cu	
SHAREHOLDERS:	State-owned, under Ministerio de la Industria Basica	
EMPLOYEES IN MDI PLANT:		
YEAR ESTABLISHED:	1991	

Line 1. Laboratorio Farmacéutico "Julio Trigo López" Production Equipment

EQUIPMENT	MAKE/MODEL	SERIAL No.	YEAR	PROPOSED ACTION	DISPOSAL PLAN
CFC-11 Pump	GRACO 226845	185 a	1994	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
120 Litre Drug Suspensión Preparation Vessel	D.H. INDUSTRIES 3R4035 x 12	N/A	1994	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Drug Suspensión Preparation Vessel Recirculation/Chiller System	ALFA-LAVAL 3 kW	N/A	1994	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Product Filler 43 ml	PAMASOL 2001	N/A	1994	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
CFC-12 Propellant Pump	PAMASOL 2008/12	9778-15644	1994	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Propellant Filler	PAMASOL 2011	N/A		Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Aerosol Filling Machine	PAMASOL 2045/14	N/A	1994	Replace with equivalent R134a	Destruction When Conversion

	Type A			Equipment	Complete

Line 2. Laboratorio Farmacéutico "Julio Trigo López" Production Equipment					
EQUIPMENT	MAKE/MODEL	SERIAL No.	YEAR	PROPOSED ACTION	DISPOSAL PLAN
CFC-11 Pump	GRACO 226845	186a	1991	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
40 Litre Drug Suspensión Preparation Vessel	Local Manufacture	N/A	1991	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Drug Suspensión Preparation Vessel Recirculation/Chiller System	ALFA-LAVAL 2 kW	N/A	1991	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Product Filler	PAMASOL 2001/10	7145-12381	1991	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Product Filler	PAMASOL 2001/3-1	6262-10969	1991	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Crimping & Gassing Unit	PAMASOL 2005/2	6262-10971	1991	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Crimping & Gassing Unit	PAMASOL 2005/10	7146-12382	1991	Replace with equivalent R134a Equipment	Destruction When Conversion Complete

BASELINE PRODUCTION DATA - 1999 – 2001

Product	Production Volume (Millions of units)			
	1999	**2000**	**2001**	**2002 (Forecast)**
200 dose Salbutamol MDI	3.9	4.0	4.8	4.8
50 µg Beclomethasone MDI	0.2	0.7	1.2	1.2
Total	**4.1**	**4.7**	**6.0**	**6.0**

BASELINE CFC CONSUMPTION DATA - 1999 – 2001

Product	CFC Consumption (ODP Tonnes)							
	1999		2000		2001		2002 (Forecast)	
	CFC-11	CFC-12	CFC-11	CFC-12	CFC-12	CFC-12	CFC-11	CFC-12
200 dose Salbutamol MDI	23.1	47.9	23.8	59.8	28.9	59.8		
50 µg Beclomethasone MDI	1.4	1.9	5.0	11.6	8.8	11.6		
Annual Substance Total	24.5	49.8	28.8	71.4	37.7	71.4		
Annual Grand Total	**74.3**		**84.7**		**109.1**		**109.1***	

*** Estimated about the same as 2001**

The project is prepared based on the total annual consumption of CFC-11 and CFC-12 in 2001 of 109.1 ODP tonnes (including losses).

ANNEX 2 – REPLACEMENT EQUIPMENT INCREMENTAL CAPITAL COSTS

Budget Costs for a HFC Aerosol MDI Manufacturing Facility with a Production Capacity of 6.6 million cans/year based on 230 working days/single shift operation

Specifications and details for Production Equipments:

- ***Mixing Vessel .....US$659,899***

  - 500 Lt. Capacity,
  - Weight platform or load cell.
  - Drug addition system,
  - With complete pipe work &valves,
  - Electrical control panel for process control.
  - Seals & gaskets compatible with 134a.
  - Insulated Jacket - For chilled water circulation
  - Stirrer – Top entry flame proof agitator.

  Connection on vessel lid
  - Stirrer entry port.
  - Spray balls
  - Pressure / vacuum gauge
  - Sight glass & Light
  - Relief valve
  - Level probe
  - Propellant supply port.
  - Drug addition port.
  - Air, vacuum or N_2 connection

  Connection on the vessel –
  - Outlet valve (high flow)
  - Product return line entry from filling machine
  - Vessel recirculation system
  - Temperature probe for product

  Jacket: Chilled water supply & return, pressure gauge, & temperature probe for chilled water,

Weighing system : Least count: 0.5 kg.

Drug addition vessel –
- Capacity – approved 15 Lt.
- Vessel with removable lid for cleaning.

<u>High shear dispersion unit Model No: Dispax 2000</u>
- Capacity – 500 Lt. / hour

- Differential Pressure – 1 bar
- Inlet pressure: 3 to 8 bar
- Seal damage detection system
- Product Contact parts: SS316

Pressure Vessel

- Pressure: 10 bar
- Capacity: 100 lt
- Dish end removable lid
- Dish end bottom
- Mounted on legs with wheel
- Inlet and outlet connection of propellant
- Size- 15 nab with ball valve
- Pressure gauge 0-16 bar
- Pressure relief valve
- View glass

Propellant 134a transfer pump

For transfer of P134a from storage tank to process tank
Model GG895 capacity – 25 GPM

2. P2045 Macromat Line for Filling MDI with HFA Suspensions/Solutions..... US$ 507,169
Capacity 2.5 litres/min. at 10 bar Including flexible supply/return hoses.

2.1 ONE only conveyor system comprising: -
- Can loading table for manual feeding of cans.
- Conveyor from loading table through Macromat and Checkweigher to unloading table.
- Can unloading table.

For the sum of..... US 42,500

2.2 ONE P2045 Macromat aerosol filling machine indexing unit with: -
- Quick release 18 pocket starwheel/outer guide to suit 22 mm ø cans.
- Inlet/Outlet rotary unscrambler to suit adjacent conveyor.
- Stainless steel frame with stainless steel clad base unit.
- Pneumatically driven central height adjustment column.
- Fully pneumatic operation.
- 'DH' Syma fully interlocked enclosure.
- Integral extraction system with spigot for connection to house extract.

The machine is entirely pneumatic in operation and has a security system which prevents the starwheel from rotating if a head has not completed its

cycle, or the rotary unscrambler is not switched on. This system can be easily extended with outer interlocks to the customers exact requirements.

Each head can be individually controlled from the operators panel for changeover and quality control purposes. A counting device with zero setting and pressure gauges for air and vacuum supply are situated above the control panel.

An air receiver is situated in the base of the machine with a pressure regulator, automatic oiler and 'exhaust' shut off valve for each head.

The whole unit is clad in stainless steel panels with easily removable access doors exposing all working parts. An exhaust manifold to which all exhausts are connected is provided, enabling quiet operation.

For the sum of ..... US 86,955

Machines fitted to above base unit: -

2.2.1 Valve Inserter

ONE P2058 Valve Inserter to handle 20 mm valves without diptubes comprising:-

- Insertion device mounted on Macromat central column.
- Press down device prior to Crimper with no valve detector.
- Oil free pneumatic operation.

For the sum of ..... US 13,090

2.2.1.1 Vibratory Valve Sorter

ONE free standing vibratory valve sorter comprising:-

- Electrically driven vibratory valve sorting bowl tooled to handle 20 mm metering valves.
- Output speed up to 120 valves per minute.
- Stainless steel base and stand
- DH Cleanline acoustic enclosure

For the sum of ..... US 25,500

2.2.1.2 Valve Transport System

ONE valve transport system to deliver the valves from the vibratory valve sorting bowl to each Macromat comprising:-

- Starwheel driven valve transport system.
- High level valve feed rail.
- Dividing piece to divert valves on demand to each Macromat.

For the sum of ..... US 46,750

2.2.2 Vacuum Crimper.

ONE X02002 Vacuum Crimper suitable for use with or without vacuum.

For single stage HFA formulations vacuum is required and for two stage CFC or HFA formulations vacuum is not required.

Vacuum Crimper comprising:-
- Vacuum crimp unit mounted to bracket above Macromat starwheel.
- External depth/diameter adjustment.
- Vacuum dwell adjustment.
- Sub mounted, oil free pneumatic control system.
- Collet and depth stop for one type of aerosol valve.

For the sum of..... US 31,790

2.2.2.1 ONE OFF pneumatically operated PIAB pump for vacuum crimper.

For the sum of..... US 4,250

2.2.3 Diaphragm Suspension Filler

ONE diaphragm suspension filler to pressure fill product through the aerosol valve and aspirate residue.

Diaphragm suspension filler suitable for filling:-

- HFA product suspensions.
- CFC propellant only.
- HFA propellant only.

Filler comprising:-

- 20 cc Diaphragm metering unit with recirculation system.
- Quick release mounting bracket for metering unit with pneumatic control manifold mounted in Macromat back cabinet.
- Diaphragm inlet/outlet shut off valves to enable recirculation.
- Diaphragm aspirator type filling nozzle with filling nozzle insert to suit one valve type mounted above Macromat starwheel.
- Vacuum filter and pipework to work in conjunction with aspirator filling head and vacuum pump to evacuate residue after filling.
- Sub base mounted oil free pneumatic control system.
- Product contact parts in stainless steel 316L and PTFE complete with material certificates for validation purposes.

For the sum of..... US 36,677

2.2.3.1 Vacuum Pump

ONE vacuum pump to work in conjunction with diaphragm filler aspirator nozzle when filling HFA product suspensions comprising:-

- Pneumatic vacuum pump assembly type PIAB P14019/004.
- Suction capacity 135-190 l/min.
- Vacuum up to 90k Pa.
- Air supply control valve, regulator and pressure gauge.
- Cuno filter type V12098/002
- Cuno filter cartridge type V12098/002-001

For the sum of..... US 4,250

2. 3 Checkweigher.

To supply only ONE OFF P2023/3 pneumatically driven indexing unit comprising: -

- 12 Pocket indexing starwheel for 22 mm diameter container.
- Position for fitting weigh cell.
- Stainless steel clad base unit.
- Syma clean line fully interlocked enclosure.

Fitted with: -

2.3.1 ONE OFF Graseby freestyle precision weigh cell including: -

2.3.1.1 Validation support documentation for checkweigher.

For the sum of..... US 75,590

2.4 DH Electrolink Control System

ONE DH Electrolink control system for Macromat aerosol filling line comprising:-

- Free standing stainless steel enclosure
- Main isolators.
- 24 Vdc power supply.
- Motor circuit breakers.
- Motor contractors.
- Inverters.
- PILZ safety relays.
- Stainless steel stop/start stations.
- Fibre optic component queue sensors.
- Guard interlocks.

- Lighting.
- Local isolators for drive units.
- Annunciator panel.

For the sum of..... US 25,500

2.5 To supply only ONE OFF P2089/001 Pamasol double diaphragm suspension supply pump capacity 2.5 litres/min. at 10 bar. Including flexible supply/return hoses.

For the sum of..... US 37,817

2.6 Qualification Documentation

To provide the following documentation to aid the qualification of the Macromat aerosol filling line.

- Functional Design Specification.
- Software Design Specification.
- Factory Acceptance Test Protocols (F.A.T).
- Site Acceptance Test Protocols (S.A.T).
- Installation Qualification Test Protocols.
- Operational Qualification Test Protocols.
- Sensor/Device listing.
- Operator manual.
- Technical Manual.
- As built Mechanical/Electrical Drawings.
- PLC Program, Cross Reference List and Ladder Diagram.

For the sum of..... US 17,000.00

2.7 Build up/Test Run/F.A.T

- To align and connect all machines as production line.
- To supply compressed air, power and propellant pumping/pipework system to equipment.
- To run a quantity of up to 10,000 units on equipment assuming free issue of propellant and components.
- To conduct Factory Acceptance Tests to previously agreed test protocols.

For the sum of..... US 17,000.00

2.8 Installation/Commissioning/S.A.T.

To install and commission filling line on site at customer's premises and conduct Site Acceptance Tests to previously agreed test protocols.

Estimated duration – 2 weeks.

Travel, accommodation and out of pocket expenses included in price at cost.

For the sum of..... US 42,500

Summary Filling Line

2.1	Conveyor System	US	42,500.00
2.2	Macromat Base Unit/Enclosure	US	86,955.00
2.2.1	Valve Inserter	US	13,090.00
2.2.1.1	Vibratory Valve Sorter	US	25,500.00
2.2.1.2	Valve Transport System	US	46,750.00
2.2.2	Vacuum Crimper	US	31,790.00
2.2.2.1	Vacuum Pump	US	4,250.00
2.2.3	Diaphragm Suspension Filler	US	36,677.00
2.2.3.1	Vacuum Pump	US	4,250.00
2.3	Indexing Checkweigher	US	75,590.00
2.4	Electrical Control System	US	25,500.00
2.5	Suspension Supply Pump	US	37,817.00
2.6	Qualification Documentation	US	17,000.00
2.7	Line Assembly at DH/FAT	US	17,000.00
2.8	On Site Installation	US	42,500.00
	Total ...	US	507,169.00

- ***Spray checking machine..... (Common for CFC and HFA)***
  - Model: NEIS inhaler spray testing machines
  - Speed: 120 cpm
- ***Weighing balances.....(Common for CFC and HFA)***
  - Capacity: 300 gm, 600 gm and 6000 gm
  - Least count/ accuracy: 10 mg
- ***Air filters.....(Common for CFC and HFA)***
  - Filtration rating: 1 micron Model: AO –0145G
  - Filtration rating: 0.01 micron Model: AA-0145G

- End connection: 25 nab ASA 150 flange

- ***Labelling Machines*****.....Not required**

  - Speed: 150 cpm
  - Product: 22 mm dia aluminium container
  - Roll form self adhesive labels.

- ***Laser particle counter*****.....(Common for CFC and HFA)**

  - For area air cleanliness check. Model: 3313

- ***Ink jet printer:*** **.....Not required**

  - Model: A200

- ***Socoge gauge: for crimper control*****.....(Common for CFC and HFA)**

  - Model: Crimper control Digital part No. 743-03-143

For testing aerosol container (22 mm dia and 72 mm height) to reject non-spraying and continuous spray container.

Summary of Total Incremental Capital Costs

Additional Equipment Required for HFA

1. Mixing Vessel ..... US$ 659,899.00
2. Filling Line ..... US$ 507,169.00

Equipment in place or not needed

3. Spray Checking Machine..... US$ 0.00
4. Weighing Balances ..... US$ 0.00
5. Air Filters ..... US$ 0.00
6. Labelling Machine..... US$ 0.00
7. Laser Particle Counter..... US$ 0.00
8. Ink Jet Printer..... US$ 0.00
9. Socoge Gauge ..... US$ 0.00

TOTAL ..... **US$ 1,167,068.00**

All prices are ex-works, excluding packing, freight, insurance, off loading, positioning or running of services e.g. electricity, air, gas, water, drainage to or from the equipment.

DELIVERY: 9 months from receipt of order, deposit and finalization of technical details.

Including packing, freight, insurance, off loading, positioning or running of services e.g. electricity, air, gas, water, drainage to or from the equipment, the total figure will be as follows:

ITEM	COST
Equipment	1,167,068
Packing, Freight, & Insurance	116,709
Contingencies (10%)	116,223
TOTAL FOR EQUIPMENT FOR CFC-free MDI MANUFACTURING FACILITY	1,400,000

ANNEX 3 – INCREMENTAL OPERATING COSTS

200 dose Salbutamol MDI

Item	Existing CFC Formulation			Likely HFC Formulation (1)		
	Quantity per MDI	Price US$*	Cost/Can US$	Quantity per MDI	Price US$	Cost/Can US$
CFC-11	5.729 gm	4.56974 US$/Kg	0.0262	-	-	0
CFC-12	11.871 gm	6.17779 US$/Kg	0.0733	-	-	0
HFC-134a	-	-	0	17.60 gm	7.0 US$/Kg	0.1232
Ethanol	-	-	0	-	-	0
Aluminium Monobloc Can	1	0.115	0.115	1	0.6458	0.6458
Metering Valve	1	0.168	0.168	1		
Actuator	1	0.086	0.086	1		
Unit boxes	1		0.0016			
Other Costs Components			0.0225			
Salbutamol	0.023 gm	385 US$/Kg	0.0111	0.023 gm	385 US$/Kg	0.0111
Sorbitan Trioleate	0.046	17.05 US$/Kg	0.0009			
Cost per MDI	US$ 0.5046			US$ 0.7801		
Annual Production	4.8 million units			4.8 million units		
Annual Cost	US$ 2,422,080			US$ 3,744,480		

Annual Incremental Operating Cost for Conversion of Salbutamol CFC MDI to HFC 134a = US$ 1,322,400

Incremental Operational Cost 2 years = US$ 2,295,074

* As of May 2003

50 μg Beclomethasone MDI						
Item	Existing CFC Formulation			Likely HFC Formulation		
	Quantity per MDI	Price US$	Cost/Can US$	Quantity per MDI	Price US$	Cost/Can US$
CFC-11	6.9442 gm	4.56974 US$/Kg	0.032	-	-	0
CFC-12	9.2501 gm	6.17779 US$/Kg	0.057	-	-	0
Ethanol	-	-	0	3.52 gm	1.00 US$/Kg	0.00352
HFC-134a	-	-	0	14.081 gm	7.00 US$/Kg	0.09856
Aluminium Monobloc Can	1	0.115	0.115	1	0.6458	0.6458
Metering Valve	1	0.168	0.168	1		
Actuator	1	0.086	0.086	1		
Unit boxes	1		0.0016			
Other Costs Components			0.0225			
Beclomethasone Dipropionate	.01157 gm	25000	0.28925	Alternative Drug **		0.3140
Oleic Acid	0.001	1.0752	0.0011	0.001	1.0752	0.0011
Cost per MDI	US$ 0.7725			US$ 1.0630		
Annual Production	1.2 million units			1.2 million units		
Annual Cost	US$ 927,000			US$ 1,275,576		
Annual Incremental Operating Cost for Conversion of Beclomethasone CFC MDI = US$ 348,576						
IOC 2 years =				**US$ 604,926**		

* As of May 2003
** Alternative drugs considered are BDP HFA or Fluticasone

Notes:

- For the conversion of the Salbutamol CFC MDI to a HFC 134a formulation a new internally lacquered can (20% cost increase), and a new metering valve (50% cost increase), are required.
- For the conversion of both the Salbutamol and Beclomethasone CFC MDIs to Ethanol/HFC-134a formulations, a new metering valve (50% cost increase), is required.

The weight of Ethanol replacing the CFC-11 in the CFC-free formulations reflects the different liquid densities of these excipients

TOTAL ANNUAL INCREMENTAL OPERATING COST (US$ 1,322,400 + US$ 348,576) — US$ 1,670,976

TOTAL FOR TWO YEARS AT NPV — US$ 2,900,000

ANNEX 4 – LIST OF EQUIPMENT TO BE RETROFITTED, DESTROYED, OR RENDERED UNUSABLE WITH ODS, DURING PROJECT IMPLEMENTATION, OR FOLLOWING SUCCESSFUL PROJECT COMPLETION

Under this project, the existing CFC MDI manufacturing facility will be replaced by a new CFC-free MDI manufacturing facility of equivalent production capacity. The following tables summarise the existing CFC MDI production equipment at Laboratorio Farmacéutico "Julio Trigo López":

Line 1. Laboratorio Farmacéutico "Julio Trigo López" Production Equipment

EQUIPMENT	MAKE/MODEL	SERIAL No.	YEAR	PROPOSED ACTION	DISPOSAL PLAN
CFC-11 Pump	GRACO 226845	185 a	1994	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
120 Litre Drug Suspensión Preparation Vessel	D.H. INDUSTRIES 3R4035 x 12	N/A	1994	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Drug Suspensión Preparation Vessel Recirculation/Chiller System	ALFA-LAVAL 3 kW	N/A	1994	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Product Filler 43 ml	PAMASOL 2001	N/A	1994	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
CFC-12 Propellant Pump	PAMASOL 2008/12	9778-15644	1994	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Propellant Filler	PAMASOL 2011	N/A		Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Aerosol Filling Machine	PAMASOL 2045/14 Type A	N/A	1994	Replace with equivalent R134a Equipment	Destruction When Conversion Complete

Line 2. Laboratorio Farmacéutico "Julio Trigo López" Production Equipment

EQUIPMENT	MAKE/MODEL	SERIAL No.	YEAR	PROPOSED ACTION	DISPOSAL PLAN
CFC-11 Pump	GRACO 226845	186a	1991	Replace with equivalent R134a	Destruction When Conversion

Line 2. Laboratorio Farmacéutico "Julio Trigo López" Production Equipment					
EQUIPMENT	MAKE/MODEL	SERIAL No.	YEAR	PROPOSED ACTION	DISPOSAL PLAN
				Equipment	Complete
40 Litre Drug Suspensión Preparation Vessel	Local Manufacture	N/A	1991	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Drug Suspensión Preparation Vessel Recirculation/Chiller System	ALFA-LAVAL 2 kW	N/A	1991	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Product Filler	PAMASOL 2001/10	7145-12381	1991	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Product Filler	PAMASOL 2001/3-1	6262-10969	1991	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Crimping & Gassing Unit	PAMASOL 2005/2	6262-10971	1991	Replace with equivalent R134a Equipment	Destruction When Conversion Complete
Crimping & Gassing Unit	PAMASOL 2005/10	7146-12382	1991	Replace with equivalent R134a Equipment	Destruction When Conversion Complete

All of the items above that are directly capable of CFC consumption must be dismantled and destroyed, or otherwise rendered unusable with CFCs once the conversion to CFC-free MDI products has been successfully completed. Items that are not directly capable of CFC consumption, such as vacuum pumps, chillers, or mixing vessels, may be retained for use in other, CFC-free MDI manufacturing operations at Laboratorio Farmacéutico "Julio Trigo López", subject to agreement and formal authorisation by the UNDP Consultant managing project implementation.

ENTERPRISE DECLARATION

- **Laboratorio Farmacéutico "Julio Trigo López"** undertakes to dismantle and destroy, or otherwise rendered unusable with CFCs, all of the existing CFC MDI manufacturing equipment once the conversion to CFC-free MDI products has been successfully completed.

- **Laboratorio Farmacéutico "Julio Trigo López"** undertakes not to submit any of the above-mentioned existing CFC MDI manufacturing equipment that are not destroyed following project completion, for replacement under any future ODS phase-out projects.

Authorised Signature: _____

(Laboratorio Farmacéutico "Julio Trigo López")

Date: _____

ANNEX 5 – ENTERPRISE LETTER OF COMMITMENT

Submitted in separate file

➤ Empresa Laboratorio Farmacéutico
Reinaldo Gutiérrez

Havana City, September 24, 2002

ANNEX 5-ENTERPRISE LETTER OF COMMITMENT

Laboratorio Farmaceutico "Julio Trigo Lopez" both represented by Fidel Montiel Curbelo (Director) hereby confirms having received a copy of an ODS phase out project, prepared on behalf of the aforementioned enterprise and on behalf of the Government of Cuba by the United Nations Development Program (UNDP).

Laboratorio Farmaceutico " Julio Trigo Lopez " hereby acknowledges the following:

a) It agrees that the UNDP/ UNOPS will implement this project as approved by the Executive Committee of the Multilateral Fund of the Montreal Protocol and as described in the project document, for which Laboratorio Farmaceutico "Julio Trigo Lopez " will be the beneficiary;

b) It accepts this project as proposed in the project document;

c) It will completely phase- out the use of CFCs upon project completion;

d) It will use only zero- ODP technologies for MDI manufacture as stipulated;

e) It will dispose of any equipment that has been replaced under this project in compliance with the stipulations that have been drawn up in the project document;

f) It will provide funds for items that are included in this project but are specifically excluded from funding by the Multilateral Fund of the Montreal Protocol (MLF) as well as for items included in this project and required for a successful completion but that, while eligible, may not be approved because they exceed the available budget and contingencies;

g) It will allow monitoring inspections by the UNDP or designate during project implementation and thereafter to verify proper implementation and subsequent operation without the use of CFCs.

24 de Sept 2002
(date)

(Authorized Signature)

DIRECTOR

REGISTRO
S.I. 030

ANNEX 6 - ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Definitions:

Asthma is a chronic respiratory disease characterized by a persistent inflammatory disorder of the airways, which become hyperesponsive to stimuli, and show a diffuse constriction which changes in severity either spontaneously or as a result of treatment.

The term Chronic Obstructive Pulmonary Disease (COPD) refers to a condition characterized by an abnormal respiratory flow which does not vary during an observation period of several months. Symptoms are cough, expectoration, dyspnea, and signs of bronchial obstruction. COPD is a progressive and generally irreversible disease which severely restricts the capacity of breathing. Emphysema, chronic bronchitis and asthma are evolutive stages of the COPD. Nicotine poisoning is the main cause of the CODP.

Treatments:

The preferred treatment for asthma is through the use of medications send directly to the lung through some inhaling system. COPD is treated like asthma with inhaling medication.

There are two main categories of the treatment of asthma: the relief of the symptoms and the prevention of the crisis. The classification of the drugs used for asthma therapies are also classified this way:

(a) Quick Relief Medications Used During The Crisis To Relieve Symptoms: These medications include bronchodilating medicines (short-acting beta agonists, teofiline) and anti-inflammatory drugs (corticosteroids-anticholinergics). Examples are as illustrated in the following Table 1:

Table 1 - Quick Relief Medications

Name	Generic Name	Presentation	Action Mechanism
Short acting B2-agonists	Salbutamol Fenoterol	MDI Solution to nebulise MDI Solution to nebulise	Bronchodilator
Anticholinergics	Ipatropium Bromide	MDI Solution to nebulise	Anti-inflammatory Bronchodilators
Xantines	Aminofilines Teofiline	Injections Tablets	Bronchodilator
Steroids for systemic administration	Prednisone Prednisolone Hidrocortisone	Tablets Syrup Injections	Anti-inflammatory

	Metilprednisolone	Injections	

(b) Drugs For Long-Term Disease Control: These include **Preventive Medicines** (inhaled steroid-corticoids, non steroidal anti-inflammatories), and **Maintenance Medicines** (sustained acting teofiline, long acting beta 2 adrenergics, modifiers of the action of leukotriens, such as montelukast and zafilurkast and inhibitors of lipo oxigenases, such as zileuton). Examples are as illustrated in the following Table 2:

Table 2 - Preventive Medicines

Name	**Generic name**	**Presentation**
Long-acting Beta 2 agonists	Salmeterol Formoterol	MDI Dry Powder Inhaled Powder
Xantines	Teofiline	Capsules Tablets
Anti-leukotriens	Zafirlucast Montelukast	Tablets Tablets
Non steroidal anti-inflammatories	Sodium Cromoglycate Nedocromil	MDI MDI
Systemic Steroids	Hydrocortisone Prednisone Metilprednisolone Dexametasone Betametasone	
Inhaled Steroids	Beclomethasone dipioprionate Flunisolide Fluticasone Budesonide Triamcinolone	MDI MDI MDI MDI MDI

The above listed drugs can be grouped in the following categories:

Category A: Short acting beta agonist bronchodilators.
Category B: Inhaled corticosteroids.
Category C: Non steroidal anti-inflammatories.
Category D: Anticholinergic bronchodilators.
Category E: Long acting beta agonist bronchodilators.
Category F: Combination of products with two or more active ingredients.

Categories A and B altogether account for around 75% of the global consumption of metered dose inhalers, while in Cuba they represent 100% of MDI consumption.

Global Statistics on Asthma and Chronic Obstructive Pulmonary Disease (COPD):

Asthma

It is difficult to establish the prevalence of asthma at the world level and the available data is often confusing. A change of prevalence often reflects a change in the diagnosis practice and not a real change in the number of people who suffers this condition. It is also important to differentiate the concept of punctual prevalence, that is the number of people with asthma at a point in time, from the cumulative prevalence, that is the number of people who suffered from asthma at any time.

However, there is a general agreement on the fact that there has been an increase in the prevalence of asthma at the world level in the last years, and it is estimated that at least 300 million people suffer this condition at present.

Chronic Obstructive Pulmonary Disease (COPD)

The Annual Report of the World Health Organization (WHO) states that there are around 600 million people in the world who suffer from COPD, and approximately 3 million people die from this condition every year.

ANNEX 7- CUBAN TRANSITION STRATEGY FOR THE ELIMINATION OF MDIs WITH CFC, AND THE INTRODUCTION OF THE REPLACEMENT CFC-FREE MDIs

As separate file attachment.

Annex 7

CUBAN TRANSITION STRATEGY FOR THE ELIMINATION OF METERED-DOSE INHALERS WITH CHLOROFLUOROCARBONS (CFC)

Prepared by

THE TECHNICAL OFFICE FOR OZONE, ENVIRONMENTAL AGENCY OF THE MINISTRY OF SCIENCE, TECHNOLOGY AND ENVIRONMENT

IN COOPERATION WITH

THE MINISTRY OF PUBLIC HEALTH
THE MINISTRY OF ECONOMY AND PLANNING

THE CUBAN OFFICE OF INDUSTRIAL PROPERTY

THE ENTERPRENURIAL GROUP OF THE CHEMICAL-PHARMACEUTICAL INDUSTRY OF THE MINISTRY OF BASIC INDUSTRY

AND

THE UNITED NATIONS DEVELOPMENT PROGRAMME

September 2003

CUBAN TRANSITION STRATEGY FOR THE ELIMINATION OF THE METERED-DOSE INHALERS WITH CHLOROFLUOROCARBONS (CFC)

1. - Introduction

The Cuban environmental strategy sets the actions aimed at solving the main environmental problems of the country and draws the guidelines to contribute in an effective way to the efforts of the international community for the solution of global environmental problems.

In 1992, Cuba ratified the Montreal Protocol on Substances that Deplete the Ozone Layer, and in 1999, the London and Copenhagen Amendments. Since then it has developed an intensive work to comply with the commitments made as a Party country included in Article 5 of such Protocol.

Environmental Law 81, passed in 1994, sets the measures to be taken to protect the ozone layer at national level.

In line with the above-mentioned, a national program of reduction and elimination of ozone-depleting substances was approved and since 1999 a legal system was set up, which is composed by a set of regulations and norms and a control and license system for the import of such substances and of equipment and technologies that use them, with the aim of achieving a safe management and assure the reduction and elimination schedules.

The 36th meeting of the Executive Committee of the Multilateral Fund for the Implementation of the Montreal Protocol approved the design and submission of strategy projects that allow the elimination of CFC in metered-dose inhalers and the re-conversion of inhaler manufacturing plants by resorting to alternative technologies.

To meet the needs of a population of approximately 1.5M patients suffering from asthma and other obstructive respiratory bronchial afflictions, approximately 6.0M metered-dose inhalers that use over 100 tons of CFC are produced annually.

The levels of CFC use in these inhaler formulations demand a strategy aimed at decreasing their consumption, contributing in that way to the fulfillment of the ozone-depleting substances reduction and elimination schedule nationwide. It establishes the reduction of CFC by 50% by the year 2005, 85% by 2007 and the total elimination by the year 2010.

It is also fundamental to work on the required technological changes that will make it possible to stop using CFC in inhalers, taking into account the difficulties that might arise when coming to the deadline set by the Montreal Protocol for the total elimination of these substances.

Currently, alternative products without CFC suitable for health and the environment are already known and marketed in a number of countries including

some that operate under Article 5. Among the available products, there are metered dose inhalers that are the most suitable in our conditions according to the medical practice and the preferences of the patients.

This strategy defines objectives, goals and actions to gradually eliminate CFC in metered-dose inhalers, taking into consideration the guaranteed supply of necessary drugs, the preservation of health and safety of patients during and after the transition and the compliance with the objectives and policies of the Cuban public health care.

For the implementation of the foreseen actions, multi and inter-sectoral participation has been taken into account with a view to attaining the defined objectives. The formulation of the strategy pays special attention to information, dissemination and education in both health care and environmental areas aimed at target publics comprising those directly involved and the general population.

The pharmaceutical industry, its legal system and specialized bodies guarantee the control of the stages of replacement and transition of these products in the market, the registries and the aftermarket pharmacological surveillance.

The afore-mentioned conditions are based on the political willingness of the Cuban government in supporting the replacement of CFC and the fulfillment of its commitments under the Montreal Protocol.

2. General background

The changes in the health status of the Cuban population in the last three decades show the high priority given and the efforts made by the Cuban Revolution in the social sphere, and in the transformation of the qualitative living standards of the citizens.

Within the priority program to ensure better Cuban health care levels, there is the non-communicable chronic diseases program, particularly Bronchial Asthma and Chronic Obstructive Pulmonary Diseases as highly significant health problems at national level.

Bronchial asthma is considered to be a frequent disease. It is the most common chronic affection in adults and children in the developed world. It is known that over 5% of the population suffers from asthma in the industrialized societies. As to mortality rates, the 1998 and 1999 reports of the World Health Organization stated that a total of 330 000 persons had died from asthma worldwide.

Similarly, COPD is considered to be a common affection internationally, which is mostly present in smokers. In 1990, COPD held the 12th place with over 2 000 000 deaths and it is expected that in the year 2020, it will reach the fifth position as a cause of death. Likewise, medical consultation, hospital stays and economic costs have increased as a result of this disease.

2.1 Asthma and Chronic Obstructive Pulmonary Disease (COPD)

2.1.1 Definitions

Bronchial asthma is a chronic respiratory and inflammatory disease of multi-factorial origin, characterized by bronchial hyperactivity. This inflammation causes recurrent episodes of sibilant rales, dyspnea, chest oppression and cough particularly at night. These symptoms are regularly associated to a variable degree of obstruction of airways that is often reversible either spontaneously or by treatment.

Chronic Obstructive Pulmonary Disease (COPD) is the process characterized by non-completely reversible restricted airflow resulting from abnormalities in airways or pulmonary parenchyma. It is a set of diseases of progressive development and specially disabling in those persons exposed to continuous harmful agents. COPD and Asthma may co-exist and their symptoms are common but more variable in asthma. Chronic obstructive bronchitis and pulmonary emphysema are also included.

2.1.2 Epidemiology

Asthma is considered a health problem worldwide owing to its magnitude in terms of morbidity, mortality and disability in wrongly managed patients. Its impact on the patients and their relatives as well as its social costs underline the need for taking adequately coordinated actions.

There exist evidence of an increase in morbidity and mortality caused by asthma in many countries. The studies performed by Dr Rodríguez de la Vega, Dr Rodríguez Gavaldá et al. showed that asthma is prevalent in 8.2% of the population. More recent studies indicate a prevalence of asthma of 10-11% in Cuba, for a total of approximately 1 500 000 people affected by the disease.

The mortality rate of bronchial asthma in 1945 was 1 per 100 000 inhabitants. As of that date, there was a tendency to increase until 1970 when a rate of 4 per 100 000 pop was reached. This rate decreased after the implementation of the National Program of Asthmatic Patient Care in 1973. It rose again in the 80´s, affecting groups at working age mainly 15-49 years-old and 50-64 years-old for a mortality rate of 6 per 100 000 pop in 1993. However, the risk of dying from asthma has been gradually reduced up to 1.8 per 100 000 pop in the year 2000, with a rate ratio of 1.5 that favors females, the same result that has been observed for over 20 years in other regions of the world and in Cuba.

Among the non-communicable diseases, bronchial asthma is the fundamental cause of admissions to the hospital in our country; hospital lethality rate was 0.1% in the year 2000, which is an acceptable parameter at international level. The economic and social cost of this disease is sizeable due to the disabling effect associated to frequent episodes of de-compensation.

COPD is a health problem in our country. As of 1980 there has been a world rise in chronic bronchitis and emphysema caused by smoking and environmental

pollution; both diseases are responsible for 95% of cases. Heredofamiliar or genetic factors cause only 5% or less. Approximately 29% of the global population are aged over 15 years, that is, 1.142 billion persons are tobacco derivatives consumers and it is expected a higher increase in poor countries up to the year 2025, therefore there will be a marked rise in these affections.

Although there is no prevalence surveys in general population included in the most recently available COPD studies in Cuba, it is estimated that roughly 500 000 persons are affected in the smoking population aged over 50 years. In the last three years a remarkable increase of mortality rates from these causes is observed, with rates of 21 to 24.8 per 100 000 pop. The objective of paying attention to COPD lies in the state commitment to face this problem, the increase of diagnosis and particularly the prevention of risk factors such as smoking.

In Cuba, intervention on the general population with anti-smoking educational campaigns shows a decrease of smokers from 36.8% to 32%. It is hoped that this intervention leads to a slight reduction of COPD impact on the Cuban population since these results do not reach yet the expectations of the national health care system.

2.1.3 Treatment

Inhalation is clearly advantageous as a route of administration of drugs to the lungs in respiratory diseases. Although upper airways act as natural filter hindering the arrival of particles to deep areas, the aerosol therapy allows achieving high concentration of drugs such as corticosteroids, beta adrenergics and anticholinergics in airways, thus diminishing their side effects when they are used by other routes of administration.

The most used aerosols in our country are the metered-dose inhalers with chlorofluorocarbons(CFC) propellant and lubricants. CFC as propellant is non-toxic, non-reactive, non-inflammable, with no odor, no flavor and excellent solvent, but it is recognized by its capacity to damage the ozone layer.

Another disadvantage of these propellants is the "cold freon" effect, stopping inspiration when the cold propellant hits the oropharynx. There are other differences among propellants in relation to the ozone layer and the arrival of particles to airways.

Since 1997, the world has been implementing a strategy of replacement of Freon gases 11 and 12 (CFC) by hydrofluorocarbons (HFC), specifically 134a and 227 HFCs that do not damage the ozone layer and have successfully passed clinical tests as solvents and propellants in pressurized aerosols of Salbutamol, Fluticasone, Beclomethasone Dipropionate, the chromolyns and some anticholinergics. The new HFC inhalers have undergone a series of clinical studies, which have compared in vivo and in vitro both propellants (CFC and HFC) and shown similar behavior. Studies made on one formulation of a Beclomethasone inhaler using HFC (Freon 134a) as propellant have shown that it has a higher pulmonary performance compared with those using propellant CFC, therefore, it is believed to be more beneficial for patients (see consulted bibliography).

Other studies have dealt with the clinical pharmacology of Freon 134a in healthy subjects after administering simple and repeated doses; No clinically significant changes have been detected in vital signs, electrocardiogram, pulmonary function and other measured laboratory parameters; moreover, no adverse effects have been reported.

Also, comparative placebo studies have been conducted with pressurized inhalers using CFC and reformulated pressurized inhaler using HFC in double-blind randomized studies whose results have shown similar tolerability and safety although Freon 134a inhalers have less effect on plasma potassium levels.

Summing up, according to scientific evidence, this alternative has proved to have equivalent tolerability, efficacy, pharmacokinetics, pharmacodynamics and safety and to be more environmentally friendly.

The international opinion of health authorities agree that the therapeutic route of choice for these diseases is inhalation because the product administered in this way reaches more rapidly and efficiently the airways, so the risk of adverse reactions is minimum. The treatment generally requires a regular administration of more than one drug through dosing or dry powder inhalers and less frequently through nebulizers.

2.1.4 The categories and types of drugs for asthma and COPD treatment are:

Category A – Short-acting beta agonist bronchodilators like Salbutamol, Terbutaline and Fenoterol.

Category B – Inhaling steroids such as Beclomethasone, Budesonide and Fluticasone.

Category C – non-steroid anti-inflammatory like Disodium Cromoglycate and Nedochromil.

Category D - Anti-cholinergic bronco-dilators such as Ipratropium and Oxytropium

Category E - Long-acting beta agonist bronchodilators like Salmeterol and Formoterol.

Category F – Combination of products with two or more active principles.

For example, in Europe inhalation treatment is essentially administered by metered-dose inhalers that represent almost 80% of prescribed inhalers. The remaining 20% is dry powder inhalers and small quantity of nebulizers.

2.2 Metered-dose inhalers

2.2.1 Generalities

The Cuban pharmaceutical industry has undertaken in the last 12 years the production of Salbutamol in pressurized metered dose inhalers. Beclomethasone dipropionate in metered-dose inhalers was marketed in 2001.

2.2.2. Alternatives to MDI without CFC

Asthma and COPD

Based on the increased prevalence of asthma and COPD generally and in particular in Cuba, there will be a continued and growing need for MDI treatments in Cuba. The current use of salbutamol and BDP will, in time, need to be supplemented with more modern treatments. These could come from productive discussions with multinationals that currently produce these products (e.g. Terbutaline; Ipratropium Bromide; Salmeterol; Fluticasone).

3. SITUATION IN CUBA

3.1 Production and consumption

Cuba is an important consumer of metered-dose inhalers with more than 6 million MDI used every year, all of them produced in "Julio Trigo" Laboratory. This facility has a production capacity of 8 million units annually, located in "Reynaldo Gutiérrez" state pharmaceutical enterprise. This laboratory is the only manufacturer and trader of MDI with CFC in the country.

Production volume of MDI with CFC

Product	Therapeutic Effect	Production volume		
		2000	2001	2002 (Forecast)
Salbutamol 20mg	Bronchodilator	4 719000	4 800000	4 800000
Beclomethasone 50µg	Steroidal Anti-inflammatory		1 200000	1 200000
Total		4 719000	6 000000	6 000000

Annual consumption of CFC

CFC	Unit	2000	2001	2002 (Forecast)
CFC 11	Ton	28.8	37.7	37.7
CFC 12	Ton	55.9	71.4	71.4
Total	Ton	84.7	109.1	109.1

The purchase and assembly of a new production line for CFC-free MDIs is a need of the country for the following reasons:

- A new technology without CFC is required for both salbutamol and beclomethasone
- Financial resources are not available for the import of drugs in HFC MDIs.

The process will be consultative, taking the criteria of the corresponding bodies into account. Pre-investment costs will be based on the new equipment, the remodeling of the facilities and the training of the involved personnel.

HFC will be marketed by the Import, Export and Distribution Enterprise of the entrepreneurial chemical-pharmaceutical group in charge of carrying out the required formalities through the Technical Office for Ozone (OTOZ) under the Ministry of Science, Technology and Environment (CITMA).

3.3 Regulatory and legal aspects of the technology transfer.

The regulatory work is aimed at verifying the fulfillment of the requirements that assure the equality, safety and efficacy at each phase of drug development.

The technology transfer is placed in a process that produces one of the drug categories, so it is subjected to the evaluation and control program.

The regulatory work covers, among other activities, from advisory service to investment projects to the permission given to the manufacturing facilities through granting of Sanitary License for Pharmaceutical Operations. These activities are endorsed by Resolutions and Regulations in force and by Standardized Operational Procedures that contribute to the openness of our work. The same is valid for the technological productive process and the quality assessments and controls.

Another relevant work applicable to the technological transfer is the evaluation and approval of the registration in the Drug Registry, which implies pre-clinical and clinical chemical/pharmaceutical evaluation. This phase allows the movement of products in the market. Similarly, this approval encourages the evaluation of formats and texts as well as the information aimed at physicians and patients, all of which supports the acceptance of products by physicians and patients.

For the above-mentioned reasons, the important role of CECMED in the lifecycle of domestically produced drugs is obvious. This is the reason why the support to the technological transfer does not require further changes in its legal body.

This technological transfer is an opportunity for implementing a new approach to the way of exerting control by introducing higher degree of interaction, co-ordination and dynamism into the program of regulating integration of the technological phases of production; the controlling element of the transfer is included in the activities of the industry.

The result of this working style should help to reduce the time to be spent in regulatory procedures that sometimes mean important delays in the process of registration because there are faults in the productive process, the quality assurance system and/or the preparation of the required documentation for the request. In this way, we help to increase the transfer efficiency.

The work of CECMED is decisive for the encouragement of the elimination of CFC use in drugs and in the checking of the use of CFC-free products.

We encourage the elimination of the use of CFC by banning the registration of national or international drugs containing CFC in their composition, something that will become a reality by the year 2007 provided that the HFC MDI alternatives have been introduced. This also implies the withdrawal of sanitary license for pharmaceutical operations for any line of production using this technology.

The use of CFC-free products is verified as part of the pharmacological surveillance activities and inspections made to the industry and drugstores. Once the registration is taken out from the Registry, then no drug of this type can circulate throughout the country and hence, we will proceed to the destruction of products which contain CFC. This work is endorsed by a legal frame (Resolution 40/2002).

The afore-mentioned makes it possible to understand how the regulatory activity will support the process of transition to the use of CFC-free products. More information is given in Annex F.

In line with the established regulations for industrial properties in Cuba, it will be necessary to make some considerations in the process of technology transfer for the transition from the use of metered-dose inhalers with CFC to metered-dose inhalers without CFC.

As a preliminary step, a search for technology patent infringement or search for purity was made to determine the holders of patent rights or of applications for patents existing in our territory. This study revealed that there are ten international companies having patents on the same subject and our databases showed 78 companies linked in some cases to Salbutamol and Beclomethasone, which is the object of this project. All this provides the country with required elements to find out the characteristics of the technology to be acquired.

As the Cuban strategy encompasses other promising products for treating respiratory diseases, it will be advisable to thoroughly consult the available patent documentation for these technologies.

Once the firm or company that will grant the patent license is determined and the patent is identified, then further specific analysis should be made in relation to the scope of the technology.

Taking into consideration that the patent license will be granted to the country as part of the benefits given by United Nations to Cuba for its participation in this project, CITMA should approve this technology transfer according to the Resolution 13 of 1998 passed by this Ministry.

During the implementation of this project, it will be convenient to establish working relations with the Cuban Office of Industrial Property to this effect since Decree Law 68 stipulates the registration of the patent license in this Office.

For the technology transfer process it will be required to have information not only on the patent covering the technology but also on the know-how that in many cases demands the participation of expert to convey this knowledge.

It is required that the International Agency provides these data because it might be necessary to hold a know-how license linked to this patent and even there might be other rights of industrial property related to this patent that may be either a trade mark or an industrial model.

Moreover, the system of environmental regulations and its law framework on the environment, Law 81 of 1994, provides that any new investment and technological change should be subjected to the impact evaluation according to Resolution 77 of 1999 of CITMA for the granting of an environmental license.

3.4 Pharmacological surveillance and aftermarket studies

Pharmacological surveillance is the set of procedures that systematizes the detection, registration, notification and information on adverse effects caused by drugs after their approval and registration. The Cuban pharmacological surveillance system is integrated with the National Network of Pharmacological Epidemiology, based on the spontaneous notification of suspected adverse reactions and the involvement of groups of experts in charge of analyzing and assessing such reactions.

When a pharmaceutical is traded, their pharmacological and toxicological elements are already known, but the information obtained in clinical assays does not make it possible to foresee what is going to happen in the regular clinical practice as to the occurrence of adverse effects.

Therefore, we suggest the follow-up of adverse events associated to a new pharmaceutical through the spontaneous notification of the pharmacological surveillance, with the aim of identifying those that can be predictable and preventable and also detecting new effects that are not described in phases prior to the marketing of the product. As a second strategy, if an adverse effect, which is unknown or undocumented by the literature (sign), occurs, other specific studies of pharmacological surveillance will be conducted like cohort or case-control studies to confirm the hypothesis generated by the spontaneous method.