It should be considered that the new pharmaceutical will be used in risk populations (children and elderly) that are more susceptible to these adverse effects.

The aftermarket study results will be part of the required information for the elimination of metered-dose inhalers with CFC.

4. PRINCIPLES AND OBJECTIVES OF THE CUBAN TRANSITION STRATEGY.

4.1 Principles

1) The political willingness of the Cuban government to eliminate the technology that may affect the environment, so the replacement of CFC by HFC is one of the priorities of the development programs of the country.

2) Equity in health services and availability of drugs for patients are basic principles of the National Health Care System, therefore, access to MDIs will be protected during the transition period by a gradual substitution that will give rise to the circulation of products containing CFC and HFC for a period of time under the control and supervision of the National Regulatory Body.

3) The transition project will be designed and implemented with the participation of experts from the clinical sphere, pharmaceutical industry, and health education specialists, who will contribute to the viability and efficient implementation of this project at all the corresponding levels.

4) The acceptability of the CFC-free products and the reduction of the duration of gradual replacement will be encouraged by conducting clinical tests designed to train the medical staff and patients in the use of these new products, thus favoring their acceptability during the technological transition process.

4.2 Objectives

1) To assimilate the CFC-free MDI technology so that the country can have the required quantities of these products in the national market for the treatment of asthma and chronic obstructive pulmonary disease.

2) To gradually reduce CFCs by 50% by the year 2005 and reach their total elimination by the year 2006.

5- ELEMENTS OF THE TRANSITION STRATEGY

5.1 General

According to the proposed strategy for reducing the consumption of CFC in the country, there will be a gradual decrease in the production of MDI with CFC so as to introduce MDI without CFC in the next few years.

- 2005 The amount of MDIs with CFC will be reduced by 50%
- 2006 The amount of MDIs with CFC will decrease by 100%

The current use of salbutamol inhalers accounts for over 75% of CFC MDI use in Cuba. Thus the introduction of an HFC salbutamol MDI and the commencement of a phase out of production of the corresponding CFC product in 2005 should allow these targets to be met.

The duration of the transition of formulation and re-conversion of the industry will depend on the acquisition of the required technology. It is necessary to keep the installed equipment for MDI with CFC with a view to ensuring the levels of supply of the inhaler to the population, thus meeting the national needs until the re-conversion is carried out.

Those products containing CFC should be eliminated as quickly as possible to shorten the period in which the products with and without CFC will co-exist. It will be also necessary to have enough time for data gathering. Any safety problem related to products without CFC should be rapidly detected and assessed in order to take required steps to solve it before products with CFC are completely taken out of the market.

The national regulatory sanitary and environmental bodies (Regulatory Bureau for Quality Control) through the Center for the State Control of Drugs (CEDMED) and the Environmental Control Agency of the Ministry of Science, Technology and Environment (CITMA) will be in charge of supervising the reduction of the CFC volumes as part of the implementation of the referred strategy.

5.2 PRE-INVESTMENT PROJECTS

TASKS	PLAN OF ACTION	COMPLETION DATE	RESPONSIBLE
Assessment of the facilities and the technological control for the introduction of the technological transfer	• Evaluation of the facilities and the technological process • Annex A	2002-2003	QUIMEFA (Chemical-Pharmaceutical Industry)
Constructive remodeling of the facilities	• Construction investment project. • Annex A, Part 2	2003	QUIMEFA
Training of personnel who presently produces MDIs in the new technology	• Training program • Annex B	2003	Counterpart of the technology transfer.
Application of the regulatory legal basis for the control of the transition strategy	• Regulatory basis • Annex E	2003	CECMED
Development of sensitizing campaigns	• Sensitizing Program	2003-2006	Promotion Center
Development of the validation program of quality control assays	• Validation program • Annex C	2003-2005	QUIMEFA And National Control Laboratory
Clinical assays of the marketed product	• Clinical assay of the marketed product. • Annex D	2004	CENCEC (National Coordinating Center of Clinical Assays) CECMED (Center for State Control of Drugs)

5.3 TECHNOLOGICAL TRANSFER

TASKS	PLAN OF ACTION	COMPLETION DATE	RESPONSIBLE
Purchase and setting up of equipment for the technological transfer	• Annex F	2003	QUIMEFA Financiers
Starting of the zero production. Evaluation of the Quality Assurance Program	• Annex G	2004	QUIMEFA CECMED
Master file documentation project. Evaluation to be made by the regulating bodies	• Development of project and documentation • Annex H	2004	QUIMEFA CECMED
Batch production for clinical assays	• Master dossier for production • Annex I	2004	QUIMEFA
Request of permission for clinical assay starting	• Submission of the documents required by the national regulations • Annex J	2004	QUIMEFA
Starting and performance of clinical assays	• Performance of clinical assays for drug registration.	2004-2005	QUIMEFA CENCEC CECMED

5.4 SUBSTITUTION OF THE 50% OF PRODUCTION WITH CFC-FREE PRODUCTS

Tasks	Action plan	Date of completion	Responsible
Production of batches for registry request	Production plan LOF request	2005	QUIMEFA[1] CECMED[2] CENCEC[3]
Presentation of the adjusted production plan for MDI with CFC in the substitution stage. 50% Reduction.	Reduction of production plan of MDIs with CFC	2005	QUIMEFA

The annexes from A to K previously referred to, provide deeper expositions on the steps to be followed throughout the transition process.

5.5 INFORMATION, EDUCATION AND COMMUNICATION STRATEGY

Cuba decides to develop an information, education, and communication (IEC) strategy with the aim of increasing the knowledge among health professionals, patients, relatives and other sectors of society concerning the use of HFC inhalers, and how this use protects the ozone layer.

5.5.1 Objectives

Health professionals, technicians and the population at large will acquire knowledge concerning the advantages of using HFC inhalers for the protection of the ozone layer.

Direct beneficiaries:

- Health professionals
- Patients and their relatives

Indirect beneficiaries
- Formal and not formal community leaders
- The population
- Education professionals
- Management and executive staff from the state central bodies
- Governmental and political decision makers

This strategy will be developed in three provinces from the Cuban territory (western, central and eastern); being selected two municipalities from each of them. One municipality will be urban and the other rural, and they will be chosen based on the analysis of the health situation.

5.5.2 Information, Education and Communication Strategies

- **Information**

Updated information will be provided on the behavior of the disease concerning the aspects related to prevention, treatment and epidemiology, focusing on the use of HFC inhalers with the aim of promoting the preservation of the ozone layer. This information will be provided at the level of:

- The Health Councils at the different levels of the system, with information aimed at the management and executive personnel of the Central State Management Bodies.

- Offices of the family physicians and nurses and Basic Working Groups (Primary Health Care Elements).
- Debates in the communities
- Pharmacies
- Classified Patient Groups
- Orientation Centers for Women and the Family
- Teenager clubs

Education

The health professionals as well as the persons involved in the change process concerning asthma and chronic obstructive diseases at all the care levels will be trained in the use of HFC inhalers.

The following modalities will be used:

1- Workshops
2- Conferences
3- Seminars
4- Training courses
5- Distant education
6- Theoretical – practical activities
7- University for all
8- On-the-job training

Addressed at:
1- Health professionals and technicians
2- Teachers
3- Population at large
4- Medication sellers
5- Sick persons and relatives
6- Community leaders
7- Social organizations
8- Pharmacy industry

Communication

The three ways of communications will be used (face to face, group and massive communication) in order to pass on educational messages promoting behavioral changes with respect to the use of HFC inhalers with the aim of protecting the ozone layer and the Environment in general by means of:

- Dissemination in the printed press, radio, and TV of the information regarding the patterns of asthma and the chronic obstructive diseases and the advantages of the use of HFC inhalers.

- Elaboration, validation and production of leaflets addressed at the heath professionals.
- Elaboration, validation and production of brochures addressed at patients and relatives.
- Elaboration, validation and production of posters addressed at the population.
- Edition and production of an educational video related to the subject.

5.5.3 Evaluation

Process and impact indicators will be used, for the latter qualitative techniques will be applied (focal groups, deep interviews and direct observation) which will allow assessing the implementation of the strategy.

5.6 Costs of the transition strategy (1)

The following table summarizes the main costs associated with the implementation of the transition strategy for eliminating the use of CFC MDIs in Cuba.

ELEMENT	COST in US$
National Information strategy	**180,000.00**
Programme for post-marketing surveillance	**10,000.00**
TOTAL TRANSITION STRATEGY	**190,000.00**
Investment project	**(*)**

(*) Subject to CFC-Free technology selected

The estimated detailed budget for the National Information Strategy would be:

Activity	Detail	Cost in US$
Sub-Regional workshops		**40,000.00**
National workshops		**10,000.00**
Dissemination material for public events (posters, stands, etc.)		**10,000.00**
Information campaign (technical publications, booklets, videos)		**120,000.00**
TOTAL		**180,000.00**

The programme for post-marketing surveillance will need additional support to follow up on the:

1) Results of the phase out programme and its legal framework: through periodical checks in sale points and interviews with the main actors.

2) Results of the National Information Programme: through periodical surveys to know the response and acceptance by patients and health professionals of the HFC MDIs.

The data obtained from the above follow up programmes plus the programme of post-marketing surveillance should be gathered and analysed by the appropriate experts in order to prepare a report on problems and possible solutions for the Ozone Unit. This would facilitate the corrective actions necessary to ensure the success of the transition strategy.

A tentative detailed budget for the Programme for post-marketing surveillance would be:

Activity	Detail	Cost in US$
Periodical Surveys		**10,000.00**
TOTAL		**10,000.00**

5.7 TRANSITION TIME TABLE

KS	RESP	2003				2004				2005				2006			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Communication on the signing of the project	1,2				X												
Submitting of equipment specifications	4					X											
Communication on contract signing	1,2					X											
Report on carrying out of preliminary activities	4						X										
Confirmation of setting up of the production equipment at pilot scale	4								X	X							
Report on facility inspection	3									X							
Report of pilot production outcomes	4									X	X						
Confirmation of setting up of the HFC MDI production equipment at industrial scale	4											X	X				
Report of the facility inspection	3												X				
Report on the first industrial production	4												X				
Confirmation of approval for beginning of clinical trial	3										X						
Report of concluded clinical trial	5											X	X				
Notification of registration in the Medication Registry													X				
Notification of the 50% reduction of production of MDI with CFC													X				
Notification of 75% reduction of production of MDI with CFC															X		
Report on post-marketing surveillance																	X
Regulatory report on the final elimination of MDI with CFC from the national production																	X

Responsible: 1- CITMA (Ministry of Science, Technology and Environment, 2- MINSAP (Ministry of Public Health, 3- CECMED (Center for State Control of Drugs), 4- QUIMEFA (Chemical – Pharmaceutical Industry), 5- CENCEC (Center for Clinical Trials). Q: Quarter

6. Bibliography

- Dirección Nacional de Estadística, Anuario Estadístico. Ministerio de Salud Pública de Cuba. La Habana, 2002.
- Debesa, F. Informe sobre reacciones adversas medicamentosas presentado en el Primer Taller de Fármaco-divulgación. Ciudad de La Habana, 1994.
- Beroinza, W. Teresa, Moreno B. Rodrigo. Terapia en aerosol. Boletín Escuela de Medicina, Universidad Católica de Chile; 24:15-17.
- Glaxo Smith Kline. Sustainability in environment. Health and Safety 2001. http//:www.gsk.com.
- Aerosoles. Curso 2001-2002. Diapositivas. Profesor M. Bermejo. Dpto. Farmacia y Tecnología Farmacéutica. Revisión en Internet.
- Tansey I. The Technical Transition to CFC free inhalers. BR J Clin Pract Suppl. 1997 May 89: 22-7.
- Ventresca GP. Clinical Pharmacology of HFA 134a. J. Aerosol Med. 1995 Spring 8 Suppl. : S35-9
- Kirby SM, Smith J, Ventresca GP. Salmeterol inhaler using a non chlorinated propellant, HFA 134a: Systemic Pharmacodynamic Activity in healthy volunteers. Thorax 1995 Jun 50: 679-81
- Salat O. Popov D, Sylles AP. Equivalence of Salbutamol 200 microg four times daily propelled by propellant 11 and 12 or HFA 134a in mild to moderate asthmatics. Eastern European study group. Repir Med. 2000 Jun 94 Suppl. BS 22-8.
- Magnussen H. Equivalent asthma control after dose reduction with HFA 134a beclomethasone solution aerosol. Comparative inhaled steroid investigation group (CISIG). Respir. Med. 2000 Jun. 94: 549-55.
- Clinet I. Changes in metered dose inhaler propellants. Rev. Mal Resp. 2000 Feb. 17: 15-20.

ANNEX A

1. Title: Assessment of the facilities and technological process proposed for the introduction of the technological transfer

2. General Objective:

Assess the current status of the facilities and technological process proposed for the introduction of the technological transfer

3. Activities

Activities	Completion date
Solicit market offers on technological and physical-chemical control equipment used in HFC MDI	2003
Solicit market offers on the packaging material used in the production of HFC MDIs	2003/4
Survey of the area where the technological process and the physical-chemical controls will be carried out	2003/4
Contract the services of an enterprise for the implementation of the investment processes	2004
Present the investment projects to the drug regulatory agencies (CITMA[4], CECMED)	2004

4. Monitoring Indicators

- Present the facility assessment report
- Present the offer report on the packaging material and the equipment
- Acquisition of the investment project contract
- Obtain the investment project assessment report made by CECMED and CITMA.

5. Participants

Specialists from QUIMEFA, CECMED, CITMA and the project enterprise

[4] CITMA: Ministry of Science, Technology and Environment

ANNEX A. Part 2.

1. Title: Constructive adjustment of the facility

2. General Objective: Implementation of the investment program

3. Activities

Activities	Date of Completion
Carry out facility investment program	2005
Assess the facility concerning the observance of the Good Fabrication Practices and the environmental regulations	2005

4. Monitoring indicators:
- Monitoring reports for specialists that carry out the investment projects
- Report on the facility assessment by the regulatory entity

5. Participants
- Specialists from QUIMEFA and the project enterprise
- Specialists from the regulatory entity and environment specialists

ANNEX B:

1. Title: Staff Training

2. Objectives: Train the staff taking part in the technological process and the chemical-physical analysis

3. Activities

Activities	Date of completion
Training of all the personnel involved in the technological process	2005
Training of the personnel taking part in the chemical-physical analysis	2005
Training of the personnel on the subject of industrial safety for the use of HFC	2005

4. Monitoring indicators:
Report on the training files status

5. Participants:
Specialists from QUIMEFA

ANNEX C

1. Title: Validation and quality control program for HFC MDIs

2. General Objective:
- Development of analytical capacities to carry out MDI quality control in the Industry and the National Control Laboratory (CECMED) and to support the clinical trials and the surveillance and post-marketing activities

3. Specific Objectives
- Renewal of the basic equipment of the Chemical-Physical Laboratory
- Development, validation and implementation of methods for trials of control processes, quality controls and analytic assessments of bioavailability in the clinical trials and the drug surveillance.

4. Activities

Activities	Date of completion
Acquisition and setting up of the equipment and handling training	2005
Development and validation of trials to the fulfillment of the clinical assessment stage	2005
Development and validation of the control processes trials	2005
Development and validation of trials of batch release control and quality control	2005

5. Monitoring indicators
- Presentation of reports on trial validation to the Regulatory Authority (CECMED)
- Outcome report to the financing entities
- Dates: December 2003 and March 2004

6. Participants
- Specialists from the Industry Laboratories and the National Control Laboratory that must work together in the validation of the trials

ANNEX D

1. Exploratory clinical trial with the marketed product produced in Cuba

2. General Objective: Assessment of acceptability and management of the marketed product in the transition strategy

3. Specific Objectives:
- Evaluate the safety of the product's use
- Evaluate the acceptability level of the HFC inhaler among patients
- Assess the handling of this type of product

4. Activities
- Present the protocol proposal and the documentation of the product to request to CECMED the authorization for the carrying out of the Clinical Trial.
- Carrying out of the clinical trial
- Presentation of the final report, including the relevant recommendation for the clinical trial of the national product

5. Responsible institutions
   a. National Coordinated Center for Clinical Trials (CENCEC)
   b. Center for State Quality Control of Drugs (CECMED)

ANNEX E

1. Title: Application of the regulatory legal framework to support the transition strategy

2. Background

The legal basis supporting the regulatory activities in drug control includes documents in force that are applicable to the proposed technological transition. These are the following:

- MINSAP Resolution No. 67/200 approves and puts into effect the Regulation Guidelines 16/2000 on Good Fabrication Practices for Pharmaceutical Products
- Regulatory Office for the Protection of Public Health, Resolution 03/2002 approves and puts into effect the Annex to the Good Fabrication Practices Guidelines for MDIs.
- CECMED Resolution No. 34/2000 approves and puts into effect the Resolution No. 23/2000. Requirements for Stability Studies for new and old pharmaceutical products
- CECMED Resolution No. 35/2000 approves and implements the Regulation No. 24/2000. Requirements of stability studies for the registry of new active pharmaceutical agents.
- CECMED Circular No. 6/2001. Requirements for stability studies for medication registry
- CECMED Resolution No. 40/2002. It creates the post-marketing surveillance system of CECMED
- MINSAP Resolution 165/2000. It updates the information on Good Clinical Practices.
- MINSAP Resolution No. 166/2000. It approves and puts into effect the Requirements for the request of Authorization and Modification of Clinical Trials
- MINSAP Resolution No. 168/2000 approves and puts into effect the Requirements for Requests of Registration, Renewal, and Modification in the Registry of Human Use Medications
- MINSAP Resolution 169/2000 approves and puts into effect the Rules for the Health Registry of Human Use Medication
- MINSAP Resolution No. 173/2000 establishes the Health License System for Pharmaceutical Operations
- CECMED Resolution No. 10/2001 approves and puts into effect the rules for the Health License System for Pharmaceutical Operations.

Considering this Regulatory System in force, it is not necessary to carry out a reformulation of the legal framework. Instead, it is more efficient to support the transfer strategy, the participation of CEDMEC in an interactive way to make possible that the regulatory interphase incorporate efficiently in the productive interphases, facilitating the acceptance in the registry of the formulation free of CFC.

2. General and Specific Objectives
- Support the technological transfer introducing and timely verifying the observance of the regulatory component.
- Collaborate in the introduction of the regulatory component in the technological transfer projects and establish the verification program in each of the stages
- Identify the Industrial Production Guidelines to be promulgated by CECMED to support the transition to the marketing of HFC products

4. Activities
- Participate in the design of the transfer project
- Program the activities of verification and regulatory control
- Promote the understanding and observance of the regulatory component in each stage with the aim of accelerating the registration of the product
- Participate in the validation of quality control trials in the new productions
- Promulgate communications to the Industry eliminating the possibility of Registration of new CFC products.
- Limit the validity of the registry of CFC products until 2007
- Apply the Drug Surveillance Regulations to these new productions including the analytic verification
- Verify the removal from the market and destruction of CFC products in the year 2006

ANNEX F:

1. Title: Acquisition and setting up of the equipment

2. Objectives:
Acquisition of the equipment required for the production of HFC MDIs

3. Activities

Activities	Date of Completion
Acquisition of the technological and chemical-physical control equipment	2004-2005
Acquisition of packaging material compatible with HFC	2004-2005
Acquisition of raw materials	2005

4. Monitoring Indicators
Setting up of the technological and chemical-physical control equipment

5. Participants
Providers and QUIMEFA

ANNEX G

1. Title: Beginning of the zero series. Review and adjustment of the Quality Control System

2. Objectives
Carry out a zero series to assess the quality of the product

3.Activities

Activities	Date of Completion
Carry out equipment adjustment	2005
Carry out industrial scale-up	2005
Carry out chemical-physical and microbiological analysis	2005
Assess product stability	2005
Obtain a conditional indicative registration with HFC	2005

4. Monitoring indicators
- Obtaining of calibration and verification certificates
- Technological behavior report
- Industrial scale-up outcome report
- Product stability study report
- Report of certificate of conditional indicative registration with HFC

5. Participants
Specialists from QUIMEFA, specialists from CECMED and verification and calibration institutions

ANNEX H:

1. Title: Project of documentation of the master file. Evaluation of the regulatory entity

2. Objectives:
Making of the master files of the introduced products

3. Activities

Activities	Date of Completion
Find out the productive capacity of the technological equipment	2004
Making of the master file	2005
Evaluation of the file by the regulatory entity (CECMED)	2005

4. Monitoring indicators
- Carry out master file assessment report

5. Participants
Specialists from and specialists from the regulatory entity (CECMED)

ANNEX I:

1. Title: Batch production

2. Objectives: Production of commercial batches with HFC

3. Activities

Activities	Date of Completion
Making of different production orders	2006
Chemical-physical and microbiological assessment	2006

4. Monitoring indicators

- Carry out report on productive outcomes with its wastage study
- Carry out reports on chemical-physical and microbiological assessment

5. Participants

Specialists from QUIMEFA

ANNEX J:

1. Title: Request of authorization to carry out the clinical trials

2. Objectives:
Carrying out of the clinical trials

2. Activities

Activities	Date of Completion
Collect all the information required to request the clinical trial authorization	2005

4. Monitoring indicators:
- Report on Clinical trials

5. Participants
Specialists from QUIMEFA and CENCEC

ANNEX 8 - PHARMACEUTICAL QUALITY CFC & HFC PROPELLANTS, AVAILABILITY & SPECIFICATIONS FOR USE IN MDIs

CFC-11, CFC-12, CFC-114, HFC-134a, and HFC-227ea have been subjected to extensive toxicological testing to ensure their safety in use, both in industrial, and pharmaceutical applications. The testing requirements for pharmaceutical uses, such as MDIs, are naturally more stringent than for industrial applications, and with the passage of time the testing requirements for both applications have become progressively more stringent.

CFCs are relatively easy to manufacture, and they were initially manufactured by enterprises in Article 2 Countries to a high purity specification that served to meet not only the requirements for the many industrial applications, but also the then rather general specifications for pharmaceutical aerosol applications found in the British Pharmacopoeia (BP), the United States Pharmacopoeia (USP) or National Formulary (NF).

With the 1980's came the manufacture of CFCs in several Article 5 Countries, the development of HFCs as CFC replacements, and extensive toxicological testing of both CFCs and HFCs for industrial applications. By the 1990's, changes to the Montreal Protocol requiring the phase-out of CFCs, and the identification of HFC-134a and HFC-227ea as potential replacements for CFCs in MDIs, resulted in additional toxicological studies on these substances being undertaken by individual pharmaceutical companies, as well as consortia of international pharmaceutical companies.

As there are different manufacturing process options for both HFC-134a and HFC-227ea, and the processes are more complicated than the simple process involved in CFC manufacture, the number of potential impurities is much greater. This aspect was carefully studied, and strict quality specifications were defined for the HFC-134a and HFC-227ea that was used in the toxicological testing of these substances for pharmaceutical applications such as MDIs.

The toxicological studies conducted on the defined high purity specification HFC-134a and HFC-227ea confirmed that the substances meeting these specifications were safe for use in pharmaceutical products including MDIs.

While individual pharmaceutical companies may retain their own individual specifications for the CFCs, and HFC-134a or HFC 227ea, that they are now using for the commercial production of MDIs, the results of the toxicological studies on both CFCs and HFCs have been included in a draft US FDA Guidance Document – "Guidance for Industry – Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation". The purpose of this Guidance Note is to indicate the sort of information that should be provided to ensure continuing drug product quality and performance characteristics for MDIs and DPIs. It does not impose mandatory requirements but does put forth acceptable approaches for submitting CMC-related regulatory information, and it allows alternative approaches to be used.

An important feature of this Guidance Note is the section dealing with excipients. For most MDIs, excipients comprise a significant portion of the formulation content by weight and their

quality has a substantial effect on the safety, quality, stability, performance, and effectiveness of such drug products. The sensitive nature of the patient population warrants complete characterization and strict quality control of these excipients to ensure consistency in the above properties.
The major excipients in an MDI are the suspension or solvent medium, and the propellant. The Guidance Note therefore contains recommended assay and impurities criteria for the "Compendial Propellants" CFC-11, CFC-12, and CFC-114, as well as for HFC-134a propellant. Details are provided in the tables at the end of this Annex. (Note: These specifications only cover the organo-halogen impurities, there are product quality tests for moisture, acidity, etc., conducted by suppliers that form part of the overall product Sales Specification.). While not mandatory, this has effectively created a "minimum specification" for CFCs and HFCs for use in MDIs that is very different from the normal specifications for industrial applications.

Clearly manufacturers of CFCs and HFCs that wish to supply these substances to pharmaceutical companies manufacturing MDIs have to meet the quality specifications demanded by their clients, and in practice this means producing products that meet the specification of the client with the most stringent specification, rather than producing products to different specifications. This affects the price of both "Pharmaceutical Grade" HFCs and CFCs, and they are significantly more expensive that the standard products for industrial applications.

The supply of CFCs and HFCs for MDI applications is not a business activity of all HFC producers; only two companies produce "Pharmaceutical Grade HFC-134a". (HFC-227ea is a specialist propellant used by some pharmaceutical companies with difficult formulation problems and for products that are not considered cost-sensitive. Most MDI products can be formulated using HFC-134a, and HFC-227ea not considered further in this Annex).

Most of the remaining CFC production is in Article 5 countries. It is intended for industrial applications, and it does not meet the specifications referred to above for pharmaceutical applications like MDIs. One Article 5 country producer has unsuccessfully attempted to enter the "Pharmaceutical Grade" CFC market. There is ongoing production of "Pharmaceutical Grade CFC-11" and "Pharmaceutical Grade CFC-12", in the Netherlands, and Spain. However, falling demand, rising costs, and pressures from EU Governments to end all CFC production, means that the continuity of supply from these sources cannot be guaranteed indefinitely, irrespective of any decisions by the Parties to the Montreal Protocol on "Essential Uses".

In summary then:

- Manufacturers of CFC MDIs face uncertainty in the future availability of "Pharmaceutical Grade" CFCs. Closure of the manufacturing facilities in the EU is anticipated in 2003 – 2004. While there will be strategic stockpiling of "Pharmaceutical Grade" CFC-11 and CFC-12, with no supply from Article 5 countries, availability is expected to decline rapidly after 2005.

- The specifications for "Pharmaceutical Grade" CFC-11 and CFC-12 have effectively been made more stringent by the FDA "Guidance Document". Even though it is not mandatory, it is difficult for any ethical MDI manufacturer to ignore such guidelines on exipient specifications.

- Realistically, MDI manufacturers need to be looking at eliminating their dependence on CFC propellants by end-2006.

- With a target of end-2006 to eliminate CFC consumption, for MDI manufacturers in Article 5 countries there is not sufficient time remaining to independently develop and test new formulations, obtain new product approvals, install and commission new manufacturing equipment (essential as the transition process will involve manufacture of both CFC MDIs, and CFC-free MDIs) conduct patient trials with the reformulated products, and post marketing surveillance, etc. before ceasing manufacture of the CFC MDI products. Technology transfer from pharmaceutical companies with developed CFC-free MDI formulations will be essential to achieve such a CFC phase-out date.

- CFC-free MDI formulations for the most common MDI product, a salbutamol bronchodilator, developed to date are either suspension formulations (HFC-134a alone), or solvent formulations based on ethanol/HFC-134a. The ethanol formulation is not acceptable in some cultures, whereas the HFC-134a suspension formulation involves higher incremental operating costs due to the higher HFC-134a content, and can and metering valve specification changes. The short time available to reformulate existing MDI products, approve them, and evaluate patient trials, means that the new manufacturing equipment will have to be specified such that it is capable of manufacturing both suspension and solvent MDI formulations.

- MLF assistance is then urgently required for MDI conversion projects that include technology transfer elements, and the implementation of National MDI transition strategies agreed by all stakeholders. This is particularly important in countries like Cuba with a clear trend of increasing CFC consumption, and the resulting likelihood of non-compliance with its 2005 Montreal Protocol CFC consumption limit obligations.

Table I. Recommended Assay and Impurities Acceptance Criteria for Various Compendial Propellants

Impurity[1]	CFC-11 Acceptance Criteria (ppm)	CFC-12 Acceptance Criteria (ppm)	CFC-114 Acceptance Criteria (ppm)
HFC-152a		10	
HCFC-21	75	50	
HCFC-22	10	250	50
HCFC-123	10		200
HCFC-124			50
HCFC-124a			50
HCFC-133a	10	10	20
CFC-11	99.8% purity	2000	500
CFC-12	2000	99.8% purity	1000
CFC-13	10	300	
CFC-113	75	10	50
CFC-113a	15		50
CFC-114	40	150	99.8% purity
CFC-115		15	300

Impurity[1]	CFC-11 Acceptance Criteria (ppm)	CFC-12 Acceptance Criteria (ppm)	CFC-114 Acceptance Criteria (ppm)
CFC-217			200
CFC-319			10
BCFC-12B1	15	15	
CFC-1112a	10	10	10[2]
Methyl Chloride	10	40	
Dichloromethane	50	10	
Chloroform	20	10	
Carbon Tetrachloride	20	10	
Total Chloromethanes	50	50	
Total Unspecified	20	20	20
Total Impurities	2000	2000	2000

[1] ***No number for an impurity indicates its absence (below detection limit of method).***
[2] ***Acceptance criteria under evaluation.***

Table II. Recommended Assay and Impurities Acceptance Criteria for HFA-134a Propellant

Impurity	HFA-134a Acceptance Criteria (ppm)	Impurity	HFA-134a Acceptance Criteria (ppm)
HCC-40	5	HCFC-133a	5
HFC-23	5	HCFC-161	30
HFC-32	5	HCFC-1121	5
HFC-125	5	HCFC-1122	5
HFC-134	1000	HCFC-1122a	5
HFC-143a	10	CFC-11	5
HFC-152	5	CFC-12	100
HFC-152a	300	CFC-12B1	5
HFC-245cb	5	CFC-13	5
HFC-1123	5	CFC-113	5
HFC-1132	5	CFC-114	5
HFC-1225ye	5	CFC-114a	25
HFC-1234yf	5	CFC-115	5
HFC-1243zf	5	CFC-1112a	5
HFC-1336mzz	5	FC-1318my-T	5
HCFC-22	50	FC-1318my-C	5
HCFC-31	5	Total unsaturates (including HCFC-1122)	5
HCFC-123	5	Individual unidentified impurities	5
HCFC-123a	5	Total unidentified impurities	10
HCFC-124	100	Other organic impurities	50
HCFC-124a	5	Any other identified saturated impurity	5
HCFC-132b	5	Total impurities	1000
		Assay	99.9%

ANNEX 9
Implementing Agency Responsibility under the project

UNDP, upon request of the Government of Cuba has agreed to be the implementing agency for the project *"Phase-out of CFC consumption in the Manufacture of Aerosol Metered Dose Inhalers (MDIs) in Cuba"*, which is targeted for completion in 2006. As the implementing agency, UNDP will be responsible for:

(a) Ensuring performance and financial verification in accordance with specific UNDP and Multilateral Fund procedures, rules and regulations;

(b) Providing verification to the Executive Committee that the consumption targets and the activities as stated in this project document have been met as per schedule;

(c) Assisting the Government of Cuba in preparation of yearly implementation progress reports;

(d) Ensuring that technical reviews undertaken by UNDP are carried out by appropriate independent technical experts, including the designation of an independent expert when required to verify that payment milestones have been achieved;

(e) Carrying out required supervision missions to monitor the delivery of the services included in this Project Document to the designated beneficiary;

(f) Ensuring the presence of an operating mechanism to allow effective, transparent implementation of the project, and accurate data reporting;

(g) Ensuring that disbursements/compensation payments are made to Government, technology supplier and equipment and material suppliers on agreed terms upon receipt of invoices which are properly substantiated;

(h) Providing assistance with policy when required;

(i) Providing independent technical supervision missions and certify completion of the project;

(j) Through a Handover Protocol, HOP (Annex 10 of this project document), transferring the ownership of the equipment purchased under this project to the beneficiary laboratory once the project is completed and ensuring that the conditions listed in the "Certificate of Completion" (Annex 11 of this Project Document) are accomplished;

(k) Providing copy of the following relevant documentation to the Government of Cuba and the technology provider: Project Document, letter confirming UNDP role as paying agent, Handover Protocol (HOP) and Certificate of Completion (COC).

ANNEX 10

Standard Handover Protocol to be signed upon completion of the project

HANDOVER PROTOCOL

LABORATORIO JULIO TRIGO LOPEZ

CUB/ARS/41/INV/23

HANDOVER PROTOCOL

FOR PROJECT

CUB/ARS/41/INV/23

AT

LABORATORIO JULIO TRIGO LOPEZ

1 CONSIDERING that the purpose of the Multilateral Fund for Implementation of the Montreal Protocol is to help developing countries meet the incremental costs of ODS phase out measures required under the Montreal Protocol;

2 CONSIDERING that the Government of Cuba has ratified the Montreal Protocol and its Amendments of [.....] and that it has committed itself to fulfilling its obligations under the Montreal Protocol;

3 CONSIDERING that the Project Document CUB/ARS/41/INV/23 was signed by the Ministerio de la inversion extranjera y la colaboracion on behalf of the Government of Cuba and by the United Nations Development Programme (UNDP) on [DATE] based on the relevant purposes and provisions of the Montreal Protocol; and that Laboratorio Julio Trigo Lopez (hereinafter referred to as "the Company") has accepted the stipulations of the project and complies with the objectives and principles of the Project Document CUB/ARS/41/INV/23, and that the aim of this Handover Protocol is to serve as the instrument which enables the Government of Cuba and UNDP to hand over the achievements of project CUB/ARS/41/INV/23 to the Company after the project completion;

4 CONSIDERING that the successful completion of project CUB/ARS/41/INV/23 has now been achieved through the replacement of CFC-11 and CFC 12 in the manufacture of Metered dose inhalers through conversion to HFA, and that the Company will thus contribute to the objective of eliminating ozone-depleting substances (ODS) in the sector of Metered Dose Inhalers;

5 CONSIDERING that UNDP and the Company are satisfied that all project requirements have been met as stipulated in the Project Document CUB/ARS/41/INV/23, and that a Certificate of Completion (Annexed) has been issued on [DATE] by UNDP and signed by the Company certifying that all works under the Project have been fully carried out, and considering that these documents have been accepted by UNDP;

6 CONSIDERING that the Company has now completed all necessary trial testing of the new equipment (which has now been commissioned) and of the new processing technology, as certified by the UNDP Sector Expert through the signed Certificate of Completion;

7 CONSIDERING that the UNDP is satisfied that all project requirements have been met by the Company, including training of personnel, implementation of safety measures, technical inspections, etc., in accordance with the specific stipulations of the Project Document;

8 CONSIDERING that the Company has approved the plans and design for the substitution of CFC-11 and CFC 12 through the conversion to HFA, and that the Company with the cooperation of the UNDP Sector Expert has carefully inspected the new equipment and supplies and approved the work and services performed by subcontractors, suppliers and through the diligent expertise of the Company's own engineers and external consultants;

9 CONSIDERING that the Company warrants that the choice, design and installation of the new equipment and supplies has been thoroughly researched, evaluated and confirmed by the Company's engineers and Directors as technically and commercially satisfactory to the standards and requirements of its production activities, and that these installations as they now stand are fitted for production use as designed and are covered by an adequate warranty of at least one year;

10 CONSIDERING that the design, works, supplies and equipment required for this technology conversion are being funded under the Montreal Protocol for which an amount of up to US Dollars [amount] (US Dollars) has been earmarked in accordance with the decision of the Executive Committee Meeting of the Multilateral Fund for the Montreal Protocol held in December 2003;

11 CONSIDERING that the Company has already received compensation for eligible and documented costs incurred associated with trials/local works related to technology change from CFC-11 and CFC 12 to HFA;

NOW THEREFORE THE PARTIES AGREE AS FOLLOWS:

12 THAT the Company accepts full responsibility relating to the operations and ownership of the equipment, the list of which is specified in Annex B, including all necessary insurance coverage, the application of safety measures, the maintenance of the equipment, the maintenance of adequate workers protection, the compliance with public safety and environmental regulations and the liability for products generated by the equipment; that the Company shall hold UNDP, the Government of Cuba and their employees/experts harmless and the Company shall fully answer and defend against any claim or recourse against any or all of them for any damage, loss, expense, cost, whatsoever, including, without limitations, death, personal injury to or destruction of property that may at any time occur with regard to the equipment, their components, installation or ancillary works or out of services by vendors, suppliers or sub-contractors or out of the operations or performance of the equipment;

13 THAT the Company shall not hold UNDP, the Government of Cuba and their employees liable for any default or deficiencies in the equipment, supplies and ancillary works and services provided within the scope of this Project, nor for any breach of contract or discrepancy vis-a-vis the representations, the warranties, the technical specifications and/or the performance standards provided or published by the vendors, suppliers and/or sub-contractors in the procurement of their goods and services;

14 THAT any controversy or claim between the Parties arising out of, or in connection with, this Project and/or Protocol shall, unless it is settled by direct negotiation, be resolved through arbitration in accordance with Arbitration Rules of the United Nations Commission on International Trade Law (UNCITRAL-rules) and procedures; and that the parties shall be bound by any award or disposition rendered as a result of such arbitration as the final adjudication of any such claim or controversy;

15 THAT the purpose of the Project being the phasing out of the use of ODS, the Company certifies herewith that, upon completion of its portion of the Project, through the use of the new and/or retrofitted equipment financed under the Project, it has eliminated as of today the use of ODS in all its production activities; and that the replaced equipment has been destroyed or otherwise disposed of in such a manner that any further use of ODS with the equipment is not possible (as documented in Annex ...; and that the Company agrees to provide full information to the Government of Cuba to meet current and future evaluation, monitoring and reporting requirements of the Government of Cuba and the Executive Committee of the Multilateral Fund; that the Company also agrees to fully cooperate in any evaluation of the Project and agrees that the Government of Cuba may ensure that the Company fully complies with the relevant dispositions of the Montreal Protocol and the provisions made under this Handover Protocol and the Project Document;

16 THAT UNDP reserves the right to ascertain through the Government of Cuba, the Company's use and operations of the equipment and supplies, to ensure compliance with the relevant dispositions of the Montreal Protocol related to the phasing out of ODS;

17 THAT by signing this Handover Protocol, the 'Oficina Tecnica de Ozono OTOZ on behalf of the Government of Cuba accepts the report of UNDP mentioned in above paragraphs regarding the satisfactory completion of this project and accepts responsibility to ensure that the Company fully complies with the relevant dispositions of the Montreal Protocol and the provisions made under this Handover Protocol and the Project Document.

This Protocol will enter into force on the date of signature by all Parties.

ISSUED IN NEW YORK ON [DATE], AND SIGNED BY THE DULY AUTHORIZED REPRESENTATIVES OF THE PARTIES AS FOLLOWS:

FOR UNDP

Mr. Bruno Moro
Resident Representative
UNDP – La Habana

FOR GOVERNMENT OF Cuba

Raul Taladrid
Vice Minister
Ministerio de la inversion extranjera y la colaboracion

[name]
FOR THE COMPANY
JULIO TRIGO LOPEZ

ANNEX 11

Standard Certificate of Completion to be signed upon completion of the project

UNDP

CERTIFICATE OF COMPLETION

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

---

PROJECT: DATE APPROVED:
OWNER: UNDP ENGINEER:

COMPANY: ***Laboratorio Julio Trigo Lopez***
Government Counterpart: ***Ministry of Environment/OTOZ***

This Certificate of Completion applies to all work done under the following Project Document: ***Project NUMBER – Phase-out of CFC consumption in the Manufacture of Aerosol Metered Dose Inhalers (MDIs) in Cuba,*** namely:

-adequacy of installations (civil works)
-provision of technical advice
-procurement of equipment
-conduct of training and trials
-installation of equipment

The work to which this Certificate applies is herewith being confirmed as complete by the ENGINEER in presence of authorized representatives of OWNER and GOVERNMENT and the work is hereby declared to be completed in accordance with the Project Document on ***date.***

The following is a list of incomplete items as of date :

(In case of incomplete items a certificate of partial completion may be issued until incomplete items are addressed)

Responsibilities:

From the date of Completion the responsibilities between OWNER and CONTRACTOR for security, operations, safety, maintenance, utilities, insurance, warranties and guarantees shall be as follows:

OWNER: As of 12:00 [DATE] all of the aforementioned responsibilities shall be passed from UNDP to the Contractor/Company, who is Laboratorio Julio Trigo Lopez

CONTRACTOR: As of 12:00 [DATE] all the aforementioned responsibilities shall be assumed by the Contractor/Company, who is Laboratorio Julio Trigo Lopez.

This Certificate of Completion confirms that the Laboratorio Julio Trigo Lopez either have successfully undertaken training or already possess the skills for operation of equipment received from the Government Counterpart listed in ***Section number 5 of this document***, which is hereby provided to the Laboratorio Julio Trigo Lopez for its exclusive use subject to the following:

- Laboratorio Julio Trigo Lopez shall use the equipment as instructed and ensure any employees entrusted with its operation either have undertaken the requisite training or are otherwise supervised by a person who has done so.

- Laboratorio Julio Trigo Lopez shall properly operate and maintain the equipment, which includes application of safety measures and compliance with environmental regulations.

- Laboratorio Julio Trigo Lopez shall take out insurance to cover loss, theft or destruction of the equipment while in its custody.

- Laboratorio Julio Trigo Lopez shall assume full responsibility for operating the equipment and answer and defend against any claim for any damage, loss, expense, cost whatsoever, including, without limitations, death, personal injury to or destruction of property that may at any time occur with regard to the equipment or its operations.

Equipment

The equipment listed in ***Annex number*** has been received by Laboratorio Julio Trigo Lopez in good working order without any apparent damage or defect.

This Certificate does not constitute an acceptance of work not in accordance with the Contract Documents nor is it a release of each Company's obligation to complete the work in accordance with the Contract Document

Executed on behalf of UNDP by ENGINEER on ***date.***

By:_____

Name UNDP expert
Senior UNDP MDI Expert

GOVERNMENT accepts this Certificate ***on date*** on its own and Laboratorio Julio Trigo Lopez behalf.

By:_____

Mr. Raul Taladrid, Vice Minister
Ministry of Foreign Investment and Economic Cooperation

OWNER agrees with this Certificate **on date**

Signed on behalf of UNDP

By:_____

Example: Mr. Bruno Moro,
Resident Representative
UNDP Country Office- Cuba

ANNEX 12

Transmittal Letter from the Government of Cuba

Annexed in separated file

MINISTERIO DE CIENCIA, TECNOLOGIA Y MEDIO AMBIENTE
El Viceministro

CITMA

Ciudad de La Habana, 24 de Septiembre de 2003.
"Año de Gloriosos Aniversarios de Martí y del Moncada"

Dra. Suely Carvalho
Directora
Unidad Protocolo de Montreal
Programa de Naciones Unidas para el Desarrollo
New York.

Estimados Dra. Carvalho

Por el presente y a nombre del Gobierno de Cuba le solicitamos proceder a la presentación del proyecto " Phase-out of CFC consumption in the Manufacture of Aerosol Metered Dose Inhalers (MDI) in Cuba", a la Secretaría del Fondo Multilateral del Protocolo de Montreal para su consideración en la 41 reunión de Comité Ejecutivo del Fondo Multilateral del Protocolo de Montreal en Diciembre del 2003.

Por las características de este proyecto le pido se presenten a la secretaría las tres ofertas de proyecto aplicadas, por las tres Empresas que han presentado ofertas de transferencia de tecnología y que permita una valoración mas precisa, de la alternativa a decidir en el Excom y continuar el proceso de negociación con las mismas.

Le ratifico que el gobierno de Cuba y la Empresa "Reinaldo Gutiérrez" garantizarán las condiciones necesarias para la instalación del equipamiento tecnológico y la puesta en marcha de las instalaciones con las condiciones requeridas por los suministradores de la tecnología.

Aprovecho la oportunidad para reiterarle nuestras mayores muestras de consideración.

Dr. Fabio Fajardo Moros

Capitolio Nacional, La Habana 12400, CUBA, tel: (537) 8670621, Fax:(537) 8670600
e-mail: fabio@ceniai.inf.cu