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执行蒙特利尔议定书
多边基金执行委员会
第三十八次会议
2002 年 11 月 20 日至 22 日，罗马

项目提案：古巴

本文件载有基金秘书处关于下列项目提案的评论和建议：

气雾剂

•	在气雾剂计量吸入器生产中淘汰对 CFC 的消费	开发计划署

项目评价表
古巴

行业： 气雾剂 2001 年本行业 ODS 消费量： 109.1 ODP 吨

次级行业费用效益阈值： 不适用 美元/公斤

项目名称：

（ A ）在气雾剂计量吸入器生产中淘汰对 CFC 的消费

项目数据	**计量吸入器**
企业消费量（ ODP 吨 ）	109.1
项目影响（ ODP 吨 ）	109.1
提议的项目期限（ 月 ）	50
原申请经费数额（ 美元 ）	4,651,466
最后项目经费（ 美元 ）：	
增支资本费用(a)	2,025,432
酌处资金(b)	162,034
增支经营费用(c)	2,464,000
项目费用总额（ a＋b＋c ）	4,651,466
地方所有权（ % ）	100%
出口比重（ % ）	0%
申请经费数额（ 美元 ）	4,651,466
费用效益值（ 美元/公斤 ）	
对应出资是否已经确认？	
国家协调机构	Oficina Technica de Ozone
执行机构	环境规划署

秘书处的建议：	
建议供资额（ 美元 ） 项目作用（ 吨 ODP ） 费用效益值（ 美元/公斤 ） 执行机构支助费（ 美元 ）	
多边基金的费用总额（ 美元 ）	

项目说明

目标

1. 古巴政府提出了下列淘汰使用 CFC 的计量吸入器的过渡计划以及淘汰 Laboratorio Farmacéutico JulioTrigo López 生产计量吸入器使用的 109.1 吨 CFC-11 和 CFC-12 的投资项目提案。Laboratorio Farmacéutico Julio Trigo López 是古巴唯一生产气雾剂计量吸入器的厂家。现将过渡战略和投资项目提案的主要内容归纳如下。

行业背景

2. 古巴生产计量吸入器始于 1993 年。卫生部的数据显示，古巴有 10%的人口患有哮喘，8%的人口患有过敏性呼吸病，5%的人口患有慢性肺部呼吸困难疾病。

3. 古巴第一套日产 8,500 件计量吸入器的生产设施安装在 Laboratorio Farmacéutico Andrés Berro。1994 年，由于 Laboratorio Farmacéutico Julio Trigo López 安装了另一套计量吸入器生产设施，日生产能力增至 24,242 件。2000 年，两套计量吸入器生产设施合并为 Laboratorio Farmacéutico Julio Trigo López 的一处，日产总量为 3 万件（ 约每年 600 万件 ）。

4. 最初（ 1993 年 ）生产的只是使用作用短暂的 B 型兴奋剂柳丁氨醇这一剂量为 200 克的计量吸入器。1999 年推出了另一种使用倍氯米松的剂量为 50 克的控制气喘用的计量吸入器。2001 年，计量吸入器总产量达到了 600 万件，包括 480 万件（ 80% ）使用柳丁氨醇的支气管扩张器和 120 万件（ 20% ）使用倍氯米松的计量吸入器。

过渡战略

5. 古巴政府制订了逐步淘汰使用 CFC 的计量吸入器和采用无 CFC 计量吸入器的详细国家战略。现将该战略的主要内容概述如下：

6. 战略的目标是按照所有利益相关者商定的时间表和标准，淘汰使用 CFC 的计量吸入器，战略建立在下列原则上：

(a) 病人的健康应该是过渡阶段中最优先的考虑；

(b) 所有利益相关者对过渡的管理都应确保病人得到适当的治疗；

(c) 批准推向市场的新产品以及所采取后续行动，均应具有透明性和行之有效；

(d) 制订并执行有卫生专业人员、各部、制药公司和社区参加的教育方案。

7. 古巴全国对计量吸入器的需求，均由一家地方厂家满足（ 也就是说，没有进口计量吸入器 ）。这种情况还会继续下去，因此，所有无 CFC 计量吸入器均应由生产计量吸入器的

地方厂家提供。因此，国家过渡战略和使用 CFC 的计量吸入器改造项目息息相关。尽管改造项目的目标也与减少对 CFC 的消费和古巴遵守《蒙特利尔议定书》义务有联系，但改造项目不执行，国家过渡战略也不可能得到执行，反之亦然。

8. 在采用不使用 CFC 的计量吸入器之后，将尽快从市场上撤出使用 CFC 的计量吸入器，市场上不使用 CFC 的计量吸入器和使用 CFC 的计量吸入器同时存在的时间将很有限。因此，建议：

(a) 给予足够的时间进行(不使用 CFC 的计量吸入器的)售后监测数据的收集工作。开展认识和教育活动以便向主管当局报告无 CFC 新型计量吸入器的任何不利的反应；

(b) 让市场接受新产品。开展认识和教育活动，以推动在卫生专业人员和病人中使用无 CFC 的计量吸入器；

(c) 给予足够时间让计量吸入器厂家转产无 CFC 的计量吸入器。

9. 制订和执行国家过渡战略的主要利益相关者主要有：

(a) 科学、技术和环境部(通过臭氧办事处)。将负责协调教育活动、生产设施的改造、法律规定的制订(同卫生部一道)和(通过开发计划署)向多边基金申请执行国家过渡战略的技术和财政援助；

(b) 卫生部。将与其他利益相关者协调以负责执行国家教育活动；颁布批准销售无 CFC 的计量吸入器的指令和依照商定的时间表和标准淘汰使用 CFC 的计量吸入器；(与环境部一道)拟订法律规定；以及

(c) Laboratorio Farmacéutico Julio Trigo López (计量吸入器生产商)。将支持国家教育和认识方案；提供无 CFC 计量吸入器和根据国家战略规定的时限逐步淘汰使用 CFC 的计量吸入器。

国家过渡战略的费用

10. 执行过渡战略的费用，不包括与投资项目和技术转让有关的费用，为 19 万美元，分列如下：

活动	费用 (美元)
区域讲习班	40,000
国家	10,000
资讯的传播	10,000
资讯活动	120,000
售后监测方案	10,000
共计	190,000

11. 古巴政府提议通过执行国家过渡战略和让生产使用 CFC 的计量吸入器的厂家转产使用 HFC-134a 的计量吸入器，到 2005 年时逐步淘汰计量吸入器中使用的 CFC。该项目完成后，古巴政府将禁止在所有气雾剂、包括计量吸入器的生产中使用 CFC。

投资项目提案

12. Laboratorio Farmacéutico JulioTrigo López 目前在气雾剂计量吸入器的生产中消耗 CFC-11 和 CFC-12（ CFC-11 的用途是让有效成分暂时失效以便于向容器内的冲加量准确，CFC-12 则用作推进剂 ）。这种生产流程适用于柳丁氨醇和倍氯米松 CFC 计量吸入器产品。

13. 该公司选择替代目前 CFC 计量吸入器产品的技术的主要考虑是基于：对人口特别需要的评价；CFC 计量吸入器产品目前的生产情况以及生产厂家工作人员的经验和专门知识；使用 HFC-134a 计量吸入器技术的成熟程度和已确立的商业化程度，包括 HFC-134a 的价格、产品的供应情况以及新制剂的成本效益。

14. Laboratorio Farmacéutico JulioTrigo López 已决定将计量吸入器继续作为帮助服药的设备。对于柳丁氨醇，该公司提议只以 HFC-134a 制剂为基础，对于倍氯米松，该公司提议将乙醇分解和使用 HFC-134a 推进剂。

15. 采用有选择的技术，需要一家或几家知名的多国企业提供技术转让，这些多国企业具有使用这种技术生产计量吸入器的经验，并拥有转让这种技术的权利，不会侵犯任何药物分子、制剂方式、计量阀或致动器的设计或加注流程方面的知识产权。目前，技术转让的细节尚待最后确定。没有这种技术转让，Laboratorio Farmacéutico JulioTrigo López 可能需要用 6 至 10 年的时间才能研制成功取代目前使用 CFC 的计量吸入器的无 CFC 计量吸入器并得到批准。这么长的时间将使得古巴无法遵守根据《蒙特利尔议定书》规定的 CFC 消费量的限制，并影响古巴的 CFC 计量吸入器的生产和供应。

16. 替代技术需要有别于现有生产 CFC 计量吸入器的生产流程。将柳丁氨醇 CFC 计量吸入器转向使用 HFC 的计量吸入器，需要完全不同的生产设备；而生产使用倍氯米松的 HFC 计量吸入器与现有流程相近。由于 HFC-134a 与现有的密封装置之间的兼容性很差，又由于加注的新转位方法，无法改造现有的生产设备。转产的总资本建设费用，不包括相关的技术转让费用，估计为 1,835,400 美元，分列如下：

	费用（ 美元 ）
资本建设费用	1,405,432
材料、试验、实验规模的生产、临床试验、生产稳定性	250,000
新产品测试、临床试验性测试、生产登记与核准	140,000
项目技术监督、视察、完工证书	40,000
合计费用	1,835,432

17. 柳丁氨醇和倍氯米松每年转产所需增支经营费用分别为 1,155,520 美元和 260,640 美元。申请增支经营费用的使用期限为两年。

秘书处的评论和建议

评论

18. 执行委员会第三十六次会议核准了古巴政府（ 通过开发计划署 ）提出的计量吸入器过渡战略筹备工作（ 3 万美元 ）和淘汰 Laboratorio Farmacéutico Julio Trigo López 生产中所使用的 109.1 ODP 吨 CFC-11 和 CFC-12 投资项目的筹备工作（ 3 万美元 ）的两项申请。

19. 秘书处初步审查了过渡战略和投资项目，并与开发计划署以及开发计划署计量吸入器专家进行了讨论。在初步审查中，秘书处注意到国家过渡战略与投资项目密切相关。古巴政府提议 2005 年底之前完成两种 CFC 计量吸入器产品向 HFC-134a 的转产，并（ 通过讲习班和资讯的传播 ）向使用新的无 CFC 计量吸入器的主要利益相关者提供教育和认识。

20. 正如生产厂家所说，目前还没有 HFC-134a 计量吸入器生产方面的许可证、技术援助和技术转让协议。而没有技术转让或许可证协议，投资项目的执行便不能开始。秘书处从开发计划署得知，开发计划署一直在努力寻找 HFC-134a 计量吸入器技术的潜在的提供者。

21. 与工厂转产有关的资本建设费用意味着必须安装新的生产线，在过渡时期内，新生产线将和 CFC 计量吸入器的生产线同时存在。秘书处注意到，申请的某些设备，即洗罐器（ 费

用为 77,500 美元)、测重仪(55,800 美元)、装载机(116,250 美元)和传送带(62,000 美元),看来与逐步淘汰 CFC 并没有关系。在与开发计划署顾问就此事进行讨论后,秘书处得出结论认为,可以将这些设备看作是基准的一部分,因此不属于增支性质。为此,在排除这些设备后,经修正的资本建设费用为 1,057,667 美元(而不是 1,405,432 美元)。

22. 秘书处还接到建议称,项目提议中提出的设备是转产无 CFC 的计量吸入器所需的最起码的设备,这些设备可以与各主要制药公司现行的无 CFC 技术并用。

23. 增支经营费用(两年期限内的净现值为 2,464,000 美元)主要是由于改造铝罐(每套的增支费用为 0.012 美元)和计量阀(每套的增支费用为 0.21 美元)以及 CFC 价格(每公斤 CFC-11 为 5.54 美元,每公斤 CFC-12 为 6.09 美元)与 HFC-134a 价格(每公斤 7 美元)之间的差距造成的。开发计划署顾问的意见是,这些费用也受所使用技术的影响,因此只是说明性质。一旦选择和购买技术后,增支经营费用还将重新计算。

建议

24. 谨建议执行委员会:

(a) 注意到古巴政府转向使用无 CFC 计量吸入器的过渡战略以及相关的淘汰 Laboratorio Farmacéutico Julio Trigo López 生产中所使用的 CFC 的投资项目;

(b) 注意到经修订的资本建设费用为 14.88 万美元(包括用于试验、试生产、临床试验、产品稳定试验、技术监督、视察和完工证书的 43 万美元);

(c) 请开发计划署继续帮助古巴政府最后完成过渡战略和确定 HFC-134a 计量吸入器技术的潜在提供者,并在古巴政府确定并选择提供者后重新提交过渡战略和投资项目;

(d) 在 2002 年开发计划署业务计划中保留古巴转产无 CFC 计量吸入器的过渡战略和淘汰计量吸入器中的 CFC 的投资项目。

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
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:	50 months after MLF Approval
Costs of Conversion:	
National MDI Transition Strategy (Annex)	**US$ 190,000**
Incremental Capital Cost Conversion Project:	**US$ 1,835,432**
Contingency:	**US$ 162,034**
Incremental Operating Cost:	**US$ 2,464,000**
Total Project Cost: (Excluding Technology Transfer for conversion project/license)	**US$ 4,461,466**
Total Cost	**US$ 4,651,466**
LOCAL OWNERSHIP:	**100%**
EXPORT COMPONENT:	**0%**
REQUESTED GRANT: (Excluding Technology Transfer)	**US$ 4,651,466**
AGENCY SUPPORT COSTS:	**US$ To be determined**
TOTAL COST TO THE MLF: (Excluding Technology Transfer)	**US$ To be determined**
COST-EFFECTIVENESS: (Excluding Technology Transfer)	**US$ 42.6/Kg** (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 HFC-134a MDI manufacturing technology at Laboratorio Farmaceutica “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 HFC propellant technologies (e.g. GlaxoSmithKline; Norton Healthcare), and who own 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 project proposal therefore includes a request for funding for such technology transfer,

although at present the details still have to be finalised.

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. The project covers an HFC MDI Manufacturing Facility (US$ 1,405,432) of similar production capacity to the baseline facility (>6 million units per annum). Funds are also requested for materials that will be consumed in, Equipment Proving Trials, Pilot Scale Production, Clinical Trials, Product Stability (US$ 250,000) as well as for Product Stability Testing, Clinical Trials, Testing, and Product Registration (US$ 140,000), and Overall Project Supervision (US$ 40,000).

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.

Excluding the funding for CFC-free MDI technology transfer that has not yet been finalised, the Incremental Capital Costs are then US$ 2,025,432, and with Contingencies (US$ 162,034) the total becomes US$ 2,187,466. The net Incremental Operating Costs calculated for two years amount to US$ 2,464,000, making a total project cost of US$ 4,651,466 (excluding CFC-free MDI technology transfer). With no sector cost-effectiveness threshold applicable to the aerosol MDI sector, the total project costs of US$ 4,651,466 (excluding CFC-free MDI technology transfer) are requested. It must be noted that MLF funding of the CFC-free MDI technology transfer costs is essential to successful project completion.

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 it's Montreal Protocol CFC Consumption Limits, although with project completion currently scheduled only in 2006 it will not contribute to the 50% reduction required by 2005, unless project implementation can be accelerated.

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 THE USE OF HFC-134a PROPELLANT TECHNOLOGY AT LABORATORIO FARMACEUTICA "JULIO TRIGO LOPEZ":TO MANAGE THE RESULTING TRANSITION FROM CFC MDIs TO HFC MDIs IN THE COUNTRY

• 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 Aerosol Metered Dose Inhalers (MDIs) in Cuba, and (b) to manage the transition from CFC based MDIs to HFC MDIs in the country. This involves conversion to the use of HFC 134a propellant technology at 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.

• 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.

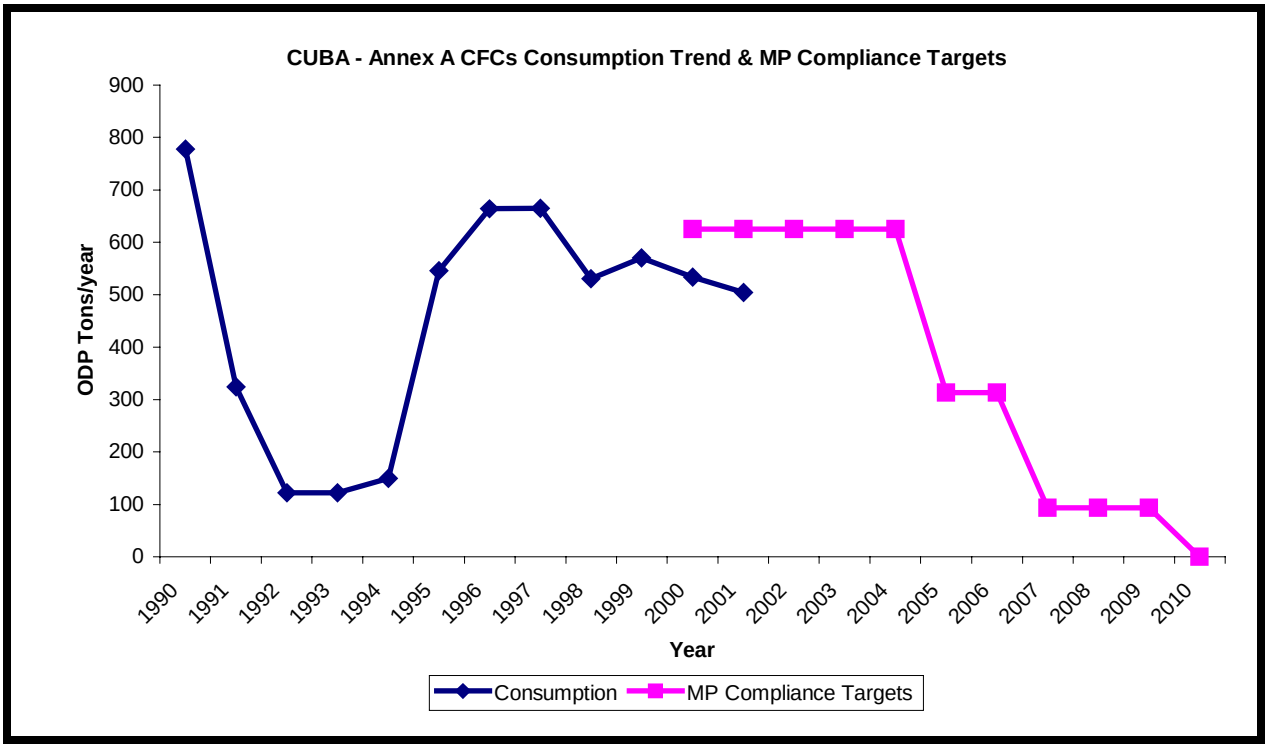
To meet its obligations under the Montreal Protocol, Cuba must now ensure that the annual consumption of Annex A Group I substances (CFCs 11, 12, 113, 114, and 115) does not exceed the "Baseline Consumption" of 625 ODP tonnes for each of the years 2000 through 2004. Thereafter, the maximum permitted 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	30.0
Aerosols MDIs	74.3	84.7	109.1	117.9
Total	**77.8**	**99.7**	**134.1**	**147.9**

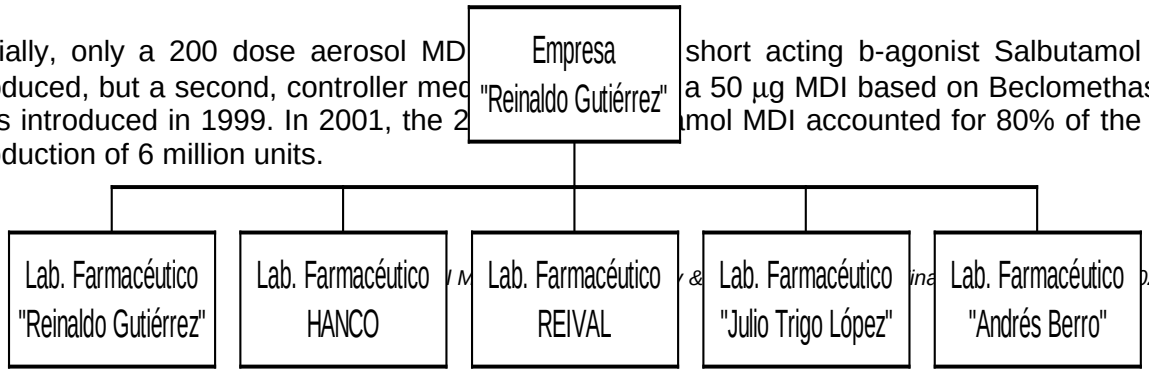
Considering that all of the remaining CFC consumption in the refrigeration and air-conditioning sector is for repair and service activities where reduction in consumption is difficult to achieve without equipment replacement or retrofit, this growth trend in CFC consumption in the aerosol MDI manufacturing 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.

- **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 MD short acting b-agonist Salbutamol was produced, but a second, controller med a 50 μg MDI based on Beclomethasone was introduced in 1999. In 2001, the 2 mol 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**.

• PROJECT DESCRIPTION

The requested MLF funding is to address two distinct needs, conversion of CFC MDI production in Cuba to HFC 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 HFC MDIs.

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 in

non-Article 5 countries (e.g. GlaxoSmithKline; 3M Pharmaceuticals) 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 (e.g. GlaxoSmithKline; Norton Healthcare; Cheisi) that have experience in the manufacture of HFC MDIs using these technologies, and who own 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 project proposal therefore includes a request for funding for such technology transfer, although at present the details have yet to be finalised.

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

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).

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 compatability 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 HFC 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.

4.2.2 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.

4.2.3 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. The phase-out of CFCs in industrial aerosol manufacture is scheduled for April 2003. With the required MLF assistance, the phase-out of the majority of CFC's used to manufacture is achievable in 2005. Once completed, then the Cuban Government will prohibit the use of Annex A CFCs in all aerosol products, without exemption.

• PROJECT COSTS

5.1 INCREMENTAL CAPITAL COSTS - CFC MDI CONVERSION PROJECT

CFC-free MDI Manufacturing Facility - The following represents a summary of the budget costs for a flexible aerosol MDI manufacturing facility that is designed for use with most of the current CFC-free MDI formulations, including both of the CFC replacement technologies selected in this project proposal. 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.

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).

Item	Cost (US$)
Can Cleaner/Unscrambler	**77,500.00**
Double Macromats	**412,300.00**
DH Cleanline Environmental Enclosure	**108,500.00**
Automatic Checkweigher	**55,800.00**
Delta Trayloader	**116,250.00**
DH R800 Conveyor System	**62,000.00**
DH Electrolink Control System	**85,250.00**
Product Re-circulation Multilobe Pump	**5,890.00**
Suspension/Solution Supply Hoses and Couplings	**2,790.00**
Propellant Only Supply Pump	**5,890.00**
Propellant Supply Pipe-work	**2,325.00**
Tandem Diaphragm Pump	**42,625.00**
Suspension/Propellant Re-circulation Pipe-work	**2,945.00**
Mixing Vessel	**147,250.00**
Build up/Test Run/FAT	**23,250.00**
Installation/Commissioning/SAT	**85,250.00**
Qualification Documentation	**23,250.00**
Sub-total for equipment for CFC-free MDI Manufacturing Facility	**1,259,065.00**
Packing, Freight, & Insurance	**18,600.00**
Contingencies (10%)	**127,767.00**

TOTAL FOR EQUIPMENT FOR CFC-free MDI MANUFACTURING FACILITY	**1,405,432.00**

TOTAL CAPITAL COST SUMMARY - CFC MDI CONVERSION PROJECT	Cost (US$)
TOTAL FOR EQUIPMENT FOR CFC-free MDI MANUFACTURING FACILITY	**1,405,432.00**
Materials Consumed in Equipment Proving Trials, Pilot Scale Production, Clinical Trials, Product Stability (10 batches at 25K per batch)	**250,000.00**
Costs of New Product Testing, Clinical Trial Testing, Product Registration and Approval	**140,000.00**
Overall Project Technical Supervision, Inspections, Certification of Completion	**40,000.00**
TOTAL CAPITAL COST FOR CFC MDI CONVERSION PROJECT **	**1,835, 432**

Notes:

* Includes General Technical Advisory Services, Consultants Fees, Travel Costs, Communications, etc.

** Excluding CFC-free MDI Technology Transfer Costs

5.2 TECHNOLOGY TRANSFER COSTS – CFC MDI CONVERSION PROJECT

Royalties/fees for transfer of CFC-free MDI technology will need to be negotiated with at least one multinational. Given the Cuban governments preference for using a non-ethanol salbutamol formulation, this intellectual property and know how belongs to GlaxoSmithKline and negotiations are underway to see if they would be willing to enter into an agreement. Further details will be forthcoming as negotiations continue.

US$ To be determined

5.3 INCREMENTAL CAPITAL COSTS – NATIONAL MDI TRANSITION STRATEGY

Development and implementation of the National MDI Transition Strategy **US$ 190,000.00**

5.4 INCREMENTAL OPERATING COSTS - CFC MDI CONVERSION PROJECT

Incremental operating costs are requested for TWO years and are based on the production volume of CFC MDIs in 2001. Details of the calculations are provided in **ANNEX 3**.

TOTAL ANNUAL INCREMENTAL OPERATING COST (based on salbutamol and beclomethasone at current production levels)	**US$ 1,416,000**
TOTAL FOR TWO YEARS AT NPV (US$ 1,416,000 x 1.74)	**US$ 2,464,000**

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)

TOTAL COST (Capital + Operating Costs – Operating Benefits)	**US$ 4,651,466**
% Article 5.1 Country Ownership	100%

5.6. PROJECT COST EFFECTIVENESS & FUNDING REQUESTED FROM THE MLF

TOTAL PROJECT COST (**excluding MDI Technology Transfer**)	**=**	**US$ 4,651,466**
FUNDING REQUESTED FROM THE MLF	**=**	**US$ 4,651,466**
TOTAL ODS ELIMINATED	**=**	**109,100 ODP Kg**

BASED ON THE TOTAL PROJECT COST EXCLUDING THE CFC-FREE MDI TECHNOLOGY

TRANSFER, THE PROJECT COST-EFFECTIVENESS IS 42.6 US$/Kg

• FINANCING PLAN

The total project incremental costs excluding the CFC-free MDI technology transfer are US$ **4,651,466.00**. There is no cost-effectiveness threshold for the aerosol MDI sector, and in line with the 100% Article 5.1 country ownership of the enterprise, Laboratorio Farmacéutico "Julio Trigo López" requests reimbursement of these total incremental costs of US$ **4,651,466.00**, plus the as yet undefined costs for transfer to Laboratorio Farmacéutico "Julio Trigo López" of the CFC-free MDI technology.

• PROJECT IMPACT

This project will eliminate the use of 109.10 ODP tons per year. This is based on the actual ODS consumption during the calendar year 2001.

• 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 HFC 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. Given the uncertainty regarding gaining access to the HFC MDI product formulation, subsequent clinical trials in Cuba, product registration and approval, it is not possible to accurately estimate a date for overall completion of the project. The proposed project implementation schedule as indicated below, and the milestones for monitoring of the project as indicated in the following table, must be regarded as extremely tentative at this time.

8.2 PROJECT SCHEDULE

TASK	2002		2003				2004				2005				2006			
	Q3	Q4	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	x															
Project Document Signature		x																
Implementation Appraisal		x	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	Xxx	Xxx	Xxx												
Bid Analysis & Vendor Selection				x														
Equipment Supply Contracts Awarded				xx														
Installation & Commissioning of CFC-free MDI Manufacturing Equipment							xx											
Initial Transition Strategy Implementation Activities						xxx	xxx	xxx										
CFC-free MDI Formulation, Stability Testing & Clinical Trials						x	xxx	xxx	xxx	xxx	xxx							
CFC-free MDI Manufacturing Equipment Delivered									xxx									
Production of CFC-free MDIs on manufacturing equipment for Stability Testing, Clinical Trials, Registration, & Approval										xx	xxx	xxx	xxx					
Major Transition Strategy Implementation Activities										xxx	xxx	xxx	xxx	xxx	Xxx			
CFC-free MDI Approval													xxx	xxx				
Full Scale CFC-free MDI Manufacture														xxx	Xxx	xxx	xxx	
Post Market Surveillance Data Collection															xx	xxx	xxx	
Phase-out of CFC MDI Manufacture																	x	
Verification & Certification of Project Completion																		x
Confirmation of Destruction/Disablement of baseline CFC MDI equipment replaced with MLF funding																		x
Submission of Project Completion Report																		x

- **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	12
(5) Equipment Bid Documents prepared and Bids requested	4
(6) Bids Analysis, Vendor Selection, & Contracts Awarded	5-7
(8) Commence MDI Transition Strategy Activities	12
(10) MDI Manufacturing Equipment Delivered, Installed, & Commissioned	16-20
(11) Start Main Transition Strategy Implementation Activities	24->
(12) Commence Production of CFC-free MDIs on manufacturing equipment for Stability Testing, Clinical Trials, Registration, & Approval	20-34
(13) CFC-free MDI Approval	32-37
(14) Start of Commercial CFC-free MDI manufacture	37->
(15) Post Market Surveillance Data Collection	39 ->
(16) Phase-out of CFC MDI Manufacture	45
(17) Verification & Certification of Project Completion	46
(18) Confirmation of Destruction/Disablement of baseline CFC MDI equipment replaced with MLF funding	46
(19) Submission of Project Completion Report	48

* As measured from project approval

• ANNEXES

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

ANNEX 2: CFC MDI Conversion Project Replacement Equipment Incremental Capital Costs.

ANNEX 3: CFC MDI Conversion Project 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 9: Regulatory Requirements for the Testing, Approval, and Licensing of New MDI/DPI products in Cuba.

ANNEX 10: Project Technical Reviews.

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 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 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	5.0
50 µg Beclomethasone MDI	0.2	0.7	1.2	1.5
Total	**4.1**	**4.7**	**6.0**	**6.5**

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-11**	**CFC-12**	**CFC-11**	**CFC-12**
200 dose Salbutamol MDI	23.1	47.9	23.8	49.3	28.9	59.8	30.1	62.3
50 µg Beclomethasone MDI	1.4	1.9	5.0	6.6	8.8	11.6	10.9	14.6
Annual Substance Total	24.5	49.8	28.8	55.9	37.7	71.4	41.0	76.9
Annual Grand Total	**74.3**		**84.7**		**109.1**		**117.9**	

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 60 cans/minute (6.6 million cans/year based on 230 working days/single shift operation)

Double Macromat HFA MDI Aerosol Filling Line

1.0 Can Cleaner/Unscrambler

ONE x 02046-023/003 can cleaner/unscrambler for 22 mm diameter cans suitable for speeds up to 100 cpm comprising:

- Horizontal rotating selector disc 900mm ø for one size of can.
- Drives by variable speed units with torque limiter fitted with 0.25 kW, 3 ph motor.
- Outlet chute for one size of can.
- Adjustable air jets to aid sorting process.
- Stainless steel frame with stainless steel cladding.
- Integral elevator and hopper.
- Stainless steel skirt to floor.

- Can cleaning device fitted into can feed rail with:
    - Can inversion scroll.
    - Ionised air-blowing unit with air filter.
    - Extraction unit.

For the sum of US$ 77,500.00

2.0 Double Macromat Filling Machines

ONE x P2045 Macromat aerosol filling machine-indexing unit with:

- Quick release 18 pocket starwheel/outer guide to suit 22mm 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 customer's exact requirements.

Each head can be individually controlled from the operator's 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$ 72,075.00

Machines fitted to above base unit:

2.1 Suspension/Solution Filler

ONE x P2039 5ml filler with re-circulation system.

Suspension/Solution filler suitable for filling:

- CFC product suspensions
- Ethanol product suspensions
- Ethanol product solutions

Filler comprising:

- Quick release mounting bracket for metering unit with pneumatic control manifold in Macromat back cabinet.
- P2039 5ml metering unit with re-circulation system.
- Diaphragm inlet/outlet shut off valves to enable re-circulation.
- Diaphragm filling nozzle mounted on quick release coupling to slave cylinder above Macromat starwheel.
- Sub base mounted oil free pneumatic control system.
- Quick release, self sealing couplings for product supply and return.
- Product contact parts in stainless steel 316L and PTFE complete with material certificates for validation purposes.

For the sum of US$ 21,700.00

2.2 Valve Inserter

ONE x P2058 Valve Inserter to handle 20mm valves without dip tubes 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$ 10,850.00

2.2.1 Vibratory Valve Sorter

ONE x free standing vibratory valve sorter comprising:

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

For the sum of US$ 37,200.00

2.2.2 Valve Transport System

ONE x 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$ 38,750.00

2.3 Vacuum Crimper

ONE x 02002 Vacuum Crimper suitable for use with or without vacuum.

For single stage HFA formulations vacuum is required, and for two stage 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$ 26,350.00

2.3.1 Vacuum Pump

ONE rotary vane vacuum pump to work in conjunction with up to 2 vacuum crimpers comprising:

- Rotary vane vacuum pump assembly type Busch R5 P14012.
- Suction capacity 40m^3/hr.
- Final vacuum 20 mbar.
- Separator type 025-040.

- 1.1kw, 380v, 50hz drive motor.

For the sum of US$ 4,650.00

2.4 Diaphragm Suspension Filler

ONE x 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:

- 20cc Diaphragm metering unit with re-circulation 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 re-circulation.
- Diaphragm aspirator type filling nozzle with filling nozzle insert to suit one valve type mounted above Macromat starwheel.
- Vacuum filter and pipe-work 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$ 31,000.00

2.4.1 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$ 3,875.00

Summary of Section 2.0 Costs

First Macromat

2.0	Macromat Base Unit/Enclosure	US$	**72,075.00**
2.1	Suspension/Solution Filler	US$	**21,700.00**
2.2	Valve Inserter	US$	**10,850.00**
2.2.1	Vibratory Valve Sorter	US$	**37,200.00**
2.2.2	Valve Transport System	US$	**38,750.00**
2.3	Vacuum Crimper	US$	**26,350.00**
2.3.1	Vacuum Pump	US$	**4,650.00**
2.4	Diaphragm Suspension Filler	US$	**31,000.00**
2.4.1	Vacuum Pump	US$	**3,875.00**
	TOTAL	US$	**246,450.00**

Second Macromat as above

2.0	Macromat Base Unit/Enclosure	US$	**72,075.00**
2.1	Suspension/Solution Filler	US$	**21,700.00**
2.2	Valve Inserter	US$	**10,850.00**
2.3	Vacuum Crimper	US$	**26,350.00**
2.4	Diaphragm Suspension Filler	US$	**31,000.00**
2.4.1	Vacuum Pump	US$	**3,875.00**
	TOTAL	US$	**165,850.00**

TOTAL FOR DOUBLE MACROMAT..... US$ 412,300.00

3.0 DH Cleanline Environmental Enclosure

ONE x Cleanline environmental enclosure designed to enclose the can cleaner/unscrambler, valve sorter, valve transport system and double Macromats with each partitioned separately comprising:

- Cleanline anodised aluminium frame for easy cleaning.
- Glazed in 6mm laminated glass and 16swg anodised aluminium panels.
- Fully interlocked access doors.
- Hepa filter air re-circulation system to maintain clean air to class 10,000 or 1,000 standard at the discharge side of the Hepa filters.
- Magnahelic pressure gauges to monitor the pressure differential across the Hepa filters.
- Process extract system for the filing enclosure.
- Air, propellant, suspension and process extraction are run and terminated at various points within the streamline enclosure.

For the sum of US$ 108,500.00

4.0 Automatic Checkweigher

ONE x Garvens S2 automatic aerosol can check-weighing machine to operate at speeds up to 100cpm comprising:

- Can infeed conveyor with scroll and infeed can stop.
- Can outfeed conveyor fitted with air blast reject device and catch bin.
- Outfeed side belts for transfer onto line conveyor system.
- High accuracy weighing conveyor ± 50mg.
- Colour display monitor.
- Acrylic cover over weighing conveyor.
- Consecutive reject detection system.
- Reject confirmation device.
- Statistics package with integral printer.
- Validation documentation package.

For the sum of US$ 55,800.00

5.0 DH Delta Trayloader

ONE x DH Delta Twin Tayloader to automatically load filled aerosol cans in three sided trays at speeds of 100cpm. Machine has positions for 2 trays comprising:

- Stainless steel clad base unit.
- Can shuttle to transfer cans in rows from conveyor system.
- Can transfer, to transfer rows of cans into 3 sided trays.
- Tray lifting piston to elevate filled trays once loaded.
- Fully interlocked enclosure.
- Integral electrical panel with PLC control system.
- Change parts for two tray types

For the sum of US$ 116,250.00

6.0 DH R800 Conveyor System

ONE x DH R800 Conveyor System comprising:

- R800 conveyor system to transport cans from can sorter outlet to dividing station inlet.
- Dividing station to divert cans in batches of 10, on demand to either Macromat.
- Duplex Macromat infeed conveyor to transport cans from dividing station through the Macromats.
- Can combining guide rail system.
- R800 Conveyor system to transport cans from combining system through the checkweigher to the trayloader.

For the sum of US$ 62,000.00 *(depending on layout)*

7.0 DH Electrolink Control System

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

- Free standing stainless steel enclosure.
- PLC controller.
- 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.
- Colour touchscreen graphic operator interface.

For the sum of US$ 85,250.00

8.0 Product Re-circulation Multilobe Pump

ONE x stainless steel Multilobe pump suitable for supply of product to the 5ml filling head with re-circulation.

Suspension re-circulation pump suitable for:

- CFF product suspensions.
- Ethanol product suspensions.
- Ethanol product solutions.

Comprising:

- Stainless steel Multilobe PTFE impregnated rotorform material.
- Stainless steel 316 product contact parts.
- Assembly mounted on mile steel in-line baseplate.
- Ex mechanical variable speed drive unit suitable for siting in Zone 1 area.

For the sum of US$ 5,890.00

8.1 Suspension/Solution Supply Hoses and Couplings

To supply the following suspension re-circulation pipe-work to use in conjunction with the suspension/solution filling machine and product re-circulation Multilobe pump.

All re-circulation hoses PTFE lined with stainless steel braiding and 316 stainless steel end fittings.

Re-circulation hoses from:

- Vessel outlet to pump inlet.
- Pump outlet to P2039 suspension/solution filler supply.
- Self-sealing coupling on P2039 suspension/solution filler supply.
- Self-sealing coupling on P2039 suspension/solution filler return.
- P2039 suspension/solution filler to vessel inlet.

For the sum of US$ 2,790.00

9.0 Propellant Only Supply Pump

ONE x P2008/12 pneumatically operated propellant only supply pump.

Propellant only supply pump suitable for the supply of HFA propellant only comprising:

- Air cylinder with changeover valve.
- Double acting propellant supply pump.
- Contact parts stainless steel.
- Seals UHMWP/PTFE/Nitrile.
- Stable base housing air exhaust silencer.
- Through put:
    - Theoretically 20 litres per minute.
    - Efficient approximately 15 litres per minute.
- Air requirements: 5-10 bar.
- Propellant delivery pressure: 10-20 bar.
- Maximum propellant feed: 50m.
- Propellant: air ratio approximately 2:1.

For the sum of US$ 5,890.00

9.1 Propellant Supply Pipe-work

To supply the following propellant supply pipe-work to use in conjunction with the diaphragm suspension filler and propellant only supply pump.

All propellant supply hoses PTFE lined with stainless steel braid and 316 stainless steel end fittings.

Propellant pipe-work:

- Inlet hose to pump from gas bottle with gas bottle adaptor and in-line strainer.
- Outlet hose from pump to diaphragm filler complete with 5 micron propellant filter and shut off tap.

For the sum of US$ 2,325.00

10.0 Tandem Diaphragm Pump

ONE DH/Pamasol P2089 Tandem Diaphragm Pump suitable for feeding re-circulation filling heads with minimum pressure fluctuation to ensure high accuracy of fill. Operation fully pneumatic.

Tandem diaphragm pump suitable for:

- HFA product suspensions.
- HFA propellant only.

Pump comprising:

- Output 13 litres per minute.
- Normal output pressure 10 bar.
- Air supply pressure 5-10 bar.
- Air/output pressure ratio 1:3.

Connections:

- Inlet 10mm/fitting SO51521-10.
- Outlet 8mm/fitting SO51521-08

For the sum of US$ 42,625.00

10.1 Suspension/Propellant Re-circulation Pipe-work

To supply the following re-circulation pipe-work to use in conjunction with the tandem diaphragm pump and diaphragm suspension filler.

All re-circulation hoses PTFE lined with stainless steel braid and 316 stainless steel end fittings.

Re-circulation pipe-work:

- Inlet hose to pump from mixing vessel.
- Outlet hose from pump to diaphragm suspension filler inlet terminating in quick release coupling.
- Return hose from diaphragm suspension filler to mixing vessel.

For the sum of US$ 2,945.00

11.0 Mixing Vessel

ONE x 100 litre capacity stainless steel mixing vessel suitable for operation up to 10 bar.

Mixing vessel suitable for use with:

- Ethanol product suspensions.
- Ethanol product solutions.
- HFA product suspensions.

Mixing vessel comprising:

- Vertical, cylindrical vessel with hemispherical bottom.
- Dished head bolted to vessel neck via mating flange.
- Flush fitted diaphragm valve bottom outlet.

Vessel fitted with:

- Temperature probe.
- 25mm Re-circulation connection.
- 100mm Charge port with interlock.
- 100mm Sight n' light unit.
- 25mm Product inlet complete with manual butterfly valve.
- Pressure gauge.
- Pressure relief valve.
- 2 x Spray balls.

Heating/cooling jacket over the bottom and sides of the vessel, suitable for chilled water or steam at 3 barg.

Jacket connections include:

- 40mm water inlet.
- 40mm water outlet.
- Pressure gauge.
- Pressure relief valve.
- Insulation in mineral wool clad with stainless steel is included over the jacketed area.
- Three OFF tubular support legs complete with flanged feet.
- Agitator is top entry propeller type mixer mounted on top of the vessel. Entry to the vessel is via a mechanical seal. The mixer is fixed speed approximately 300rpm.

- Electrical controls mounted in a stainless steel cabinet to be used in a flameproof environment:
    - Agitator stop/start.
    - Outlet valve open/close.
    - Temperature controller with display.
- Drug additional vessel to be charged in the dispensary then, carried to the vessel and locked on using dry break couplings.
- Material of construction is 316L grade stainless steel with mirror finish inside and dull polish outside.
- All interior welds to be smooth and crevice free.

For the sum of US$ 147,250.00

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

- To align and connect all machines as production line.
- To supply compressed air, power and propellant pumping/pipe-work system to equipment.

12.1 Factory Acceptance Tests F.A.T

- To run a quantity of up to 30,000 units on equipment assuming free issue of propellant and components.
- To conduct Factory Acceptance Tests to previously agreed test protocols.

12.2 To dismantle line and mark for ease of on-site re-assembly.

For the sum of US$ 23,250.00

13.0 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 – 4 weeks.

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

For the sum of US$ 85,250.00 *(depending on location)*

14.0 Qualification Documentation

To provide the following documentation to aid the qualification of the double 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$ 23,250.00

Summary of Total Costs

1.0	Can Cleaner/Unscrambler	US$	**77,500.00**
2.0	Double Macromats	US$	**412,300.00**
3.0	DH Cleanline Environmental Enclosure	US$	**108,500.00**
4.0	Automatic Checkweigher	US$	**55,800.00**
5.0	Delta Trayloader	US$	**116,250.00**
6.0	DH R800 Conveyor System	US$	**62,000.00**
7.0	DH Electrolink Control System	US$	**85,250.00**
8.0	Product Re-circulation Multilobe Pump	US$	**5,890.00**
8.1	Suspension/Solution Supply Hoses and Couplings	US$	**2,790.00**
9.0	Propellant Only Supply Pump	US$	**5,890.00**
9.1	Propellant Supply Pipe-work	US$	**2,325.00**
10.0	Tandem Diaphragm Pump	US$	**42,625.00**
10.1	Suspension/Propellant Re-circulation Pipe-work	US$	**2,945.00**
11.0	Mixing Vessel	US$	**147,250.00**
12.0	Build up/Test Run/FAT	US$	**23,250.00**
13.0	Installation/Commissioning/SAT	US$	**85,250.00**
14.0	Qualification Documentation	US$	**23,250.00**

TOTAL .....**US$ 1,259,065.00**

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.

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	5.54 US$/Kg	0.03174	-	-	0
CFC-12	11.871 gm	6.09 US$/Kg	0.07229	-	-	0
HFC-134a	-	-	0	17.60 gm	7.0 US$/Kg	0.1232
Ethanol	-	-	0	-	-	0
Aluminium Monobloc Can	1	0.06	0.06	1	0.072	0.072
Metering Valve	1	0.42	0.42	1	0.63	0.63
Actuator	1	0.058	0.058	1	0.058	0.058
Salbutamol	0.023 gm	385 US$/Kg	0.00886	0.023 gm	385 US$/Kg	0.00886
Sorbitan Trioleate	0.046	10 US$/Kg	0.00046			
Cost per MDI	**US$ 0.65135**			**US$ 0.892**		
Annual Production	4.8 million units			4.8 million units		
Annual Cost	US$ 3,126,480			US$ 4.282,000		
Annual Incremental Operating Cost for Conversion of Salbutamol CFC MDI to HFC 134a = US$ 1,155,520						

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	5.54 US$/Kg	0.03847	-	-	0
CFC-12	9.2501 gm	6.09 US$/Kg	0.05633	-	-	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	0.06	0.06	1	0.06	0.06
Metering Valve	1	0.42	0.42	1	0.63	0.63
Actuator	1	0.058	0.058	1	0.058	0.058
Beclomethasone Dipropionate	N/A	N/A	N/A	N/A	N/A	N/A
Oleic Acid	N/A	N/A	N/A	N/A	N/A	N/A
Cost per MDI	**US$ 0.6328**			**US$ 0.85**		
Annual Production	1.2 million units			1.2 million units		
Annual Cost	US$ 759,360			US$ 1,020,000		

Annual Incremental Operating Cost for Conversion of Beclomethasone CFC MDI = US$ 260,640

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.

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 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

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

Laboratorio Farmacéutico "Julio Trigo López"both represented by Lic. 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 Farmacéutico "Julio Trigo López" 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 Farmacéutico "Julio Trigo López" will be the beneficiary;

b) It accepts the 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.

……..
(date)

…….
(Authorised Signature)

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 Metilprednisolone	• Tablets • Syrup • Injections • Injections	Anti-inflammatory

(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 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
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 - REGULATORY REQUIREMENTS FOR THE TESTING, APPROVAL, AND LICENSING OF NEW MDI/DPI PRODUCTS IN CUBA

ANNEX 10 - PROJECT TECHNICAL REVIEWS

➢ 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 Goverment 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 Farmacéutico "Julio Trigo Lopez " will be the beneficiary;

b) It accepts the 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)

EMP. LAB. FTCO. REINALDO GUTIERREZ
DIRECCION
MINSAP

REGISTRO
SALIDA 030
FECHA 25/9/02

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 2002

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	5 000000
Beclomethasone 50µg	Steroidal Anti-inflammatory		1 200000	1 500000
Total		4 719000	6 000000	6 500000

Annual consumption of CFC

CFC	Unit	2000	2001	2002 (Forecast)
CFC 11	Ton	28.8	37.7	41.0
CFC 12	Ton	55.9	71.4	76.9
Total	Ton	84.7	109.1	117.9

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.

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$**
Investment project	**4,461,466.00**
National Information strategy	**180,000.00**
Programme for post-marketing surveillance	**10,000.00**
TOTAL	**4,651,466.00**

(1) Excluding technology transfer and agency support costs

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	2002		2003				2004				2005				2006			
		Q 3	Q4	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								
Report on facility inspection	3										X								
Report of pilot production outcomes	4										X								
Confirmation of setting up of the HFC MDI production equipment at industrial scale	4										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					
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

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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	2002
Solicit market offers on the packaging material used in the production of HFC MDIs	2002/3
Survey of the area where the technological process and the physical-chemical controls will be carried out	2002/3
Contract the services of an enterprise for the implementation of the investment processes	2003
Present the investment projects to the drug regulatory agencies (CITMA[4], CECMED)	2003

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	2003
Assess the facility concerning the observance of the Good Fabrication Practices and the environmental regulations	2003

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	2004
Training of the personnel taking part in the chemical-physical analysis	2004
Training of the personnel on the subject of industrial safety for the use of HFC	2004

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	2004
Development and validation of trials to the fulfillment of the clinical assessment stage	2004
Development and validation of the control processes trials	2004
Development and validation of trials of batch release control and quality control	2004

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	2003-2004
Acquisition of packaging material compatible with HFC	2003-2004
Acquisition of raw materials	2004

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	2004
Carry out industrial scale-up	2004
Carry out chemical-physical and microbiological analysis	2004
Assess product stability	2004
Obtain a conditional indicative registration with HFC	2004

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	2003
Making of the master file	2004
Evaluation of the file by the regulatory entity (CECMED)	2004

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	2005
Chemical-physical and microbiological assessment	2005

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	2004

4. Monitoring indicators:
- Report on Clinical trials

5. Participants
Specialists from QUIMEFA and CENCEC