



Full-Sized Project



# UNIDO / GEF

Phase out of CFC Consumption in the  
Manufacture of Aerosol Metered –Dose  
Inhalers (MDIs) in the Russian Federation

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## Table of contents

### Contents

Executive summary.....	4
1. Background.....	7
1.1. REGULATION AND POLICY FOR THE MDI SECTOR AND CFC PHASE OUT .....	10
1.2. POLICES RELATED TO CFC PHASE OUT .....	10
2. ASTHMA AND COPD IN THE RUSSIAN FEDERATION.....	11
2.1. INCIDENCE OF RESPIRATORY DISEASE .....	11
2.2. CHRONIC OBSTRUCTIVE PULMONARY DISEASE.....	13
3. The Pharmaceutical Aerosol Manufacturing Sector in the Russian Federation .....	16
3.1. MDI Market in the Russian Federation .....	16
3.2. Import of MDIs in the Russian Federation .....	17
4. PRODUCTION OF MDIS IN THE RUSSIAN FEDERATION .....	20
4.1. MDI PRODUCTION AT MOSCHIMPHARMPREPARATY.....	21
4.2. MDI PRODUCTION AT ALTAYVITAMINY.....	24
4.3. METERED DOSE INHALERS (MDIs).....	27
4.3.1. ALTERNATIVE EXCIPIENT - HYDROFLUOROALKANES (HFA).....	29
4.3.2. USE OF HFA AS A PROPELLANT IN MDI .....	30
5. PROJECT DESCRIPTION .....	31
5.1. NATIONAL CFC MDI MANUFACTURE CONVERSION PROJECT .....	31
5.2. OVERVIEW & SELECTION OF REPLACEMENT TECHNOLOGIES FOR CFC MDIS .....	32
5.3. THE MDI PROJECT AT MOSCHIMPHARMPREPARATY .....	35
5.4. THE MDI PROJECT AT ALTAYVIATMINY .....	36
5.5. PROCESS IMPLICATIONS OF THE SELECTED TECHNOLOGIES .....	37
6. EXPECTED OUTCOMES .....	37
6.1. TECHNICAL ASSISTANCE IN CONVERTING CFC-BASED MDI PRODUCTION TO HFA .....	37
6.2. PHASE OUT OF CFC CONSUMPTION IN THE MDI SECTOR .....	41
6.2.1. INCREMENTAL CAPITAL COSTS.....	41
6.2.2. MOSCHIMPHARMPREPARATY .....	50
6.2.3. ALTAYVITAMINY .....	51
6.3. TECHNOLOGY TRANSFER.....	52
6.3.1. MOSCHINPHARMPREPARATY .....	53
6.3.2. ALTAYVITAMINY .....	55
7. REGISTRATION .....	57
7.1. PREPARATION OF TECHNICAL DOSSIER REQUIRED FOR NON-CFC MDI REGISTRATION.....	57
7.2. GOOD MANUFACTURING PRACTICES (GMP).....	59
7.3. BENEFICIARY COUNTERPART FUNDING.....	60
8. ENVIRONMENTAL IMPACT .....	62
8.1. OZONE DEPLETION.....	62
8.2. GLOBAL WARMING.....	63
8.2.1. REPLACEMENT OF CURRENT CFC PRODUCTS.....	63
8.2.2. IN COMPARISON TO IMPORTED HFA MDIS.....	65
9. Financing Plan.....	66
10. Project Impact.....	66

11. Project Implementation .....	66
11.1. Management.....	66
11.2. Tentative Project Schedule.....	67
11.3. Milestones for Monitoring and Project Implementaion.....	68
12. Risk, Sustainability and Replicability .....	68
12.1 RISK .....	68
12.2 SUSTAINABILITY.....	70
12.3. REPLICABILITY.....	70
Section B.....	71
Reasons for UNIDO Assistance.....	71
Section C .....	71
The Project Objectives.....	71
The UNIDO Approach.....	71
Rationale for GEF Intervention .....	72
Section D Inputs.....	73
D1. Counterparts Inputs .....	73
D2. UNIDO INputs .....	73
Section E Budget .....	73
E1. Project Budget.....	73
UNIDO B/L Format.....	74
Section F .....	74
Monitoring, evaluation, reporting and lessons learned .....	75
Section G .....	77
Legal Context.....	77

## Executive summary

The Russian Federation, in its capacity as the legal successor to the former USSR in respect of the international obligations flowing from the Vienna Convention on Protection of the Ozone Layer (1985), the Montreal Protocol on Substances that Deplete the Ozone Layer (1987) and the London Amendment and adjustments to the Montreal Protocol (1990), was under an obligation to phase out the production of ozone-depleting substances (ODS) by 1 January 1996 and also to fulfill a number of other obligations associated with the phase-out of ODS in the consumption sector. In compliance with the decisions adopted by the Government of the Russian Federation in 1999 and 2000, the production of substances listed in Annexes A and B to the Montreal Protocol (including CFC-11 and CFC-12) was fully phased out on 20 December 2000. However, the Russian Federation has required CFCs for the production of metered-dose inhalers (MDIs) to meet patient demand.

The Russian Federation has demonstrated a significant commitment to the elimination of the use of Ozone Depleting Substances (ODS) in a number of industrial sectors. With the assistance of significant grants from the Global Environmental Facility (GEF) CFC manufacture has ceased in Russia and the use of CFC has been dramatically reduced. However the issues associated with the use of CFCs in MDIs were effectively deferred. It became evident that without some intervention in the form of financial assistance, it is most probable that the MDI projects would either continue to slip, or that the enterprises may be placed in a position where they have to consider ceasing manufacture of MDIs, as they are no longer commercially viable or the approved materials (CFCs) are no longer available.

A number of reasons for the slippage in the programme for the development of HFAs have been cited, including lack of funding from the procurement of equipment required to develop the new MDI formulations and lack of funding for the procurement of new industrial scale equipment to produce stability batches etc. Technical assistance need to be provided to convert the production of CFC metered-dose inhalers (MDIs) to ozone-friendly HFC -134a at the two local MDI producers in the RF. Due to the continuous increase in cost of CFC propellant as a result of the Montreal Protocol, which accounts for 30 – 40% of the total cost of the MDI, any further delay with this project may have a negative impact on the costs of provision of medicine and hence Russian patients.

This Project is the GEF funding operation for complete CFC phase-out in Russia. It targets priority ODS consumption phase-out activities in the medical aerosol sector, along with the provision of a technical assistance at the government and enterprise levels. It is structured as a individual project for a total GEF grant, which amounts to US\$ 2.55 million. The co-finance from the two sub-projects, i.e. Federal State Enterprise «MosChimPharmPreparaty», «Altayvitaminy Ltd.» is US\$ 5.6 million of local contribution.

The two MDI companies in the RF will also require technology transfer from one, or more, established multinational enterprises that have experience in the development and manufacture of MDIs using CFC-free technologies, and who have the right to transfer such technology to the Russian Federation (RF) 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 within the domestic market.

Upon approval of the Project UNIDO will proceed with equipment procurement for the two companies according to the rules and regulations of UNIDO. The two Russian MDI producers, project counterparts, in their turn will proceed with assigning a pharmaceutical company for technology transfer, i.e. development and formulation of a new MDI Salbutamol aerosol product with HFA propellant.

This project represents the first comprehensive international effort to consider the entire scope of work required to achieve complete CFC phase-out in the Russian Federation and minimise the climate impact taking into consideration both, the Montreal and Kyoto Protocols, as well as the National environmental policy and targets. The project is aimed at achieving direct GHG emissions reduction through lower GWP of the new HFA propellant in comparison with GWP of CFCs used in the MDI production at the two Russian companies. This GHG emission reduction will be of approximately 1.7 MMT CO<sub>2</sub> equivalents in one year. Applying 10 allowable for calculation years under the CDM mechanism of the Kyoto Protocol, the GHG emission reduction will achieve the amount of 17 MMT CO<sub>2</sub> equivalent.

The objectives of this project are:

- a) to phase-out the consumption of 212 ODP tonnes of CFC-11 and CFC- 12 (2010), used in the manufacture of Aerosol Metered-Dose Inhalers (MDIs) in the Russian Federation (RF), through appropriate technology transfer;
- (b) to manage the transition from CFC- based MDIs to CFC-free MDIs in the country. The primary objective is the direct phase out of 212 ODP tonnes of CFCs (2010) in the medical aerosol sector in the Russian Federation, and as a secondary objective is
- c) to reduce future GHG emissions by approximately 1.7 MMT CO<sub>2</sub> t/equivalent by introducing, through technology transfer a lower GHG propellant, HFC-134a.

This proposal addresses the requirements for conversion of manufacturing facilities, currently using CFCs to manufacture MDIs, to one only using HFC-134a at the two Russian enterprises.

During the preparation of the PIF and the Full Size Project proposal, the UNIDO project team has held discussions with a range of potential project counterparts at the enterprise and institutional level in the Russian Federation. Preliminary discussions have also been held with potential international suppliers of technology and know-how transfer. All the data received as a result of discussions have been reflected in this project document.

## ABBREVIATIONS

CDM	Clean Development Mechanism
CFC	Chlorofluorocarbon
COPD	Chronic Obstructive Pulmonary Disease
CEIT	Countries with Economies in Transition
ExCom	Executive Committee of the Multilateral Fund
EUN	Essential Use Nominations
GHG	Greenhouse gas
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GMP	good manufacturing practices
GWP	global warming potential
HC	hydrocarbon
HCFC	hydrochlorofluorocarbon
HFA	hydrofluoroalkaline
HFC	hydrofluorocarbon
HPMP	HCFC phase-out management plan
ICC	incremental capital costs
IOC	incremental operating costs
IOS	incremental operating savings
IPAC	International Pharmaceutical Aerosol Confederation
API	Active Pharmaceutical Ingredients
LCCP	life-cycle climate performance
MDI	Metered-dose inhaler
MLF	Multilateral Fund
MOH	Ministry of Health and Social Development of the RF
MOP	Meeting of the Parties of the MP
NOU	National ozone unit
MP	Montreal Protocol
ODP	ozone-depleting potential
ODS	ozone-depleting substance
RFPC	Russian Federal Pulmonology Centre
RF	Russian Federation
FSNS	Rosdravnadsor
SMEs	small and medium-sized enterprises
TEWI	total equivalent warming impact
TLV-TWA	threshold value – time-weighted average
UNFCCC	United Nations Framework Convention on Climate Change
VOC	volatile organic compound
WHO	World Health Organization

## **SECTION A    CONTEXT**

### **1. Background**

The Russian Federation as a legal successor of the former Soviet Union is a party to the Vienna Convention for Protection of the Ozone Layer (hereinafter referred to as the Vienna Convention) and to the Montreal Protocol on Substances that Deplete the Ozone Layer (hereinafter referred to as the Montreal Protocol). In January 1992 Russia ratified the London Amendment to the Montreal Protocol and in December 2005 it ratified the Copenhagen, Montreal and Beijing Amendments to the Montreal Protocol.

Under the Montreal Protocol and London Amendment the Russian Federation was obliged to phase-out the production of the controlled substances listed in the Annexes A and B to the Montreal Protocol by 1 January 1996. In 1995 the Russian Federation requested a delay in the fulfilment of its obligations under the Protocol. Significant phase-out of CFCs and Halons started however, in December 2000.

As far as the phase out of Ozone Depleting Substances (ODS) in the Russian Federation is concerned a project entitled "Russia Ozone Depleting Substance Consumption Phase-out Project" was established in 1996 with a total budget estimated at US\$ 104 million, comprising US\$ 60 million grant from Global Environmental Facility (GEF) to be supplemented by US\$ 44.3 million from enterprise contribution.

The origin of the Project was the international community's recognition of the difficulty that the Countries with Economies in Transition (CEITs) in Eastern Europe and the Former Soviet Union (FSU) would have in meeting their obligations under the 1990 London Amendment to the Montreal Protocol (MP), namely the elimination of Annex A and B Ozone Depleting Substances (ODS) consumption and production by December 31, 2000. As non-article 5 countries under the MP they were not eligible for international assistance available under the Montreal Protocol Multilateral Fund (MPF). As a consequence, the Global Environmental Facility (GEF) formally opened an Ozone Focal Area in 1995 for CEITs, who had Country Programs endorsed by the Parties to the MP and had ratified the London Amendment. The World Bank (WB) was a key participant in the development of the Ozone Focal Area starting in 1992 which coincided with an initial project concept being developed for assistance to the Russian Federation. However, the preparation of an actual project could not be completed until GEF Operational Strategy including the Ozone Focal Area was adopted and bilateral programs supporting the Country Program development were completed.

At a general level, the Project's original objectives adequately defined what the Project was intended to accomplish within the context of international and national priorities at the time. However, unlike GEF initiatives in other CEITs, this Project was not intended to be a comprehensive country phase out in that it was initially limited to phase out investment in only two high consumption sectors (aerosol and refrigeration equipment). As a result of the implementation of the ODS phase out programme CFC production ceased in 2000 in the Russian Federation and further import of Essential-Use CFCs only for MDI production is being now regulated on the basis of the annual quota from the Ministry of Natural Resources and

Ecology (MNRE) or supplied from the stockpile. Russia has been importing ODSs from China and India since 2003. In the last years the import was only from China.

Three producers of medical aerosols continued to operate, (Federal State Enterprise «MosChimPharmPreparaty», «Altayvitaminy Ltd.» and «ICN- October Ltd.») and they were reported to consume 450 MT of CFC-11/12 mixture in 2000, of which between 300 and 350 MT was for Metered Dose Inhaler (MDI) products (the rest was used for production of other medical aerosols, not MDIs). This is estimated to have increased to 516 MT in 2001, but all three enterprises elected to continue ODS use for MDI on the basis that they would be granted an essential use exemption under an application currently being made by the Russian Federation.

It is most probable that, these enterprises will likely have to close MDI production when access to and/or affordability of banked material no longer exists. After 2005, it was assumed that these producers would have converted MDI production to non-ODS technology or ceased production.” «ICN- October Ltd.» ceased the production of MDIs, however as there is still a critical market need, the two other enterprises, i.e. MosChimPharmPreparaty and Altayvitaminy Ltd continue the use of CFCs for production of MDIs with total consumption of 264 MT of CFCs in 2008, 241 MT in 2009 and 212 MT in 2010. Both enterprises have applied for Essential Use Nomination (EUN) for CFCs in order to ensure the supply of pharmaceutical-grade CFCs for the Aerosol Metered-Dose Inhaler (MDI) Applications after 31<sup>st</sup> December 2010. The approved quota for the Russian Federation for 2011 was 248 MT of CFCs.

It became evident that the CFC Phase out Programme in the Russian Federation has not included the technical assistance in phasing out CFCs in the production of Metered-dose Inhalers (MDIs) in the country. MDIs are being presently produced by the two Russian enterprises, i.e. Altayvitaminy Ltd., Altay region and “Federal State Enterprise N.A Semashko” also known as MosChimPharmPreparaty, Moscow. These two MDI producers are still consuming annually about 212 MT (2010) of CFC-11 (solvent) and CFC-12 (propellant) for the production of the asthma rescue medicine - Salbutamol.

Another attempt was made in 2007 by Russia Programme for Organization of Investments for Environment Protection, when the two investment projects, one for Altayvitaminy Ltd., Bijsk, Altay region and the second one for Federal State Enterprise N.A Semashko”, Moscow were prepared by the WB with the participation of a local bank within the frame of “Russia Programme for Organization of Investments for Environment Protection.” These two investment projects dealt with the provision of the monetary assistance to both companies in making conversion from CFC-based MDI production to non-CFC MDIs. However, both companies were unable to accept the associated credit terms of the local bank, as a result the much needed unspent GEF funds have been returned back by the WB to the GEF.

Decision XXI/4(8) of the MOP requested the Technology and Economic Assessment Panel and its Medical Technical Options Committee to “organize and undertake a mission of experts to examine the technical, economic and administrative issues affecting the transition from CFC metered dose inhalers to CFC-free alternatives in the Russian Federation, and to report the results of this mission to the meeting of the thirtieth Open-ended Working Group. The Technology and Economic Assessment Panel (TEAP) is requested to examine:

- (a) The status of transition in the enterprises manufacturing CFC MDIs;
- (b) Technical, financial, logistical, administrative or other barriers to transition;
- (c) Possible options to overcome any barriers and facilitate the transition.”

The recommendation of the TEAP was that financial support is the main priority and GEF funding should be investigated urgently as the first option since finance governs the success of the transition in the Russian Federation. Based on the TEAP/MTOC mission, the Parties could expect that 18-24 months would be the overall time for conversion of the two enterprises once funding is approved by the implementing agency.

In 2008, the Ministry of Health and Social Development through FSNS (Rossvdravnadsor) requested UNIDO to render technical assistance in developing an MDI project to phase out the use of CFCs in MDI manufacture in the Russian Federation. On 20 September 2009 the Ministry of Natural Resources and Environment officially requested UNIDO to investigate the possibility of formulating an MDI project. Funding for the project is yet to be committed. The Russian Federation brought the issue of difficulties in its transition from CFC to CFC-free MDIs to the attention of the 21<sup>st</sup> Meeting of the Parties in late 2009, which was the basis for Decision XXI/4(8) and the TEAP/MTOC mission.

From communication and interaction with both MDI producing companies it is clear that to achieve transition from CFCs in a realistic timeframe they both need technical and monetary assistance in converting their CFC-based MDI filling lines to MDI production with a non CFC propellant. Further they will require some form of technical input if they are to develop products and processes that also meet the objectives of the Russian Federation of eliminating ODS and manufacturing pharmaceutical products in line with the requirements of Good Manufacturing Practices (GMP). Both companies have indicated a desire to select UNIDO as an Implementing Agency (IA) which has already implemented four similar projects in the world, for rendering such assistance and both companies have made statements that they do not have sufficient funds to make the conversion on their own. This was clearly reported in the UNEP "Report of The Technology and Economic Assessment Panel May 2010 Volume 2 Progress Report, which stated:

*"The manufacturing conversion from Salbutamol CFC MDIs has been repeatedly delayed in the Russian Federation due mainly to a lack of finance. The TEAP/MTOC mission on "Issues affecting the Transition from CFC metered dose inhalers in the Russian Federation" has reported on these issues in more detail under its response to Decision XXI/4(8) in Chapter 3.*

*GEF funding is currently being investigated and the Russian Federation has stated that, if this funding becomes available, phase-out could be achieved by the end of 2012."*

*"Financial support is critical for successful transition in the Russian Federation. The potential for GEF funding should be investigated urgently. National commercial loans with better terms should be investigated as another option, but this would take much longer. Bilateral funding between the Russian Federation and one or more donor countries also remains a possible option to be explored. Once funding is secured, about 24 months will be needed for overall conversion of the two companies. Since the time to complete the transition commences when the finance is secured, securing finance as soon as possible is by far the most important governing factor if the transition to CFC-free MDI manufacture in the Russian Federation is to be completed by the end of 2012."*

*"It is now 13 years since the Russian Federation was first approved an essential use exemption for CFCs in 1997. The National Plan of Action submitted in 2004 by the Russian Federation stated that the two companies would phase out their use of CFCs for MDIs by 2008, but this was not achieved due to lack of funds. Nonetheless the Parties have continued to approve CFCs past the time that the Russian Federation said it would complete the transition."*

### 1.1. Regulation and Policy for the MDI Sector and CFC Phase out

CFCs are used as an inactive carrier substance (excipient) in the production of MDI. According to the laws, regulations and policies concerning drug management in the Russian Federation, strict procedures must be followed when formulation of the drug including the excipient is changed. The main laws, regulations and policies governing the drug management are as follows:

**Drug Administration Law of the RF.** This law is a national law to be observed strictly by all pharmaceutical products related production enterprises and institutions. The stipulations of the Drug Administration Law of the RF are used as the guiding principle in this project of CFCs Phase out in manufacture of aerosol MDIs. This law aims to strengthen drug administration, guarantee drug quality, safeguard the safety of use of drugs in human body, safeguard human health, and protect legal rights to use the drug. This law must be observed strictly by any unit or individual functioning in R&D, production, operation, use, and supervisory administration of drugs within Russian territory.

The MDI aerosol is one kind of drugs, and thus its supervisory administration (including the substitution of excipient/propellant and the modification of the form of drug) shall comply with various regulations of Rosdravnadzor – the drug regulatory department of the Ministry of Health and Social Development (MOH). Some clauses related to the MDI phase-out plan include, but not limited to:

- a) Control over Manufacturers. The drug regulatory department shall inspect drug manufacturers on their compliance with the current requirements and issue a certificate to the manufacturers passing the inspection of a drug.
- b) Control over Drugs. The law states that the dossier on a new drug research and development, including the manufacturing process, quality specifications, results of pharmacological and toxicological study, and the related data and the samples shall, in accordance with the regulations of the Rosdravnadzor, be truthfully submitted to the said department for approval, before clinical trial is conducted. Measures for verifying the qualifications of clinical study institutions for drugs shall be formulated jointly by the drug regulatory department and the administration department of MOH. When a new drug has gone through clinical trials and passed the evaluation, a New Drug Certificate shall be issued upon approval by Rosdravnadzor.
- c) Control over Production. The law states that “A drug manufacturer may produce the drug only after an approval number (production license) is granted to it.”

### 1.2. Policies Related to CFC Phase out

Notice on Terminating the Use of Chlorofluorocarbons (CFCs) as Excipient for Medical Aerosols: This notice issued by Rosdravnadzor in 2004, specified the following relevant matters in order to accomplish the commitment of the Russian Government and guarantee the smooth phase out of CFCs in line with accelerated CFC Phase-out Plan of the RF:

- a) The RF stopped importing CFC-based MDIs from 1 January 2000. The aerosols produced with CFC based excipient before this date can be circulated and used until the expiration of their validity date. The RF wanted to stop using CFCs as pharmaceutical excipient in the production of metered dose inhalant aerosols in the RF from 1 January 2010, and the CFC based metered inhalant aerosol produced before 1 January 2010 can be circulated and used until the expiration of their validity date.

However, two MDI producers in the RF have not made yet conversion to CFC-free MDI production. The objective of this project is to achieve, if possible the cease of CFCs for MDI production by end of 2013. It is so important that the GEF project would be approved in September-November 2011, that also requires making a request to the MOP of the Montreal Protocol for Essential Use Nominations (EUNs) for CFCs in order to ensure the supply of pharmaceutical grade CFCs for MDI production in the RF.

- b) In October 2005 the technical committee of Roszdravnadzor finalized a decision to give Russian companies using CFC gas in pharmaceutical/ medical products a permission period until 2013 to replace the use of CFC with another substance. Any new propellant used must undergo for toxicity and safety tests, or have suitable data available from the suppliers to demonstrate its safety.
- c) The RF stopped examining and approving registration applications for CFC based aerosols (including that for imported ones) from 1 July 2007 and that of CFC based metered inhalant aerosol (including that of imported ones) from 1 January 2010. The two Russian MDI-Salbutamol producers, however, have to stop the CFC-based production in Dec. 2013.
- d) To eliminate CFCs in line with this project, drug producers shall, according to the relevant requirements of the Regulations on Drug Registration, apply for modification of the pharmaceutical excipient or drug form of pharmaceutical aerosols.

## **2. Asthma and COPD in the Russian Federation**

### **2.1. Incidence of Respiratory Disease**

Asthma is estimated to affect as many as 300 million people worldwide, a number that could increase by a further 100 to 150 million by 2025. When a person with asthma comes into contact with something that is an irritant or a trigger for asthma, the muscles around the walls of the airways tighten so that the airways become narrower and the lining of the airways becomes inflamed and starts to swell.

Asthma is a very common condition in developed countries between three and six per cent, of the total population have asthma. Asthma occurs more frequently in children with approximately one in five children suffering from the condition. In children, it is more common in boys than girls. In adults, men and women are equally affected. In recent years there has been a disturbing increase in the incidence of respiratory disease within the community at large in the UK, especially in children. The reasons for this have been linked to environmental issues but as yet are not conclusive.

The incidence of Asthma, is known to be influenced by a range of socio-economic factors; as a result distribution of asthmatics is greater in populated areas. The incidence of asthma is higher among low-income populations within a society (even though it is more common in developed countries than developing countries), which in the western world are disproportionately minority, and more likely to live near industrial areas. Additionally, asthma has been strongly associated with the presence of cockroaches in living quarters, which is more likely in such neighbourhoods. The prevalence of "severe persistent" asthma is also greater in low-income communities compared with communities with better access to treatment. The rate of asthma increases as communities adopt western lifestyles and become urbanised. With the projected increase in the proportion of the world's population that is urban from 45% to 59% in 2025, there is likely to be a marked increase in the number of asthmatics worldwide over the next two

decades. It is estimated that there may be an additional 100 million persons with asthma by 2025.

As is common with respiratory disease, smoking adversely affects asthmatics in several ways, including an increased severity of symptoms, a more rapid decline of lung function, and decreased response to preventive medications. Asthmatics who smoke typically require additional medications to help control their disease. Furthermore, exposure of both non-smokers and smokers to second-hand smoke is detrimental, resulting in more severe asthma, more emergency room visits, and more asthma-related hospital admissions.

From the Summary of the region identified as Russia & Former Socialist Republics of Eastern Europe, taken from the Global Initiative for Asthma (GINA) Report on the global burden of Asthma (1), the following is taken:

**Number of persons with asthma: 9.8 m**  
**Total population: 264.0 m**  
**Mean prevalence of clinical asthma: 3.7%**

#### **Key Points:**

1. The prevalence of asthma is generally low in countries within this region, with some of the lowest prevalence rates recorded worldwide.
2. The prevalence of asthma is likely to increase markedly during the next decade due to the rapid changes in lifestyle that are currently occurring within the region. Indeed, in some countries within the region, such as the Czech Republic, asthma is already of a similar prevalence as in countries in Western Europe. The prevalence of asthma is generally higher in urban areas compared with rural areas. With the trend of increasing urbanisation it is likely that this social phenomenon will lead to further increases in the prevalence of asthma.
3. The speed and magnitude of the increase in asthma (and associated bronchial hyper responsiveness and atopic sensitisation) in the former East Germany (with the changes in lifestyle that have occurred since reunification) indicate the potential burden of asthma facing Eastern Europe, in terms of the likely increase in the prevalence of asthma, as socio-economic conditions improves.
4. The underestimation of severity of exacerbations, **lack of access to medical care, and inadequate treatment contribute to asthma morbidity and mortality within the region.**
5. The implementation of locally adapted asthma education and management programmes based on the GINA guidelines has been shown to be effective in terms of changing prescribing and management practices, and reducing morbidity in patients with severe asthma in a number of countries within the region.
6. The poor economic conditions in many countries within the region, together with the low expenditure on health by national governments, represent major barriers to the delivery of health care services, including those related to asthma. For example, Russia's national government expenditure on health, which is currently around 4% of the Gross National Product, is too low to provide adequate health care.
7. Many communities within the region are exposed to high levels of air pollution, greater than those observed in Western Europe. Developing strategies to reduce the level of air pollution remains one of the many public health priorities for the region.
8. Political and public health measures to reduce tobacco smoking also represent important priorities. Russia is the fourth-largest cigarette market in the world and one of the fastest growing. While cigarette sales have fallen in many Western countries over the last decade, they have increased in Eastern Europe and the former Soviet Union during this period.

specific numbers exist on the rate of increase in prevalence of Asthma in Russia, however based on estimates of global growth in the incidence of Asthma and other Chronic Respiratory diseases endorsed by GINA, GARD and WHO. The number of patients in Russia requiring treatment could **easily double** in the next 10 years.

*“Statistics compiled by the Ministry of Health and Social Development of the Russian Federation show a yearly increase of 7 per cent in the number of bronchial asthma sufferers. A steady rise can also be observed in the mortality rates of patients in this category aged between 5 and 35, due to the spread of the disease and the greater severity with which it takes its course.”* Taken from the National Plan of Action to phase out the use of ozone-depleting substances in the manufacture of metered-dose inhalers in the Russian Federation over the period 2005–2007.

Also

*“Figures compiled by the Russian Federal Pulmonology Centre (RFPC) indicate that more than 1.5 million people in Russia suffer from bronchial asthma and between 2.5 and 3 million from chronic bronchitis or emphysema. Unofficial estimates put the total number of sufferers in this category at between 7 and 8 million. As a rule, a single Salbutamol inhaler should last a patient about one month.”*

## **2.2. Chronic Obstructive Pulmonary Disease**

Chronic Obstructive Pulmonary Disease (COPD) is a chronic, progressive disorder related to tobacco abuse and characterized by airway obstruction (FEV1 <80% predicted and FEV1 / FVC ratio <70%). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as "a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with abnormal inflammatory response of the lungs to noxious particles or gases."

According to WHO estimates, 80 million people have moderate to severe chronic obstructive pulmonary disease (COPD). More than 3 million people died of COPD in 2005, which corresponds to 5% of all deaths globally. Most of the information available on COPD prevalence, morbidity and mortality comes from high income countries. Even in those countries, accurate epidemiologic data on COPD are difficult and expensive to collect. It is known that almost 90% of COPD deaths occur in low- and middle-income countries.

At one time, COPD was more common in men, but because of increased tobacco use among women in high-income countries and the higher risk of exposure to indoor air pollution (such as biomass fuel used for cooking and heating) in low-income countries, the disease now affects men and women almost equally. In 2002 COPD was the fifth leading cause of death. Total deaths from COPD are projected to increase by more than 30% in the next 10 years unless urgent action is taken to reduce the underlying risk factors, especially tobacco use. Estimates show that COPD becomes in 2030 the fourth leading cause of death worldwide.

The main risk factor in the development of COPD is smoking. Approximately 15% of all chronic smokers will develop the disease. In susceptible people, this causes chronic inflammation of the bronchi and eventual airway obstruction. Other aetiologies include alpha 1-antitrypsin deficiency (augmented by smoking), bossiness, and idiopathic disease. COPD can also be caused by prolonged exposure to certain dusty and polluted environments. For example, many people develop COPD after working in the coal mining industry and being exposed to high levels of irrespirable coal dust.

COPD can also be caused by prolonged exposure to certain dusty environments. For example, many people develop COPD after working in the coal mining industry and being exposed to high levels of respirable coal dust.

COPD is a progressive disease. Obstructive changes in spirometry and decreases in diffusion capacity are typically seen before symptoms occur. Early signs and symptoms are shortness of breath on exertion, recurrent respiratory infections or a morning cough. As the disease continues, the symptoms are seen with increased frequency and severity. In the late stages, the patient often experiences severe cough, constant wheezing, and shortness of breath with minimal exertion or rest. At this late stage, progression to respiratory failure and death is common. Progression is typically caused by the patient's continued exposure to tobacco smoke. Although medications often decrease symptoms, it is not believed that they prevent the progression if the patient continues to smoke.

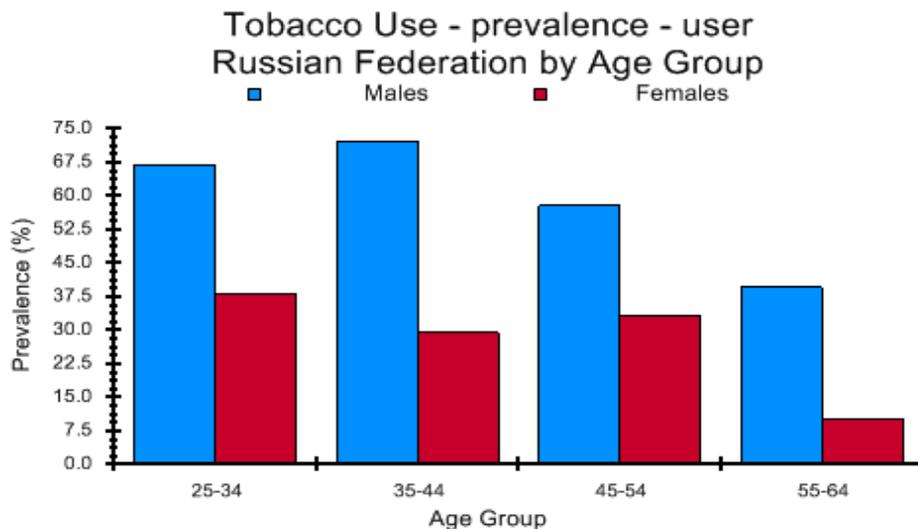
COPD is not curable. Medicines are often used to control symptoms or to reverse acute exacerbations. COPD in all forms typically progresses, if the patient continues to smoke. Therefore, smoking cessation is one of the most important factors in slowing down the progression of COPD.

The use of bronchodilators, nebulizers and corticosteroids has been shown to be effective. Patients with chronic disease and significant lung function impairment ( $FEV_1 < 50\%$  predicted) may also benefit from the regular use of inhaled steroids. The figure below is reproduced from the GOLD Global Strategy for Diagnosis, Management, and Prevention of COPD. Bronchodilator (e.g. Salbutamol) medications are central to the symptomatic management of COPD (Evidence A). They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms and exacerbations.

The principal bronchodilator treatments are  $\beta_2$ -agonists (Salbutamol, Fenoterol etc.), anticholinergics (Ipratropium Bromide, Tiotropium Bromide), and methylxanthines (oral theophylline, intravenous aminophylline or doxofylline) used singly or in combination. Regular treatment with long-acting bronchodilators (Salmeterol Xinafoate, Formoterol Fumarate etc.) is more effective and convenient than treatment with short-acting bronchodilators. The addition of regular treatment with inhaled glucocorticosteroids to bronchodilator treatment is appropriate for symptomatic COPD patients with an  $FEV_1 < 50\%$  predicted (Stage III: Severe COPD and Stage IV: Very Severe COPD) and repeated exacerbations. An inhaled glucocorticosteroid combined with a long-acting  $\beta_2$ -agonist is more effective than the individual components.

Russia has the fourth-highest annual per capita consumption of tobacco in the world, and smoking is responsible for 42 percent of early deaths among Russian men 35 to 59 years old, according to Euromonitor International, a consulting firm. It is estimated that in Russia, smoking kills between 400,000 and 500,000 Russians every year from smoking ailments. These figures are feeding fears about what will happen to the Russian economy in the coming years if, as the United Nations Population Division suggests, the Russian population will experience a drop of 21 million from 2000 to 2025, to 120 million people.

The figure below shows the prevalence of smokers in Moscow, which is indicative of the general position within the Russian Federation.



Source: State Science Research Centre of Preventive Medicine (Ministry of Health).

Moscow Behavioural Risk Factor Survey 2000-2001, 2002 (<http://www.who.int/infobase>

IBRef: 101239)

The approach to the management of COPD is very similar to that of asthma in that the disease state is classified in terms of severity and the treatment regimen is then tailored to this and the individual needs of the patient. Bronchodilator (e.g. Salbutamol) medications are central to the symptomatic management of COPD. They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms and exacerbations. The principal bronchodilator treatments are  $\beta$ 2-agonists (Salbutamol, Fenoterol etc.), anticholinergics (Ipratropium Bromide, Tiotropium Bromide), and methylxanthines (oral theophylline, intravenous aminophylline or doxofylline) used singly or in combination. Regular treatment with long-acting bronchodilators (Salmeterol Xinafoate, Formoterol Fumarate etc.) is more effective and convenient than treatment with short-acting bronchodilators. Therefore a proportion of the patients diagnosed with COPD will also require access to MDIs in order to treat their symptoms and improve their quality of life.

The Russian Government determines priorities for health care where one of the main goals is the treatment of a group of diseases categorised as socially important, including heart, lung and oncological diseases. MoH determines a list of life-saving drugs that provides the basis for government reimbursed medicines, and makes affordability of medicines very important to the Government. The list is updated annually and includes medicines for treating asthma including some, but not all, MDI products. Asthma patients on a disability, or about 5 million people, are eligible for free medicines from regional authorities.

Roszdraznadzor, or the Federal Service of Health Supervision (FSNS), is the government authority responsible for the control of medical products, including their registration and placement on the market. FSNS also regulates the maximum wholesale prices for the medicines on the list of life-saving drugs. Retail mark-ups of life-saving drugs are determined by the regional authorities and limited to 30 percent of the wholesale prices. This does not apply to all asthma drugs because only some are included on the list of life-saving drugs. FSNS is also the project partner responsible for registration of non-CFC MDI Salbutamol.

In August 2008 the Russian Ministry of Industry and Trade announced a new draft strategy for the development of the national pharmaceutical industry, called "Industry Development to 2020",

which focuses on developing the local industry to produce medicines according to international quality standards and increasing patient access to innovative drugs. By 2020, the Ministry wants the market share of locally produced pharmaceuticals to reach 50 percent.

### 3. The Pharmaceutical Aerosol Manufacturing Sector in the Russian Federation

#### 3.1. MDI market in the Russian Federation

There are two established domestic manufacturers of MDIs, currently operating in Russia. In addition to the locally produced MDIs a number of inhalation products are imported from multinational companies.

The two Russian enterprises supply Salbutamol to the Russian market, only one drug produced by these two local companies, which covered in 2009 83% of the total market. Salbutamol supplied by foreign companies amount to 17 %. The both companies have launched in 2009 the experimental batches of Beclamethasone, 99 doses, which could be produced in 2011 onwards. The cost of one can of Salbutamol is US\$ 1.5 and this is the lowest cost worldwide. About 10% of Russian population are covered by this product. Primarily two Russian enterprises supply Salbutamol to the Russian market, the balance being supplied by imported product.

The both companies are still using CFCs for MDI production. The cost of CFCs is expected to go up, especially after 1 January 2010, CFC deadline target and as a result the cost of MDI products would be increasing. The quick conversion of MDI production facilities to the non-CFC MDI production at the both Russian companies would allow these producers to keep prices at affordable level for low-income population and thus facilitating access to vital medication for poor people in the Russian Federation. Thus, the conversion of the current CFC-based production lines is of strategic importance contributing to the protection of both, environment and population's health, in particular the millions of people suffering under respiratory diseases.

The table below shows the main therapies available in MDI format globally. There is a significant trend in all countries towards management of the disease with the use of steroids or combination products, as opposed to treating the symptoms only with a  $\beta$ 2 agonist, such as Salbutamol. The need for the newer generation of therapies is recognised by many groups in Russia, however the only source currently is expensive imports. This results in a conflict for the patient between provision of the most up to date therapy vs the most cost effective therapy. As with the rest of the world the majority of MDI sales in Russia are accounted for by Salbutamol, fast acting bronchodilators.

Newer products

Short acting $\beta$ 2 agonist	Long acting $\beta$ 2 agonist	Cortico-steroid	Anti-cholenergic	Combination products	Others
Fenoterol	Formoterol fumarate	Beclamethasone dipropionate	Ipratropium bromide	Salbutamol/ Beclamethasone	Sodium cromoglycate
Salbutamol	Salmeterol xinofoate	Budesonide	Tiotropium bromide	Fenoterol/ Ipratropium	Nedocromil sodium
Terbutaline		Fluticasone propionate		Salbutamol/ Ipratropium	
Procaterol hydrochloride		Mometasone		Salmeterol/ Fluticasone	
Levalbuterol		Ciclesonide		Formoterol/ Budesonide	
				Formoterol/ Beclamethasone	

### 3.2. Import of MDIs in the Russian Federation

The Russian market was well represented by foreign pharmaceutical companies in 2010. The foreign MDI and DPIs were available on the Russian Market in the wide assortment at the unit price level:

- a) MDIs from 84 Rbl - 2,865 Rbl (US\$ 2.80 – US\$ 95.50)
- b) DPIs from 450 Rbl - 580 Rbl (US\$ 15.00 – USD\$ 19.33).

It should be noticed that the portion of DPIs on the Russian market is very low and amounts only to 1%, which is 20 times lower than their portion on the EU market. In 2010 the State Register of Rossdranadzor, Ministry of Health and Social Development registered 81 brand names of MDIs and DPIs and 28 international non-patented names of medicines for treatment of asthma. According to the Governmental statistics data of 2007-2010 on import of medical preparations 28 different medical preparations for asthma treatment (sprays, aerosols, suspensions for inhalation, etc.) including Salbutamol and Beclamethasone (the last one is not yet produced in the RF) were imported into the country. A number of companies recognised in the field of MDI manufacture, import MDIs into Russia, this includes Boehringer-Ingelheim (Germany), Chiesi Pharmaceutical (Italy) and TEVA (Ireland). The imported products include:

- o Salbutamol
- o Salbutamol (non-CFC)
- o Beclamethasone Dipropionate
- o Beclamethasone Dipropionate (non-CFC)
- o Fenoterol hydrochloride.

Currently, ozone – friendly metered-dose inhalers using the halon 134a and absolute (anhydrous) ethanol, and also the halon 227ea are manufactured by such firms as Chiesi, (Italy), Boehringer Ingelheim, Germany, Chipla, India, Orion, Finland, Teva, Ireland and others. As mentioned previously due to the higher costs of these imported products although they make up a minor share of the market by volume the percentage in terms of value is much more significant.

The table below captures the registered and market prices and market shares for both domestic and imported MDIs.

Brand name	Manufacturer	Country	Packer	Страна	Registration number	Registration date	Form	Registered price	Currency	Registered price in roubles	Wholesale price min-max	Retail price min-max	Sales (cans)		Weighted average registered price in roubles
													2008	2009	
Asthalin	Cipla Ltd	India	~	~	N015251/04	13.08.2008	MDI 0.1 mg/dose, 200 doses, 15 g.	2.29	USD	69.26	64,9	91-111	230,713	no information	113.51
Ventolin	GlaxoSmithKline	Poland	GlaxoSmithKline	Poland	П N014212/01	01.06.2010	MDI 0.1 mg/dose, 200 doses,	107.41	roubles	107.41	106,27-126,96	121-168	1,848,369	no information	
Salamol Eco	Norton Waterford	Ireland	IWAX	Czech Republic	П N013290/01	24.12.2009	MDI 0.1 mg/dose, 200 doses,	98.5	roubles	98.50	81,37-116,50	94-373	693,238	no information	
Salamol Eco Easy Breathe	Norton Waterford	Ireland	~	~	П N014097/01	17.04.2007	MDI 0.1 mg/dose, 200 doses,	255.76	roubles	255.76	248,13-269,58, 526,08	108-362	224,121	no information	
Salbutamol	ZAO Altayvitaminy	Russia	~	~	П N001105/01-2002	05.03.2009	MDI 0.1 mg/dose, 90 doses, 12 ml	43.89	roubles	43.89	34,00-97,69	45-115	4,944,320	4,530,662	52.26
Salbutamol	Moschemfarm preparaty im. Semashko	Russia	~	~	ЛС-001925	29.12.2006	MDI 0.1 mg/dose, 90 doses, 12 ml	57.58	roubles	57.58	62,97-75,59	39-115	7,781,436	6,646,224	
Salbutamol	ZAO Binnopharm	Russia	~	~	ЛСР-006937/10	21.07.2010	MDI 0.1 mg/dose								
													15,722,197		

The Table below shows the consumption of all imported anti-asthmatic preparations in comparison with the MDIs produced in the Russian Federation in 2005-2009 as a total.

MDI import and production in the RF	2005		2006		2007		2008		2009	
	Quantity in %	Sales in %								
Produced in Russia	66%	43%	60%	82%	69%	31%	79%	58%	83%	61%
Imported anti-asthmatic preparations in %	34%	57%	40%	18%	31%	69%	21%	42%	17%	39%

Source: Rosdravnadzor Data on MDI Sector in the RF, 2010

The table below shows the sales of Salbutamol and its analogues on the market in 2010.

Salbutamol MDI and its analogues sales in the RF in 2010							
Russian companies sales							
№	Trade name	Technical specification	Company	Country	The total volume of sales in 2010		
					,000 Rbl	,000 US\$	,000 cans
1.	Salbutamol	MDI, 12 ml, 90 dose, 100 µgr/dose	Moschimpharmpr eparaty	RF	600 067	19 759	8 520
2.	Salbutamol	MDI, 12 ml, 90 dose, 100 µgr/dose	Altavitaminy	RF	274 053	9 024	5 560
3.	Saltoc	Pils 7.23 mgr №30	Pulmomed	RF	9 760	321	55
4.	Salgim	Solution for inhalation, 1 mgr/ml, 10 ml	Pulmomed	RF	3 485	115	16
5.	Salgim	Solution for inhalation, 1 mgr/ml, 2.5 ml	Pulmomed	RF	421	14	5
6.	Salgim	Solution for inhalation, 1 mgr/ml, 5 ml	Pulmomed	RF	604	20	4
7.	Salgim	Powder for inhalation, 250 µgr/dose, 200 dose	Pulmomed	RF	4	0.1	0.03
<b>Total:</b>					<b>888,393</b>	<b>29,252</b>	<b>14,160</b>

<b>In comparison with the total sales in 2009</b>					<b>3%</b>	<b>7%</b>	<b>-</b>
<b>In comparison with 2009 in number of cans</b>					<b>-</b>	<b>-</b>	<b>8%</b>
<b>Foreign companies sales</b>							
1.	Ventolin	MDI, 200 dose, 100 µgr/dose	GlaxoSmithKline	UK	325 904	10 731	2 744
2.	Salamol-Eco	MDI, 200 dose, 100 µgr/dose	Teva Pharmaceutical Industries Ltd	Israel	81 266	2 676	728
3.	SDalamol-Eco Easy Breath	MDI, 200 dose, 100 µgr/dose	Teva Pharmaceutical Industries Ltd	Israel	100 689	3 315	292
4.	Astalin	MDI, 200 dose, 100 µgr/dose	Cipla Ltd	India	18 706	616	219
5.	Ventolin Nebuly	Solution for inhalation, 1 мг/мл, 2.5 мл	GlaxoSmithKline	UK/Russia	28 861	950	120
6.	Ventolin Easy Breath	MDI, 200 dose, 100 µgr/dose	GlaxoSmithKline	Uk/Russia	3 645	120	27
7.	Salamol	MDI, 200 dose, 100 µgr/dose	Teva Pharmaceutical Industries Ltd	Israel	840	28	8
8.	Salbutamol	MDI, 200 dose, 100 µgr/dose	Warsaw Pharmaceutical Works Polfa S.A.	Poland	334	11	5
9.	Salbutamol	MDI, 200 dose, 100 µgr/dose	Pharmchem International Ltd	UK	349	11	4
10.	Salbutamol	Pils 4 mgr, №30	Warsaw Pharmaceutical Works Polfa S.A.	Poland	157	5	3
11.	Salbutamol	Pils 2 mgr, №30	Warsaw Pharmaceutical Works Polfa S.A.	Poland	14	0.5	0.3
<b>Total:</b>					<b>560 767</b>	<b>18 465</b>	<b>4 149</b>
<b>In comparison with sales in 2009</b>					<b>-18%</b>	<b>-14%</b>	<b>-</b>
<b>In comparison with 2009 in number of cans</b>					<b>-</b>	<b>-</b>	<b>-15%</b>

To sum up the data presented in the above tables showed that the cheapest MDIs being produced in the RF are the most popular among the local population. In addition to the locally produced MDIs a number of inhalation products are imported from multinational companies. The data on the foreign imports into the RF indicates that the number of inhalers imported in to the Russian Federation was and would be in the region of 2 – 4 million inhalers per year.

The analyses of the Russian market for the imported anti-asthmatic preparations in comparison with the Russian domestic production proves that for Asthma patients the most important preparation is Salbutamol being produced in Russia and in case of its production cease MDI expenditures for treatment of Asthma in Russia, would considerably increase.

It is important to take a balanced view based on registered price and availability in the RF. Much issue was made over the fact that the enterprises currently produce a 90 dose MDI whereas the imported products are typically 200 dose.

Two key issues were not discussed in this respect. They are:

- a) It is well documented that with Salbutamol, it is unusual to use a MDI to the end of its label-claimed life as it is typically discarded due to either time in use being exceeded (typically 2-3 months) or hygiene associated issues.
- b) Again equally well documented for many patients on low incomes the actual purchase price (and hence outlay) is far more important than the cost per dose.

These facts being considered the MTOC evaluation would have been better based on a MDI to MDI comparison as opposed to a per dose comparison. However both RF companies have indicated that their new HFA MDIs would be 200 dose. The enterprises have also indicated that based on the estimates of cost of goods for the HFA MDIs they believe that they will be able to achieve a registered price for a 200 dose HFA MDI of around 70 Roubles. If this is the case this represents approximately \$1.5 per MDI saving, when compared to the weighted average of imported MDIs, on a true like for like comparison.

The cost/ price for the domestic produced MDI was \$2.00 per unit and the imported cost of an equivalent MDI in the region was \$5.45.

<b>MDI Production</b>	<b>2004</b>	<b>2005</b>	<b>2006</b>	<b>2007</b>	<b>2008</b>	<b>2009</b>	<b>2010</b>
Domestic, US\$	28.35	24.05	35.56	26.35	26.77	25.70	24.00
Imported, US\$	9.28	21.77	21.91	15.30	20.27	21.90	22.16
<b>Total, US\$</b>	<b>37.63</b>	<b>33.82</b>	<b>45.82</b>	<b>41.65</b>	<b>47.04</b>	<b>47.60</b>	<b>46.16</b>

If the ratios of Domestic vs Imported manufacture are used and a model cost for the Manufacture of Domestic (\$2.00) and Imported (\$6.00) are used this translates in to a market for Salbutamol valued of around US\$ 40 million.

As the global phase out of CFC in pharmaceutical MDIs is increasingly implemented the countries associated with scale manufacture of pharmaceutical grade CFCs, will disappear and there is an expectation of very significant increases in the costs of CFC propellants in the future. As in a typical Salbutamol the propellant may account for 30 – 40% of the total cost of the MDI, then any increase in the cost of propellant will impact in the cost of the MDI. Therefore, any further delay with this project may have a negative impact on the costs of provision of medicine and hence Russian patients. It is clearly identified that on a unit for unit basis the cost of an imported MDI product is far greater than that of a domestically produced item. Using a very conservative cost difference estimate of \$2.00 per MDI and if all the domestically produced MDIs in the Russian Federation were replaced with imported equivalents, then as a minimum the impact on the cost of provision of MDIs at the current level would be US\$ 30 million bearing in mind that the total number of MDIs manufactured in the Russian Federation may exceed 15 million. This would either result in additional pressure on public and private funding of medicine or would result in a decrease in the number of patients with access to essential medication.

#### **4. Production of MDIs in the Russian Federation**

The objective of the two enterprises, Altayvitaminy and Moschimpharmpreparaty, is to manufacture MDIs for the local market, particularly for the regional markets, with Altayvitaminy supplying Siberia, Far East, Altay and Ural regions of the Russian Federation and

Moschimpharmpreparaty supplying the Europe part of the Russian Federation. They have stated that they “work as colleagues and not as competitors on the national market, both trying to provide affordable products to patients”. They have informal agreements on market split across Russia and on the price of products to make them competitive with imported products. These companies have good commercial connections even to the remote regions of the Russian Federation. They each produce roughly 50 percent of the Russian-made Salbutamol CFC MDIs.

Based on the knowledge gained from the companies so far, it is anticipated that a programme, which can see the transition fully from CFC to HFA MDIs, could be implemented within the ultimate timeframe of availability of CFCs. If Russia did submit an essential use nomination for CFC propellant for MDIs in 2011 for 2012 this will mean that no new CFC would be available in Russia for the manufacture of MDIs. If there is no current stock-pile of pharmaceutical grade CFCs then this potentially represents the premature cessation of manufacture of CFC MDIs in Russia. If at that time manufacture of a HFA replacement is not viable then this either means a chronic shortage of MDIs (Salbutamol) in the Russian market (placing patients at risk), a massive cost burden associated with increased imports of MDIs, or a combination of the two.

The primary objective of the project will be the direct phase out of 212 ODP tones of CFCs (2010) in the medical aerosol sector consisting of the two MDI producers in the Russian Federation. The secondary objective will be to reduce future GHG emissions by approx. 1.965 MMT CO<sub>2</sub> equivalent, by introducing, through technology transfer a lower GHG propellant, HFC-134a. The two MDI companies in the RF will require technology transfer from one, or more, established multinational enterprises that have experience in the development and manufacture of MDIs using CFC-free technologies, and who has the right to transfer such technology to the Russian Federation (RF) 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 within the domestic market. This proposal addresses the requirements for conversion of a manufacturing facility currently using CFCs to manufacture MDIs to one only using HFC -134a. With regard to technology transfer both companies.

#### **4.1. MDI Production at Moschimpharmpreparaty**

Federal State Enterprise N. Semashko is one of the leading Russian pharmaceutical companies and was incorporated in 1982. It is currently producing more than 130 pharmaceutical products covering about 130 different pharma products, i.e. about 4.5 billion pills, more than 3.0 million capsules, about 2.0 million bottles of infusion solutions and 0.6 million of bottles of oil manufactured annually. The enterprise employs about 1,500 people.

In addition to the MDIs Federal State Enterprise Moschimpharmpreparaty manufactured in the past another aerosol product, Kameton. This product was manufactured on the same equipment used for the manufacture of the MDIs, through the use of change parts of the machine. CFC-12 was used as propellant for this aerosol.

Currently the manufacturing capability at the Federal State Enterprise Moschimpharmpreparaty, Moscow facility comprises two separate manufacturing lines. The main manufacturing line is based on the two Pamasol Macromat machines with an estimated maximum output of 50 canisters per minute, which based on a single shift, 5 day operation with typical efficiencies has a capacity in the region of 10.0 million units per annum. The year of manufacture of the equipment is circa 1995.

The Tables below shows the production of Salbutamol MDI by Moschimpharmpreparaty in 2000-2010 and corresponding use of CFCs in production.

#### Production of Salbutamol at Moschimpharmpreparaty

Year	Salbutamol, cans
2000	3 742 203
2001	4 310 904
2002	4 576 650
2003	4 959 396
2004	6 624 696
2005	5 724 885
2006	7 817 082
2007	6 936 000
2008	6 756 000
2009	6,646,224
2010	5 986 530

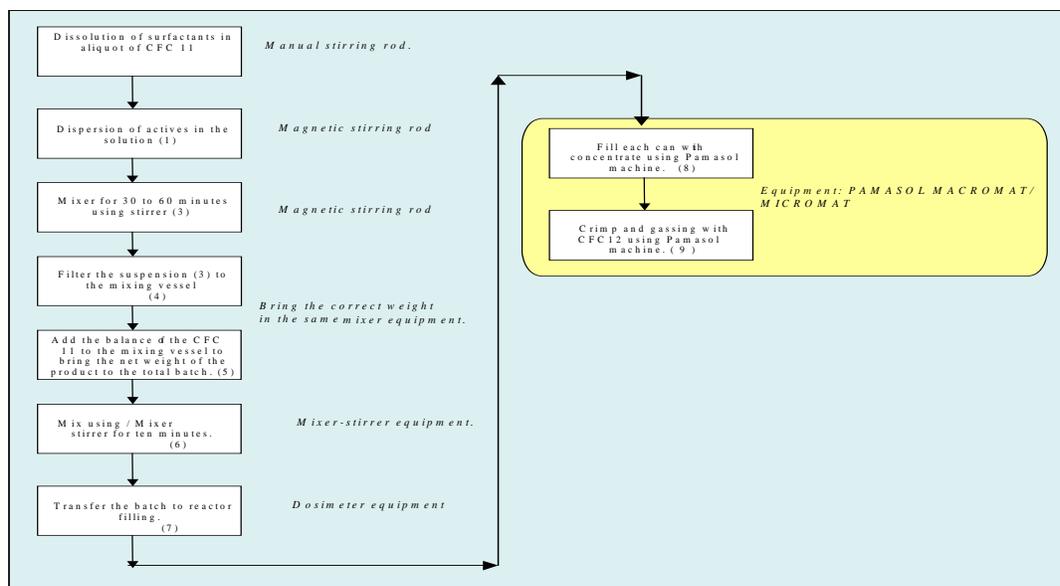
#### Consumption of CFCs at the Federal State Enterprise Moschimpharmpreparaty

Preparation	ODS	2005	2006	2007	2008	2009	2010
Salbutamol MDI, cans		5,724,885	7,817,082	6,936,000	6,756,000	6,646,224	5,986,530
Kameton, in MT	CFC-12	124,4	81,4	93,1	0	0	0
Salbutamol in MT	CFC-11	43,0	58,9	25.56	24,4	27,54	21.2
Salbutamol in MT	CFC-12	77.6	105.5	102.24	97.6	110.16	84.8
Total, in MT		245.0	245.8	220.9	140.8	137.7	106.0

\*Source: All above Tables are from TEAP's response to Decision XXI/4(8): Technical, Economic and Administrative issues affecting the Transition from CFC Metered Dose Inhalers to CFC-free Alternatives in the Russian Federation, TEAP, February 2010.

The conversion of available production facilities to the manufacture of about 10,000 million of cans would require a new filling line with the total investment about US\$ 2.0 million bearing in mind that all other old equipment on the line, like a weigher, automatic packing machine, etc. will be further used or to be procured by the company using its own funds.

The new product is to be developed. It is: Salbutamol 200 dose, 100 µg/ dose label claim.



**Figures 1. Outline of the typical MDI manufacturing process used at Moschimpharmpreparaty**

This process is dependant on a higher boiling point propellant (e.g. CFC 11), which is both a good solvent (to dissolve the surfactant, e.g. oleic acid) and which can be handled as a non pressurised liquid at room temperatures. No such propellant is available as a non CFC and therefore alternate manufacturing approaches will be necessitated. All of the above to be suitable for the manufacture using a pressure filling process.



**Figure 2. Pamasol filling machines at Moschimpharmpreparaty**



**Figure 3. MDI Salbutamol 99 dose, 100 µg/dose produced at Moschimpharmpreparaty**

Formulation development and technology transfer manufacturing will be undertaken at the Moschimpharmpreparaty facilities in Moscow on approved automatic manufacturing equipment, designed and approved for manufacture of HFA pMDI's.

To implement the selected replacement technologies at Moschimpharmpreparaty as well as at Altayvitaminy will require technology transfer from one, or more, established multinational enterprises that have experience in the development and manufacture of MDIs using CFC free technologies, and who have the right to transfer such technology without infringement of any intellectual property related to either the drug molecule, the method of formulation, the design of the metering valve or actuator, or the filling process.

#### **4.2. MDI Production at Altayvitaminy**

The pharmaceutical company Altayvitaminy was established in 1949. The most important event in the company's activities was the first pilot batch of sea-buckthorn oil. The elaboration of more progressive dosage forms began together with the development of sea-burn technology. The aerosol medicinal preparations were manufactured in cooperation with various scientific research institutions in the Russian Federation. The company became one of the leading pharmaceutical companies in Russia especially in the field of manufacturing medicinal and vitamins preparations. The company produces over 80 products of medicinal preparations of various pharma-therapeutically groups used in cardiovascular, gastric-intestinal, gynaecological, proctologic, stomatological and other diseases.

Altayvitaminy is the largest local producer of pharmaceuticals in Russia, capturing 40% share of the local pharmaceutical market. The company began manufacturing MDIs in 1984. Altayvitaminy currently manufacture around 5.5 million pMDI's per annum marketed domestically and exported, their current CFC product is the short acting  $\beta_2$  Salbutamol. The original format of the product offered by Altayvitamins was a 99 dose product.

The MDI production in cans at Altayvitaminy in comparison with Moschimpharmpreparaty is given in Table below. The two companies have a similar rate in production of MDI Salbutamol.

Producer	2006	2007	2008	2009	2010
	Number of cans				
Moschimpharmpreparaty	7,817,082	6,936,000	6,643,000	7,337,000	6,500,000
Altayvitaminy	9,964,000	6,240,000	6,743,000	5,512,000	5,500,000
Total	17,781,082	13,176,000	13,386,000	12,849,000	12,000,000

Annual production rate of the two filling machines (one is made by Coster, Italy and the second one is designed by Altayvitaminy) is 5.5 in million pieces with CFCs. The quantities of CFCs consumed for the MDI production at Altayvitaminy is given in Table below.

Salbutamol	2003	2004	2005	2006	2007	2008	2009	2010
Production in thous. units	6,898	7,750	7,339	9,994	6,240	6,743	5,512	5,650
CFC-11, MT	9.84	44.0	38.2	48.56	44.0	49.52	41.36	44.24
CFC-12, MT	59.76	66.0	57.3	72.84	66.0	74.28	62.04	61.76
Total, MT	99.6	110	95.5	121.4	110	123.8	103.4	106.0

Source: TEAP's response to Decision XXI/4(8): Technical, Economic and Administrative issues affecting the Transition from CFC Metered Dose Inhalers to CFC-free Alternatives in the Russian Federation, TEAP, February 2010



**Figure 4. Coster filling machine at Altayvitaminy**



**Figure 5. Altayvitaminy's design of locally made filling machine**

The conversion project will include the conversion of one product: Salbutamol 99 dose, 100 µg/ dose label claim to the new product. It is: Salbutamol 200 dose, 100 µg/ dose label claim.

Moschimpharmpreparaty and Altayvitaminy obtain CFC-11 and CFC-12 from the Futon Holding Company in Volgograd, which imports these propellants under an annual quota accorded by the Parties to the Montreal Protocol. These CFCs are used by companies exclusively for the manufacture of Salbutamol sprays.



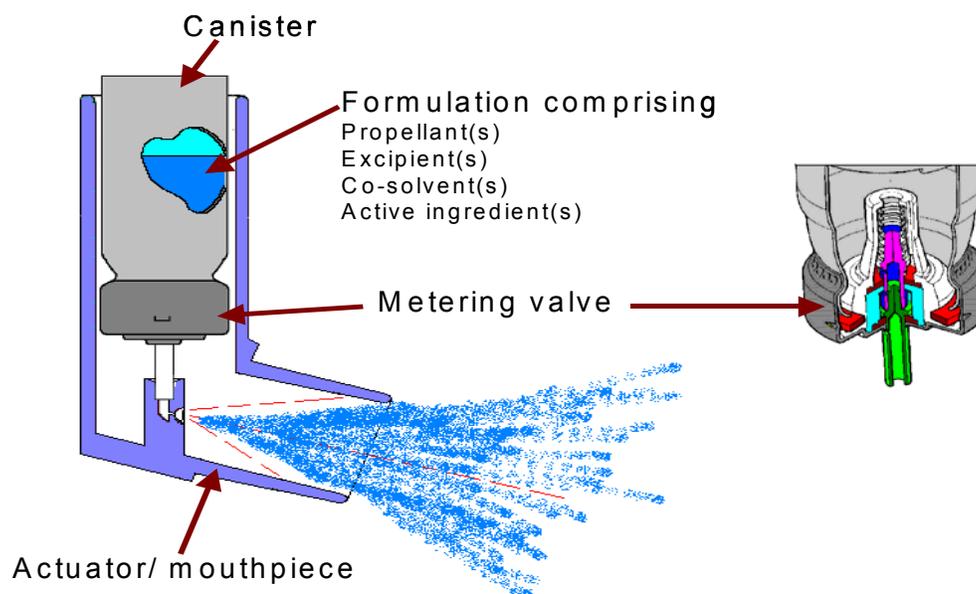
**Figure 6. Salbutamol MDI 99 dose, 100 µg/ dose produced at Altayvitaminy**

The two MDI companies in the RF will require technology transfer from one, or more, established multinational enterprises that have experience in the development and manufacture of MDIs using CFC-free technologies. This proposal should address the requirements for conversion of a manufacturing facility currently using CFCs to manufacture MDIs to one only using HFC -134a. Both companies are in cooperation with the State Scientific Centre for Medicines Development, Kharkov, the Ukraine, the centre which is upon agreement with the two Russian enterprises has

been involved in technology transfer to the Russian Federation. It is also expected that an international consultant will be assigned using the GEF monetary component to assist the both companies in conducting stability tests of the new Salbutamol MDI products within the frame of the project.

### 4.3. Metered Dose Inhalers (MDIs)

The metered dose inhaler (MDI) is a complex system designed to provide a fine aerosol (where aerosol means a fine dispersion of either solids or liquids in a gas) of medicament, generally with an aerodynamic size less than 5 microns, for inhalation directly to the airways for the treatment of respiratory diseases such as asthma or COPD.



**Figure 7. Two sections through a typical MDI showing the basic construction of the system**

The main components of an MDI are:

- The active ingredient (the drug): may be either dissolved in the propellant or in a co-solvent or suspended in the propellant
- The propellant (a liquefied gas): usually CFCs (CFC-12 and CFC-11, and sometimes CFC-114), and more recently HFC-134a and HFC-227ea (in the pharmaceutical sub sector, HFC is referred to as HFA)
- The metering valve: is the key to measuring and presenting a consistent and accurate dose to the patient and is made up of a number of precision-made plastic and/ or metal components
- The canister typically made of aluminium or stainless steel and sometimes internally coated
- The actuator/mouthpiece: holds the canister and through which the patient inhales the dose.

MDIs possess numerous characteristics that, taken together, set them apart from other inhalation delivery systems, such as dry power inhalers and nebulizers.

The table above shows a comparison between these three types of inhalers.

### Comparison of advantages/ disadvantages of various types of Inhaler

Type of inhaler	Advantages	Disadvantages
Metered dose inhalers (MDI)	<ul style="list-style-type: none"> <li>- Simple actuation system</li> <li>- Reliable accurate dose regardless of the patient's breathing capacity</li> <li>- Compact and portable</li> <li>- Easy to use</li> <li>- Economical</li> <li>- Good resistance to moisture</li> </ul>	<ul style="list-style-type: none"> <li>- Mostly use CFCs as propellants</li> <li>- The method of pressing and breathing requires coordination between actuation and breathing (breath-actuated systems do not have this drawback)</li> <li>- Dosage accuracy may be dependant on the formulation</li> <li>- Complex manufacturing process</li> </ul>
Dry Power Inhalers (DPI)	<ul style="list-style-type: none"> <li>- No propellant used</li> </ul>	<ul style="list-style-type: none"> <li>- Drug release depends on the patients breathing capacity</li> <li>- The inhaled fraction is reduced if the patient breath is directed into the system</li> <li>- Relatively expensive</li> </ul>
Nebulizers	<ul style="list-style-type: none"> <li>- No special breathing coordination required</li> <li>- Works with patients using mechanical ventilation</li> <li>- Useful to administer new or less used drugs</li> </ul>	<ul style="list-style-type: none"> <li>- Not portable</li> <li>- Depends on an electric supply</li> <li>- Expensive</li> <li>- Operation takes a long time</li> <li>- Requires the use of preservatives to reduce risk of bacteria contamination</li> </ul>

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 inhaling therapy has been so widely used for the treatment of reversible diseases of human airways, and it has been used in approximately 80% of the patients with asthma.

Viable alternatives to CFC-containing MDIs include Dry powder inhalers (DPIs).

The first dry powder inhaler was introduced in 1968. Until the late 1980s, it consisted in a single pre-measured inhaler but the technological innovation introduced multi-dose systems. Dry powder inhalers have been formulated successfully for most anti-asthma treatments.

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 sufficient small aerodynamic diameter to make it to deposit on the airways. However, young children, some patients with severe asthma and elderly COPD patients, may not always be able to achieve adequate breathing flow to ensure optimal medication delivery from DPIs.

Another alternate to CFC MDIs are HFA (also designated HFC)-containing MDIs HFA-134a and HFA-227ea, which are novel pharmaceutical propellant/excipients developed for widespread and long-term use as replacements for CFCs in MDIs. Nowadays both of them are widely accepted as appropriate propellants for the use in metered dose inhalers.

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

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

For the time being, the potential substitutes of CFCs used for MDI are HFA 134a and HFA 227. Since the HFAS 134a is cheaper than HFA 227, we have only one alternative technology to be selected for the conversion of CFC-based MDIs.

#### 4.3.1. Alternative Excipient – Hydrofluoroalkanes (HFA)

HFA have similar properties as CFCs, however their polarity is slightly lower than that of CFCs. The table below shows the comparison between HFA and CFCs in terms of the physical and chemical characteristics and their environmental properties.

<b>Comparison of Properties between Fluoroalkanes and CFCs</b>					
<b>Property</b>	<b>CFC-11</b>	<b>CFC-12</b>	<b>CFC-114</b>	<b>HFA-134a</b>	<b>HFA-227</b>
Chemical formula	CFCl <sub>3</sub>	CF <sub>2</sub> Cl <sub>2</sub>	CF <sub>2</sub> ClCF <sub>2</sub> Cl	CF <sub>3</sub> CFH <sub>2</sub>	F <sub>3</sub> CHFClF <sub>3</sub>
Vapour pressure (kPa, 21.1°C)	92.4	484	88.9	569(20°C)	3.99
Boiling point (°C)	-24	-30	4	-26.5	-17.3
Density (g / ml)	1.49	1.33	1.47	1.22	1.41
ODP	1	1	1	0	0
GWP	4,000	8,500	9,300	1,300	2,900
Life circle of the atmosphere (year)	75	111	7200	15	33

#### Advantages and Disadvantages of using HFA for MDIs

	<b>Advantages</b>	<b>Disadvantages</b>	<b>Comments</b>
HFA	<ul style="list-style-type: none"> <li>- Low inhalation toxicity</li> <li>- Higher chemical stability</li> <li>- High purity</li> <li>- No harm to ozone layer</li> </ul>	<ul style="list-style-type: none"> <li>- Bad solvent, low polarity</li> <li>- High GWP - greenhouse effect</li> <li>- Higher cost</li> </ul>	<ul style="list-style-type: none"> <li>- HFA may be used by the MDI aerosol producers in the RF as a potential substitute to CFCs</li> </ul>

#### 4.3.2. Use of HFA as a Propellant in MDI

In recent years, international MDIs producers did intensive research on the technology currently used in the world are mainly HFA-134a and HFA-227a. Except for terbutaline, the CFCs used with all the other active ingredients could be replaced by HFA. The leading companies in the world such as Boehringer, Fisons, 3M, Glaxo and Riker have obtained relevant formulation patents, which cover the propellant system including components, co-solvent, hydrocarbon surfactant and fluoro-surfactant.

Many issues have to be resolved for introduction of Hydrofluoroalkane as propellants for MDIs:

- **Co-solvent with Low Boiling Point.** Both tetrafluoroethane (HFA-134a) and heptafluoropropane (HFA-227a) have higher vapour pressure and are in gaseous state under normal atmospheric temperature. No Hydrofluoroalkane is available, which has the same high boiling point as CFC-11 does. Therefore, it brings challenges to design the formulation and production process. One of the solutions is to seek for proper solvents without toxicity or irritation but with certain volatility and good compatibility with Hydrofluoroalkane. Today, the commonly used co-solvents include low-molecular-weight alkane (e.g propane and butane) and low-molecular-weight alcohols (e.g ethanol and isopropanol).
- **Surfactant Selection.** Surfactant is used to disperse medicament particles and lubricate the valve. As Hydrofluoroalkane has lower polarity than CFCs, it cannot dissolve majority of surfactants. One solution is to identify surfactants with good solubility and compatibility with medicaments. Another solution is to add a co-solvent which can dissolve the surfactant.
- **Drug Characteristics.** Some medicaments easily form solvates in the new propellant system, thus increasing the tendency of crystal growth. Some poly-crystalline drugs (such as steroid hormone) are easier to have crystalline transformation and promote crystal growth. Thus, drug characteristics should be taken into account in formulation design, particularly in the design for suspended aerosols.
- **Valve Selection.** As Hydrofluoroalkane is chemically less stable than CFCs, valve components (e.g. airproof rubber and its additive) should be compatible with the new propellant. Similarly, valve components should not cause HFA to decompose. At present, several major valve companies such as Bepak, 3M and Valois conduct research on the valve system for Hydrofluoroalkane.
- **Alternative Actuator.** In case a medicament can not be formulated into suspended aerosol, it is generally made into solution aerosol. In general, solution aerosol has poorer atomisation effect. Decreasing vapour pressure of the canister results in bigger atomized particle size. Though increasing the pressure can reduce the particle size, it also causes majority of particulate medicaments to be accumulated at throat due to the bumping of particles arising from the increase of initial speed. Thus, it is needed to design new actuators, which can both crush the particles and reduce the initial speed.

Phase-out of CFC is the commitment made by the Government of the RF. The obstacles include lengthy and costly drug registration, lack of funds and technologies. Based on “The Drug Administration Law”, change of excipient leads to the re-registration of the drug. The preparation of the technical dossier required for the re-registration, in which a lot of pharmaceutical and

pharmacodynamic studies must be done. Modification of production and market promotion of new drugs also cost money. It's a heavy burden for most of the MDI enterprises.

The patent issue is also a big obstacle to conduct CFC phase-out at the two enterprises in Russia. The cost for the patent transfer is extremely high. It seems, however it is possible to develop new technologies without any infringement of intellectual rights.

Another concern is the high GWP of HFAs, (GWP of HFA 134a is 1300) even though, HFA used for MDI propellant is estimated to account for less than 0.02% of global greenhouse gas emission in 2010. The Pharmaceutical Aerosol Confederation (IPAC) is persuading the parties to the Kyoto Protocol to allow maintaining the continuous use of HFA in MDI sector.

## **5. Project Description**

### **5.1. National CFC MDI Manufacturer Conversion Project**

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 (meg) 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.

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 base is manufactured by using a typical aerosol filling method. The Salbutamol (or other active drug powder) is mixed with a special surfactant (oleic acid) 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 be 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. It is typical that production batches are clearly identified and quarantined up to 1 month, before further testing, and finally release into the market.

## **5.2. Overview & Selection of Replacement Technologies for CFC MDIs**

Ideally the conversion of CFC MDIs to a CFC-free formulation would require zero-ODP replacements for both CFC-11 and CFC-12 that possess similar physical, chemical, and toxicological properties. However, replacements with such properties are not available. The CFC MDI conversion process led by the established multinational pharmaceutical companies has spawned new formulations, new manufacturing processes, as well as non-aerosol dry powder inhalers (DPIs). Many of these products are the subject of intellectual property that cover either the drug molecule, the method of formulation, the device (in the case of DPI) or the filling process.

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

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

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

**A. HFC/Ethanol MDIs (Pressure Filled)** - The medicament drug suspension is manufactured basically by similar technology as used for the CFC MDI version, but the CFC-11 used as the liquid phase of the suspension and to solubilise the surfactant, as well as to modify the final vapour pressure of the MDI formulation, is replaced by ethyl alcohol (ethanol).

However, due to the different solubility properties of ethanol and CFC-11 the surfactant has to be replaced by a new surfactant chemical. This suspension is then, as previously described metered in the aluminium monobloc container. The propellant CFC-12 is replaced by HFC-134a. As the spray/particle size characteristics of the ethanol/HFC-134a MDI formulation are different to those of the CFC MDI version, the valve and actuator have to be redesigned to achieve the required spray and particle size characteristics for efficacious dosage. Some products use HFC-227ea as the propellant instead of HFC-134a.

**B. HFC MDIs (Pressure Filled)** - The MDI is manufactured in such a way that HFC-134a serves as the replacement for both CFC-11 and CFC-12. The medicament drug suspension is manufactured only with HFC-134a, but since HFC-134a has a boiling point of  $-26.2\text{ }^{\circ}\text{C}$  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  $-45$  to  $-55\text{ }^{\circ}\text{C}$ , 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.

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.

Selection of CFC MDI Replacement Technology for the Russian market must take in to consideration the following criteria:

- ♦ The specific needs of the Russian population;
- ♦ The current CFC MDI product manufactured by MosChimPharmPreparaty and Altayvitaminy and as a result the existing experience and skills of the MosChimPharmPreparaty personnel;
- ♦ The relatively high incidence of asthma, allergic respiratory diseases, and chronic obstructive pulmonary disease (COPD) in all ages of the Russian population;

- ◆ The familiarity of existing Russian patients with the MDI design as a device for delivery of the required medication;
- ◆ Resistance of the market/ MOH to accept a significant increase in the cost of treating patients.
- ◆ The maturity and established commercialization 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.

Following review of the various technology approaches and based on the experience from other countries, it was felt critical that the MDI format is maintained. It is a form of delivery that the patients are familiar with and therefore transition at a patient level will be far easier to manage. In addition the MDI offers the most cost effective method for inhalation delivery, therefore minimizing the potential incremental operating costs that will be realized in the transition from CFC MDIs. In addition both enterprises have confirmed they wish to stay with the MDI as the drug delivery system.

As the two local companies MosChimPharmPreparaty and Altayvitaminy are prepared to offer similar products in the market, using a similar manufacturing process, the replacement of the CFC MDIs is best viewed as two linked sub-projects. The differing needs and properties of the active substances mean that a single formulation will not be feasible. The table below shows the differing solubility of a number of actives.

API	WATER	ETHANOL
Salbutamol Sulphate	Freely Soluble	Practically Insoluble
Salbutamol Base	Sparingly soluble	Soluble (96%)
Levalbuterol HCL	180 mg/ml (Freely)	Practically Insoluble
Formoterol fumarate	Slightly soluble	Sparingly soluble
Fluticasone Propionate	practically insoluble	slightly soluble 95% ethanol
Ipratropium Bromide	freely soluble	Slightly soluble
Mometasone furoate monohydrate	practically insoluble	Slightly soluble
Beclamethosone Dipropionate	Very slightly soluble	Freely soluble/ Sparingly soluble (96%)
Salmeterol Xinofoate	sparingly soluble	slightly soluble
Salmeterol Base	Slightly soluble	Sparingly soluble
Fenoterol hydrobromide	Soluble	Soluble
Nedocromil sodium	Soluble	
Triamcinolone Acetonide	practically insoluble	Sparingly soluble
SCG	Soluble	Practically Insoluble
Bambuterol hydrochloride	Freely Soluble	Soluble
Budesonide	practically insoluble	Sparingly soluble
Terbutaline Sulphate	1 g / 1-5 ml (Freely)	1 g / 250 ml (Slightly)

***Solubilities in water and ethanol of various inhaled drugs.***

What this indicates is that a drug such as Salbutamol Base may potentially be formulated as a solution in Ethanol (Selection of MosChimPharmPreparaty), whereas Salbutamol Sulphate (selection of Altayvitaminy) would be highly problematic (requiring to high a level of ethanol to make aerosolization effective).

### 5.3. The MDI Project at MosChimPharmPreparaty

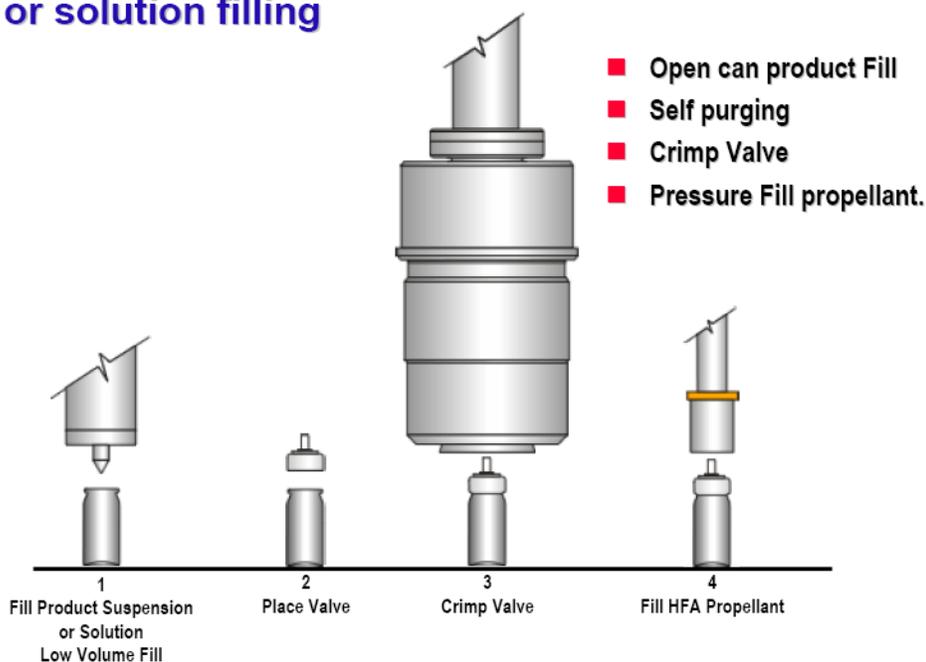
The Product to be developed

- Salbutamol Base 200 dose, 100 µg/ dose label claim

This product is to be suitable for manufacture using a pressure filling process, HFA/ ethanol formulation with surfactant in a standard container.

Following successful formulation development and technology transfer manufacturing will be undertaken MosChimPharmPreparaty facilities in Moscow on approved automatic manufacturing equipment, designed and approved for manufacture of HFA pMDI's. Any developed package and formulation should be capable of being manufactured with a single batch in the range 10,000 to 20,000 canisters. The solubility of the drug Salbutamol Base in solvent Ethanol requires a double stage filling process. Another reason makes Moschimpharm preparaty to select the double stage filling is the availability of a high pressure vessel needed for mixture of drug, solvent and propellant. The use of vessels under pressure is not allowed by the City Fire Protection Authorities since the company's workshops are situated in the center of the Moscow-city.

#### HFA Propellant system with low volume suspension or solution filling



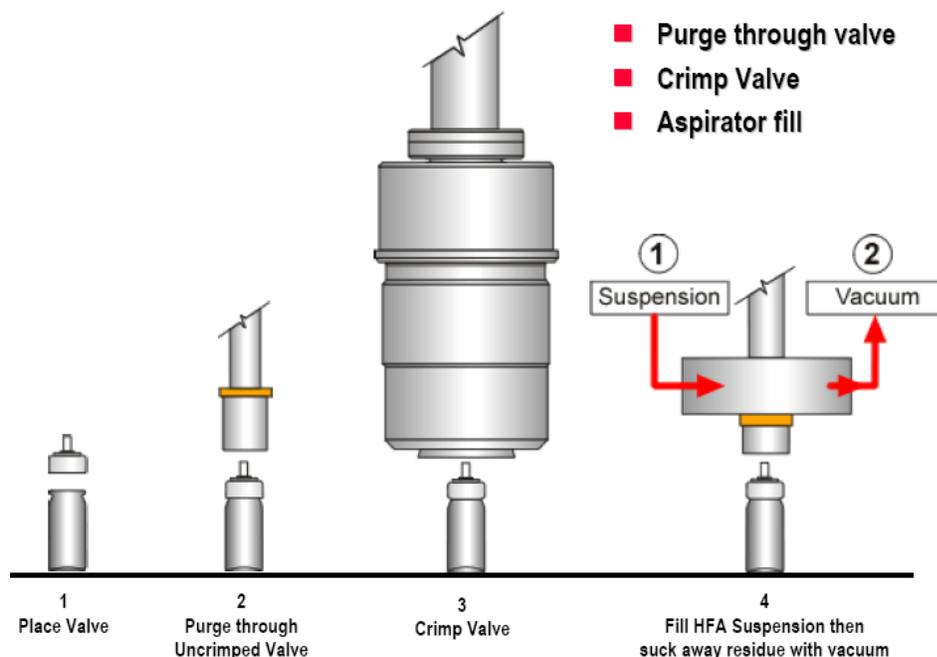
**Figure 8. Schematic of the double stage filling process**

Solution formulations like Salbutamol and formulations with ethanol to aid suspension may be filled in two stages, as per the schematic in figure 8 above. The active drug is introduced in to the open canister in much the same way as the CFC 11 slurry would have been introduced previously.

Where ethanol is not used the filling process becomes more complex. The drug and the HFA propellant need to be pre-mixed in a special pressure vessel. This mixture is then filled trough the

MDI valve after it has been fixed to the can. In order to avoid releasing residual drug amounts to the atmosphere, a vacuum system is employed in the filling attachment to safely remove the waste. Figure 9 below shows a schematic of the process. This process was selected for Salbutamol Sulphate API for Altayvitaminy.

## HFA Propellant system with Aspirator filling



**Figure 9. Schematic of the single stage filling process**

### 5.4. The MDI Project at Altayvitaminy

The Product to be developed

Salbutamol Sulphate 200 dose, 100 µg/ dose label claim, suitable for manufactured by a "Pressure" filling process, HFA/ ethanol formulation with surfactant in a standard container. The insolubility of the drug Salbutamol Sulphate in Ethanol requires a single stage filling process for suspension.

Following successful formulation development and technology transfer manufacturing will be undertaken at Altayvitaminy in Biysk on approved semi automatic "Pressure" filling, manufacturing equipment, designed and approved for manufacture of HFA pMDI's. Any developed package and formulation should be capable of being manufactured with a single batch in the range 3,000 to 5,000 canisters.

The filling equipment in Figure 8 proposed for Altayvitaminy will be capable for single stage filling allowing slightly soluble in Ethanol formulations to be used.

## 5.5 Process Implications of the Selected Replacement Technologies

As indicated above the absence of a suitable non-CFC equivalent to CFC-11, places a number of process restrictions on the manufacturing processes operated by both MosChimPharmPreparaty and Altayvitaminy. These implications include:

- Loss of the ability to prepare a “slurry” at room temperature, without the use of ethanol.
- No option product filling in to an open canister, without using ethanol.
- Systems are not self “purging” (exclusion of air by slow expansion of the CFC 11)
- Increased frictional/ wear problems if trying to fill both propellant and drug together.
- Loss of the use of accepted surfactants (to reduce drug sticking etc) in formulations.

As it is not possible to address these issues within the formulation of the product, it is more normal to resolve these issues by a combination of equipment and process changes.

## 6. Expected outcomes

The project includes four major outcomes. They are:

- Technical assistance in converting a CFC-based MDI production to HFA –based MDI
- Phase out of CFC consumption -212 MT (2010) in the Medical aerosol (MDI) sector
- Technology transfer in developing a new HFA –based MDI
- New developed MDIs registered at the Ministry of Health and Social Development.

### 6.1. Technical Assistance in Converting CFC-based MDI Production to HFA

The project aims at establishing the relevant policy and legal framework and strengthening the institutional capacities for sustainable CFC phase out, through development and implementation of training, awareness and capacity-building activities for key Government departments, legislators, decision-makers and other institutional stakeholders. Special attention will be given to the harmonisation of regulations in the Russian Federation with EC regulations, GMP as well as, the up-grading of ODS import/export legislation and ODS destruction.

The technical assistance component of the Project has been allocated a total funding of US\$ 0.1 million. Efforts should be made jointly by the Ministry of Health and Social Development (MOH) of the RF, healthcare providers, physicians, pharmacists and nursing staff and all sectors linked to Health. All these parties implementation support for the Project's investment activities. It should be understood that the transition is not optional and that, over the next few years, all patients currently using CFC products will have to change to CFC-free devices. They should be prepared to help patients to understand the reasons for the change and assist them during the transition period of two years. Patients should be reassured that:

- The new inhalers are as safe and as effective as the previous ones.
- CFCs are damaging to the global environment but not damaging to the health of the individual.
- Although they will experience differences in appearance, dosage and taste, these do not imply any reduction in the effectiveness of the medicines.

It is clear from other transition programs that they will have a pivotal role to play in the success of the transition strategy. It should be considered that either way (Domestic manufacture vs Import only strategy) there will be the need to manage patient perceptions in the transition from CFC MDIs. Asthma and/or COPD patients, as with any patient with a chronic disease, are deeply attached to any medication that proves to be effective in controlling his/her conditions. In Russia physicians and asthma/COPD related associations treat patients based on scientific facts and international guidelines as they believe. As groups of specialists and physicians are broadly using and supporting international guidelines for diagnosis and treatment of asthma and COPD as mentioned earlier, the need of a national guideline/program for asthma and COPD is strongly felt. The education and sensitising campaign for the introduction of new products (HFA MDIs) will therefore be both necessary and challenging in this situation. Considering the above-mentioned elements the implementation of an education programme involving health professionals, patients, their families and the community from the very beginning becomes a priority, led by the Ministry of Health.

Medical studies show that asthma education reduces by 50% asthma severe episodes and substantially improves patient's quality of life. The Ministry of Health strongly believe that an education campaign will be the core of a transition strategy. In this sense, in Russia with a population of about 150 million and a good health system with pro-active involvement and leadership from the MoH, this issue has an important role. At a global level, GINA (Global Initiative for Asthma) in its Programme Review of 2002 focussed its attention on the education of the patient and his/her family as one of the objectives for controlling asthma.

In this sense, there should be cooperation between the professionals involved on a local or regional basis to discuss how the transition is to be implemented. Contacts and exchange of information with Associations of "GPs", "Asthma and Allergy", "Lung Disease", the Russian Federal Pulmonology Centre, pharmaceutical and other professional associations should be established to ensure that all professional healthcare providers receive adequate and correct information regarding the new products and that; patients receive adequate information, both orally and in writing. This is essential to build the confidence of patients in the new products. Choice of medication should be made by the physician but the patient expects an explanation for such choice of a specific medicine, particularly when a change from a familiar product is involved. Several surveys have shown that when a change from CFC inhalers to alternatives is recommended by the physician and adequate information is given, most patients happily agree to the proposal.

Education is a continuous process, a partnership between professionals and patients that involves an exchange of information and adequate opportunity for patients to express their fears and concerns. Although physicians are the patients' first source of information on medications, they do consult also other physicians, pharmacists and other information sources when they have questions about the treatment of asthma. It is therefore crucial that all these parties have the same information and give consistent advice to patients. With adequate preparation and reinforcement of the key messages, the transition can be completed successfully.

Efforts should be made jointly by the MOH, healthcare providers, physicians, pharmacists and nursing staff and all sectors linked to health. All these parties should understand that the transition is not optional and that, over the next few years, all patients currently using CFC products will have to change to CFC-free devices. They should be prepared to help patients to understand the reasons for the change and assist them during the transition.

Appropriate visual and written educational materials should be developed to foster this process and media should be used for their dissemination. Mass media can and must play a fundamental role in raising awareness. In Russia, easy and broad access to mass media is available to public. The relationship with educational authorities has proved to be highly positive for the development of health programmes. Primary and secondary schools are natural centres for raising awareness and disseminating information, both for children and adolescents and their families. Therefore the education plan should consider a close relationship with educational institutions.

The pharmaceutical industry also plays a significant role in a successful implementation of the programme, not only by providing information through educational material and supporting scientific events intended for physicians, but also with dissemination of material for the general public.

Organizations involved in the transition will be approached early in the process to determine the type of support they will be able to provide to the initiatives. It is expected that domestic manufacturer, the funding from the international fund and, to a lesser extent, the MOH will be the primary sources of funding of these initiatives. Activities will have to be scaled according to the funds available.

The Key elements of this transition strategy are as follows:

- a) To ensure that the health and safety of patients during the transition will be safeguarded.
- b) To ensure that importers of CFC containing MDIs fully realise their obligations to withdraw such products from the Russian market, in a timely manner. The withdrawal to be conducted in a manner such as to manage the primary objectives of the transition strategy.
- c) To encourage importers of inhalation products in to the Russian Federation to support the patient awareness/ education programme, either directly or indirectly.
- d) To develop an educational training package to facilitate communication with patients and allow the roll out of training to a local level.
- e) To plan and execute at least two centralized training symposia to train representatives from local authorities and healthcare providers, in the use and onward training of the educational packages.
- f) To oversee the roll out of training initiatives to ensure that individuals in direct contact with patients receive both training and adequate supporting materials to support patient awareness.
- g) To generate suitable awareness enhancing media (posters, leaflets etc.) for location in environments to support patient awareness (hospitals, pharmacies, clinics, surgeries etc.)
- h) To actively promote via appropriate media (advertising, conferences, interviews etc.) awareness of the implications of the transition.
- i) To ensure that the nomination, approvals and licensing systems will be operated with efficiency, consistency and transparency.

In approval of new HFA MDIs in the RF either domestically manufactured or imported the MOH must seek to ensure that;

- Any new CFC free inhaler is at least as safe as the previous one.
- Any new CFC free inhaler is as effective as the previous inhaler it is intended to replace.

- There should be sufficient quantities of the alternative(s) available to assure an uninterrupted supply of medication. This is a key consideration and needs to consider the geography of the RF and distribution issues. Many imported MDIs are only available in a few pharmacies in Moscow and other larger cities.
- Post-marketing surveillance data must confirm the safety of the alternative product(s).
- There should be sufficient types of alternatives available to meet the needs of different patient sub-groups.

Manufacturers of the alternative(s) will be requested to confirm that they can adequately supply the whole RF market and to provide information on the production capacity of the manufacturing facilities and on the measures they intend to put in place to ensure the supply of the RF market.

The MOH with the support of external agencies where possible will develop an integrated package of materials, (printed, recorded etc.) for the purpose of training primary, secondary and tertiary training staff. Where possible importers of inhalation products to the RF will be contacted directly to review what current and future resources they can make available. It is not practical to disseminate the key messages to all individuals with direct patient interaction, in a single communication event. It is more practical to train selected individuals and provide them with materials to; in turn train key personnel at a more regional level. A number of top level training symposia need to be planned, one for MOH representatives from throughout the RF.

Support needs to be given at a local level to facilitate workshops, symposia, printed material, to ensure that the individuals trained in the primary sessions can distribute the key messages to all primary patient contacts. For the following years several local and regional workshops should be planned for information sharing, and elaboration and discussion of the guidelines to be approved, where the transition to CFC-free MDIs will be included in the National Programme of Asthma and COPD. Also where appropriate supporting materials for direct patient awareness (posters, advertisements, leaflets etc.) need to be produced and distributed via doctors and pharmacists.

The cost associated with this is at this stage not clear, however it is a cost of the transition from CFC MDIs, regardless if the products are made in the RF or imported.

All importers applicable will be formally contacted in writing by MOH and given details of the phase out programme for CFC MDIs and advised of their obligations to remove any such products from the Russian market. Encourage importers of inhalation products to support the patient awareness/ education program. Importers of inhalation products will be contacted directly to review what current and future resources they can make available.

**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 Natural Resources and Environment (MNRE) (through the Ozone Unit):**

- 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 Health and Social Development (MOH).

**Ministry of Health and Social Development (MOH):**

- Carry out the national education campaign in coordination with all other stakeholders, MOH, Local enterprises, and the MNRE
- Withdraw domestically produced CFC MDIs, if any from the market in compliance with the agreed timetable and criteria (according to Rosdravnadzor there are no CFC-based MDIs available presently on the Russian market).
- Formulate the necessary legal provisions concerning MDI import together with the MNRE.
- Support the national education campaign.

**Rosdravnadzor:**

- ♦ Grant marketing authorizations for CFC-free MDIs

**Local enterprises (Moschimpharmpreparaty and Altayvitaminy):**

- Support to the national education and sensitisation campaign.
- Provide CFC-free products within the terms agreed in this transition strategy (to achieve the CFC phase out in MDI production till 30 June 2013, and if possible till December 2012).
- Withdraw CFC products within the terms agreed.

**6.2. Phase out of CFC Consumption in the MDI Sector**

Ideally the conversion of CFC MDIs to a CFC-free formulation would require zero-ODP replacements for both CFC-11 and CFC-12 that possess similar physical, chemical, and toxicological properties. However, replacements with such properties are not available. The CFC MDI conversion process led by the established multinational pharmaceutical companies has spawned new formulations, new manufacturing processes, as well as non-aerosol dry powder inhalers (DPIs). Many of these products are the subject of intellectual property that cover either the drug molecule, the method of formulation, the device (in the case of DPI) or the filling process.

Both HFC-134a and HFC-227ea have been developed as zero-ODP replacements for CFC-12 to serve as the propellant function in CFC-free MDIs, and in some products also as the CFC-11 replacement. However, differences in the physical (e.g. boiling point) and chemical (e.g. solubility) properties of these substances and the CFCs they replace, require changes to the manufacturing process and equipment, as well as to seal materials used in both MDI valves and manufacturing equipment. HFC-134a and HFC-227ea, again manufactured to recognised pharmaceutical standards, are commercially available and are now widely used throughout non-Article 5 countries.

**6.2.1 Incremental Capital Costs**

The project deals with the design, manufacture, shipping, installation and commissioning of dedicated HFA MDI filling lines and associated equipment, vessels, pumps, etc.:

- a) one filling line with two filling dispensers in a double stage filling process at MosChimPharmPreparaty and
- b) one filling line with two filling dispensers in a single stage filling process at Altayvitaminy in order to achieve the phase out of 212 ODP tones CFC (CFC-11 and CFC-12).

The table below outlines the equipment profile (drawn from similar projects in Article 5 countries).

Company		Altayvitaminy		Moschimpharmpreparaty	
Item	Qty	Sub-total Cost CHF	Total cost US\$	Unit cost CHF	Total cost US\$
<b>Conveyor Belt 30000/008 or similar</b>	1	22,610	25,693	22,610	25,693
Length: 6.0-7.0 m Consisting of: - conveyor frame and guide rail stainless steel, slat chain 82.5 mm Delrin - conveyor supports height adjustable - drive unit and return section, motor foreseen to be controlled by frequency inverter					
<b>Can Divider X30000-054 (066203) or Similar</b>	1	30,310	34,443	30,310	34,443
Can conveyor X30000-0054-010/001 (066882) - Ejector for lying cans X30000-0054-020 (066473) - Hinged top cover in Plexiglas					
<b>1st Macromat 2045/016 Pharma Type A or similar</b>	1	116,400	132,273		
Basic installation with automatic rotary table, Ø 600 mm and 18-pitch infeed starwheel with quick changeable can guides for cans with a Ø up to 66 mm. The pitch circle allows the installation of 1 - 3 product fillers, 1 valve inserter, 1 crimper and 1 - 3 propellant fillers. The bracket with the filling heads is fitted to the central column. Joint adjustment of the working height for the filling heads and the crimper. After the adjustment an automatic locking system keeps the bracket with the filling heads in position. Cans with a height up to 315 mm can be handled. Entirely pneumatic operation. An interlock system controls the return of the filling head and the synchronisation of the indexing mechanism. The control panel allows the individual operation of all aggregates. This guarantees the function and control of each movement. A can counter with zero setting is integrated.					

<p>Set of can guides for one Ø</p> <ul style="list-style-type: none"> <li>- Frame and brackets in stainless steel AISI 304</li> <li>- 400 mm deep back cabinet</li> <li>- Skirt around the base of the machine frame in stainless steel</li> <li>- Pneumatic height adjustment, with air motor, adjustable by push button</li> <li>- Extraction duct device for product or propellant vapour (without ventilation)</li> <li>- Protection guard "SYMA" with aluminium frame and security glass. The doors are equipped with turn lock</li> <li>- Control switches "door open - machine stops". Interrupting the working process. Restart after closing of the door and confirmation.</li> </ul>					
<p><b>2x Product Filler 2001/021</b></p>				116,400	132,273
<p>Metering cylinder 0.2 - 2 ml, tolerance <math>\pm 0.02</math> ml With recirculation system.</p>					
<p>Consisting of:</p> <ul style="list-style-type: none"> <li>- Quick release bracket for metering unit</li> <li>- Modular sub base mounted, oilfree pneumatic control system</li> <li>- Slave cylinders with quick release couplings for filling nozzles</li> <li>- 2 ml metering unit with volume adjustment cartridge</li> <li>- Diaphragm inlet shut off valves</li> <li>- Diaphragm outlet shut off valves to enable recirculation</li> <li>- Diaphragm filling nozzles</li> <li>- Quick release coupling for nozzle</li> <li>- Quick release couplings to connect hoses (connection hoses between pump and filler are not included)</li> <li>- Product contact parts of 316 L stainless steel</li> </ul>					
<p>Description: The suspension/solution filling station meters a pre-set volume of solution into the open can.</p>					
<p>The suspension/solution is recirculated through the filling head then back to the mixing vessel to ensure homogenous fills. The metering unit is mounted on bracket. The filling nozzle is attached to a slave cylinder.</p>					
<p>The suspension/solution is supplied to the metering unit via the inlet shut off valve. The suspension/solution then passes through the metering unit and down to the diaphragm filling nozzle. It then recirculates through the nozzle and back through an outlet shut off valve before returning to the mixing vessel.</p>					

<p>Product supply: the 2 ml filler with recirculation system has to be connected to a feeding pump. Material Certificate according to EN 10204 - 3.1 for all stainless steel parts getting in contact with the product/propellant</p> <ul style="list-style-type: none"> <li>- Pressure gauge E 90 004 323 installed close to the filling machine with in-line diaphragm with DN ½" Tri-Clamp connection, for suspension, made of stainless steel, parts in contact with the product 1.4435 (AISI 316L) with industrial pressure transmitter 4...20 mA (0 - 20 bar), incl. 1 clamp Z 18831-01 and 1 gasket Z 18831-02.</li> </ul> <p>Manufacture calibration certificate DIN 55350 part 18 4.2.2. (5 point measure protocol). Material certificate according to EN 10204-3.1, for metal parts in contact with the product.</p>				45,200	51,364
<p><b>Valve Inserter X2058-0016/004</b> Oilfree execution. For 20 mm valves without dip tube, with swing opener incl. pneumatic control and valve presence control without feeding rail, without sorting bowl.</p>				22,400	25,454
<p><b>Crimper 2002/021</b> With crimping head X2002-0010/001 for 20 mm MDI valves, incl. stop and collet for one type of valves.</p> <p>The pneumatic control allows an individual definition of the contact pressure. The follow-up control initiated by pilot air co-ordinates the sequence of operations.</p> <p>The crimping height and the crimping depth may be fast adjusted with the crimping head in place</p>				26,700	30,341
<p><b>2x Propellant Filler 2011/021</b> Depending on filling speed of valve the capacity for 2-step formulations can be increased. Metering cylinder 0.5 - 20 ml, ± 0.1 ml With recirculation system. Consisting of: Quick release bracket for metering unit</p> <ul style="list-style-type: none"> <li>- Modular sub base mounted, oilfree pneumatic control system</li> <li>- Slave cylinders with quick release couplings for filling nozzles</li> <li>- 20 ml metering unit with volume adjustment cartridge</li> <li>- Diaphragm inlet shut off valves</li> <li>- Diaphragm outlet shut off valves to enable recirculation</li> <li>- Diaphragm filling nozzles</li> <li>- Quick release coupling for nozzle</li> <li>- Propellant contact parts of 316 L stainless steel</li> <li>- Material Certificate according to EN 10204 - 3.1 for all stainless steel parts getting in contact with</li> </ul>					

<p>the product/propellant</p> <p>Filling head insert for 2 additional valve types Pressure gauge E 90 004 323 installed close to the filling machine with in-line diaphragm with DN ½" Tri-Clamp connection, for suspension, made of stainless steel, parts in contact with the product 1.4435 (AISI 316L) with industrial pressure transmitter 4...20 mA (0 - 20 bar), incl. 1 clamp Z 18831-01 and 1 gasket Z 18831-02. Manufacture calibration certificate DIN 55350 part 18 4.2.2. (5 point measure protocol). Material certificate according to EN 10204-3.1, for metal parts in contact with the product.</p>				132,240	150,272
<b>2nd Macromat 2045/016 Pharma Type B or similar</b>	<b>1</b>	116,400	132,273	293,840	333,909
<p><b>Valve Transport System X2047-0043...</b> with chain conveyor "Paternoster" Suitable for 20 mm valves. Dual system. The aerosol valves are transported from the sorter to the inserter by a rail system. A drive unit brings the valves up to a height of 2.5 - 3.0 m, where they enter a telescope system before reaching the inserter. This system allows an easy adjustment of the individual can height. This unit is fully controlled by fibre optics. Divider to feed two Macromats is included. With orientation device for sorting and feeding Consisting of: Vibrator drive, base plate and frame, control box, vibrator bowl, connection plug, solenoid valve, bowl metaline covered. The valves are sorted in the vibrator bowl where any incorrectly orientated valves are guided off the bowl exit track. The speed of vibration can be adjusted by a potentiometer. Mounted on stainless steel base 800 x 800 mm. Including enclosure</p> <p>Noise guard with infeed opening over vibrator Skirt around base frame made of stainless steel</p>		93,480	106,227	93,480	106,227
		59,160	67,227	59,160	67,227
<b>Connection Piece 30000-070/008</b>	<b>2</b>	4,030	4,560	4,030	4,560
Lateral deviation of 500 mm length to enable the passage from one conveyor belt to the next one					
<p><b>Purger Pharma x2043-0003-500 or Similar</b> with dosing cylinder of 1 ml to purge into open can or through the valve. - Material Certificate according to EN 10204 - 3.1 for all stainless steel parts getting in contact with</p>	2			49,830	56,625
<b>Product Filler 2001/005 or similar</b>	<b>2</b>	75,600	85,909		

Metering cylinder 5 ml. With recirculation system. Consisting of: - Quick release bracket for metering unit - Modular sub base mounted, oilfree pneumatic control system - Slave cylinders with quick release couplings for filling nozzles					
<b>SSP Lobe Pump X1/0005/HO8 or similar</b>	<b>2</b>	40,000	45,454		
Rotary piston pump (3 Lobe) with safety valve in pump top with motor and gear - Suitable for recirculation system - Housing, shaft and rotors made of stainless steel 316 L - Speed of rotation: 690 rpm - Pressure pump outlet 2.5 bar					
<b>Hoses and Connections</b>	<b>2</b>	4,000	4,545		
<b>Valve Inserter 2058</b>	<b>2</b>	34,800	39,545		
For 20 mm valves with "no valve detector". Oilfree execution. The inserter is equipped with a valve presence control.					
<b>Vacuum Crimper 2002/021 or similar</b>	<b>2</b>	70,000	79,545		
Oilfree execution incl. stop and collet for one type of valve. The vacuum is used depending on the desired formulation to be filled. For single stage HFA formulations however is vacuum required. When vacuum is selected the station pulls a vacuum in the can before crimping the valve collar onto the can. A bulging seal fitted to the base of the head seals the vacuum bell around the can. Included in the price: Vacuum Pump 14019/004 Type MLD 50 Viton The pump is suitable for the suction of small volumes.					
<b>Diaphragm Filler 2079 or similar</b>	<b>2</b>	94,600	107,500		
All parts in contact with the product are made of stainless steel AISI 316L - Oilfree execution of all pneumatic elements - Filling head and metering unit are fast exchangeable - 20 ml metering unit with recirculation system - diaphragm shut-off valve incl Set of special tools incl Material Certificate according to EN 10204 - 3.1 for all stainless steel parts getting in contact with the product/propellant					
<b>Vacuum Pump 14019/004 Type MLD 50 Viton</b>	<b>2</b>	10,000	11,364		
<b>Propellant Filler 2011/021</b>	<b>2</b>	68,400	77,727		
<b>Propellant Pump X2008-0003 Pharma</b>	<b>2</b>	49,600	56,364		
<b>Valve Sorting and Transport System</b>	<b>1</b>	56,500	64,204		

<p>Sorting Bowl</p> <p>The valves are sorted in the vibrator bowl where any incorrectly orientated valves are guided off the bowl exit track.</p> <p>The speed of vibration can be adjusted by a potentiometer.</p> <p>Mounted on stainless steel base 800 x 800 mm, incl. enclosure.</p> <ul style="list-style-type: none"> <li>- Dust and noise protection Syma</li> <li>- Skirt pharma execution</li> </ul>					
<p><b>Valve Transport system X2047-0038 with chain conveyor "Paternoster"</b></p>	1	85,300	96,932		
<p>Suitable for 20 mm valves. Dual system.</p> <p>The aerosol valves are transported from the sorter to the inserter by a rail system.</p> <p>A drive unit brings the valves up to a height of 2.5 – 3.0 m, where they enter a telescope system before reaching the inserter. This system allows an easy adjustment to the individual can height. This unit is fully controlled by fibre optics.</p>					
<p><b>Ethanol Mixing Vessel MDI's (Local or from other country)</b></p>	1	130,000	147,727		

<p>For mixing of ethanol with powder (suspensions)  - Capacity: 100 litres (80 Litres usable)  Material of construction :-  · All parts in contact with the product is stainless steel AISI 316L ( 1.4404 ) and other parts that have no contact with the product are made from stainless steel AISI 304 ( 1.4301 ).  · Dimple jacket around the inner shell and bottom for high performance cool transfer and distribution  · Insulation material: suitable insulation material to make the cooling fast.  · The insulation is around the body and the bottom with 50 mm thickness .  Supports:-  Type of support: the hole tank is carried on a stainless steel tubular legs on movable castors two of them have braking system .  No. of legs: 4 legs.  The distance from outlet to the ground is 400 ±150 mm.  Finishing:-  Internal surface : brilliant finish outer surface : brilliant finish  Accessories:-  · Vertical Mixing agitator with electric geared motor with 1.5 KWpower and 1500 rpm speed .  · Dry running system for nit operating the mixer while there is no liquid inside the vessel.  · Blade shape are turbine type "may be changed according to customer request " .  · Min. mixing volume is 5 litter.  · Outlet: Tri clamp connection with manual diaphragm valve with Diameter :25.4mm.  · Inlet : Tri clamp connection only without fittings with Diameter :25.4 mm qty(2).  · Diaphragm pressure gauge with tri clamp end connection.  · Stainless steel filter with cartrage .  · Stainless steel Weighting load cell sensor for level measuring .  · Sight galss with lamp .  · Pneumatic lifting system for the complete top with the agitator  · Control panel with necessary components .</p>					
<b>Cooling Block VWK 30/1S</b>	1	24,800	28,182		
Cooling range +20°C down to -5°C Electrical control V 380, 50 Hz					
<b>Certificates for pressure gauge</b>	1	8,000	9,090	8,000	9,090
<b>Hoses and Connections</b>	1	3,000	3,409		
To connect to Pressurised vessel and Diaphragm pumps					
<b>Documentation English</b>	1	10,000	11,364	10,000	11,364
<b>Electrical Equipment</b>	1	177,520	201,727	177,520	201,727

<p>1. General</p> <ul style="list-style-type: none"> <li>- The main control cabinet painted execution for the line has to be placed in the safe area.</li> <li>- The line needs a power connection of 3x400 V+N+PE, 50 Hz. The voltage and the frequency can be changed to the customers requirements.</li> <li>- The control circuit voltage is 24 VDC.</li> <li>- The necessary control equipment and the basic operator interfaces are built on.</li> <li>- The line conforms to the specifications for electrical equipment of industrial machines. (International Electrotechnical Commission "IEC204")</li> </ul> <p>2. Main Control Cabinet</p> <ul style="list-style-type: none"> <li>- The main control cabinet has three parts: power circuit, control circuit and Eexi parts.</li> <li>- The main control cabinet contains: Main switch, maintenance switch, main contactors, contactors, motor starters, circuit breakers, terminal fuses, power supply, safety relays, thermistor control relays, terminals etc.</li> <li>- Rittal control cabinets painted execution (Pharma stainless execution)</li> <li>- Pamasol standard equipment</li> <li>- Siemens PLC</li> <li>- Electronic pressure control of product and propellant supply to Macromat</li> </ul>					
<b>Spare parts for complete line</b>	1	41,100	46,705	41,400	46,005
<b>Equipment total</b>		<b>1,425,610</b>	<b>1,620,011</b>	<b>1,133,120</b>	<b>1,287,636</b>
<b>Packing in Factory</b>	1	11,000	12,500	11,000	12,500
<b>Commissioning and Installation of Filling Equipment</b>	1	65,000	73,864	65,000	73,864
		<b>Total including commissioning</b>	<b>1,706,375</b>		<b>1,374,000</b>

This represents a total investment in equipment per site of US \$1,706,375 for Altayvitaminy and US\$ 1,374,000 for Moschimpharmpreparaty. Therefore, the investment in new equipment required at both sites will be in the region of US\$ 3.0 million.

The cost of equipment is preliminary, based on the offer from for example, one of potential suppliers dated May 2011 (this cost is due to the fluctuation of the exchange rate of Swiss CHF and US Dollar). In the above Table the exchange rate of 1US\$ was equalled to 0.88 CHF and this rate was used in all the calculations. The total cost of equipment for Altayvitaminy (single line with two filling dispensers in single stage filling) is higher than the equipment for Moschimpharmpreparaty, which selected the double stage filling equipment. The single stage filling process requires the use of a high pressure vessel for mixture IPA and propellant, which is not allowed to be in use in Moschimpharmpreparaty by Fire Protection Department of Moscow city, since the factory buildings are situated in the centre of Moscow city.

The amount of US\$ 2.3 million of the GEF is planned to be allocated for the procurement of project equipment, that is US\$ 1,15 million for each and the difference in equipment cost need to be borne by each enterprise. An international tender that will be conducted by UNIDO for equipment procurement will take place after project approval (3-6 months after project proposal submission to GEF), and the real cost of equipment is expected even to be higher than projected. Therefore, both enterprises may pay even higher equipment cost, that is subject of the exchange rate of Euro or CHF to US Dollar, at the moment of the international tender will be finalized.

Note the above costs do not include the provision of documentation data and support (IQ, OQ, PQ) from the equipment manufacturer. It will be responsibility taken by the beneficiaries to develop their own equipment and process validation protocols etc. Technical assistance will be provided by the equipment supplier during the testing and installation of the equipment. Guidance of the Russian experts on the Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ) of new equipment by equipment supplier will be also rendered. The program management of the overall project incorporating both the elements of MDI development and supervision of equipment installation will be rendered by a selected technology provider as well as technical assistance (technology transfer, engineering services, equipment and instrumentation, etc.) required for conversion of to the new HFA propellant.

### **Assumptions/comments**

For the purpose of this costing recent quotations have been obtained from the recognized suppliers.

- ◆ Capital items such as FAT/SAT, shipping, commissioning etc. have been not included.
- ◆ The quotations are either specific to this project or for similar exercises.
- ◆ An exchange rate of 0.88 CHF to 1.00 US\$ has been applied.
- ◆ Typically quotations have a validity in the range 30 to 60 Days.
- ◆ The costs of the offerings will be impacted by exchange rate fluctuations.
- ◆ Equipment profiles to replace "Like with Like" have been followed and improvements in efficiency or process have been considered outside the scope of the project.
- ◆ It is assumed that provision of building and standard services (electricity, compressed air, water and drainage) is the responsibility of the recipient.
- ◆ All equipment installations shall be safe and comply with internationally recognized safety requirements.
- ◆ Training of local personnel is the responsibility of the recipient.
- ◆ Costs include a contingency of 10%.

### **6.2.2. Moschimpharmpreparaty**

Currently, Moschimpharmpreparaty has two manufacturing lines that give them good manufacturing flexibility and a combined annual installed output capability in the region of 10 Million units per year, with batches in the range 6,000 to 15,000. However, the actual annual capacity of the two line is 7.0 million cans in one shift.

Moschimpharmpreparaty has agreed that although a reduction to one line with two filling dispensers following the conversion from CFCs, will reduce their theoretical maximum capacity to around 7.0-8.0 million a shift, which is close to the actual annual capacity. The cost of one manufacturing line based on a double Aerosol Pharma Filling Line Type Macromat P 2045 is given above. Each of them has capacity: with dosing valve 35 - 45 cans/minute (depending as on the volume and valve to be filled).

In general, the new manufacturing process will be the same at Moschimpharmpreparaty as the CFC process that they have used for many years. However the demands of the formulation approaches will require variations on the processes and equipment.

### 6.2.3 Altayvitaminy

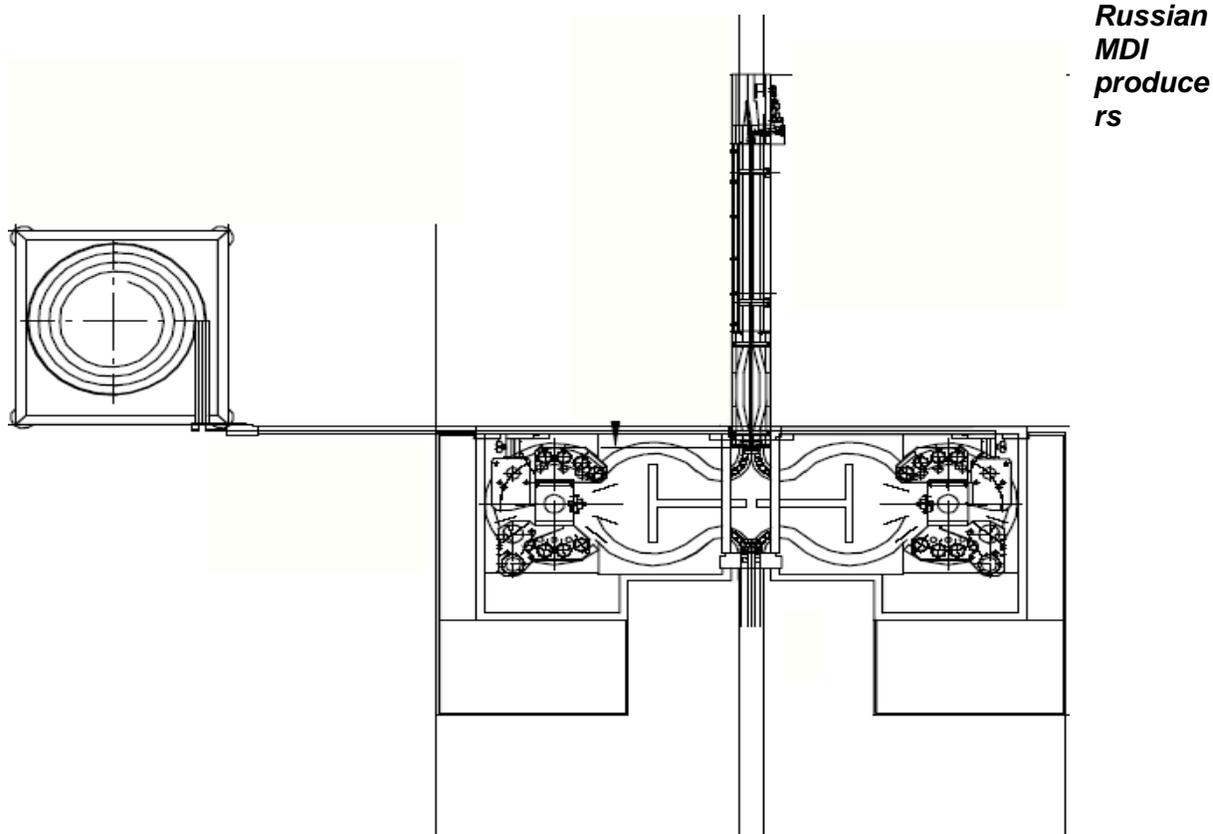
Currently Altayvitaminy has two manufacturing lines, one purchased from Coster, Italy and another locally made that give them good manufacturing flexibility and a combined annual installed output capability in the region of 7.0 Million units per year in one shift, with batches in the range 6,000 to 15,000. The actual annual capacity of the two line is 5.0 - 5.5 million cans in one shift and in single stage filling.

Altayvitaminy has agreed that a reduction to one line with two filling dispensers following the conversion from CFCs, will reduce their theoretical maximum capacity to around 5.0 million a shift, which is close to the actual annual capacity. The cost of one manufacturing line based on a single Aerosol Pharma Filling Line Type Macromat P 2045 is given above. Each of which has a capacity: with dosing valve 25 - 30 cans/minute (depending as on the volume and valve to be filled). In general the new manufacturing process will be the same at Altayvitaminy as at Moschimpharmpreparaty, the CFC process that they have used for many years, however the demands of the formulation approaches will require variations on the processes and equipment.



**Figure 10. Similar selected project equipment to be purchased for two enterprises, i.e. valve sorter with two Macromats in a single line, courtesy of Pamasol, Switzerland**

**Figure 11. Schematic layout of two Macromats connected in one line at the two**



### 6.3. Technology Transfer

Although the enterprises have skills and capabilities in the manufacture of CFC MDIs, they have no capability or experience in the development of HFA MDIs. Therefore, to implement the selected replacement technologies, both Altayvitaminy and Moschimpharmpreparaty, will require technology transfer from one, or more, established multinational enterprises that have experience in the formulation and manufacture of CFC-Free MDIs using alternative technologies.

It is important to be recognized that without such transfer of technology, it would likely take the local enterprises between 6-10 years to develop and obtain approval for CFC-free replacements for their current CFC MDIs. This timescale will likely result in the RF's non-compliance with its 2010 CFC phase out of CFC use under the Montreal Protocol, but more seriously, it is likely to impact the production and availability of CFC MDIs in the RF, with resultant adverse health consequences for the large numbers of the Russian population that suffer from asthma, chronic obstructive pulmonary disease (COPD), and other lung diseases characterized by obstruction of airflow and shortness of breath.

The present project proposal includes outline costs of US\$ 500,000 from the co-financing component of the project budget based on analysis of one technology transfer option offered by one of the potential technology providers. Certain assumptions/ considerations have been associated with this offer;

- This offer is considered as a preliminary estimate and valid for three months only.
- The offer is for the development of one MDI with one active drug compound - Salbutamol.
- Each local beneficiary will accept its MDI product from the double re-formulated HFA Salbutamol data package (Salbutamol base for Moschimpharmpreparaty - solution and Salbutamol Sulphate for Altayvitaminy - suspension).

It is anticipated that an Independent Expert may also be required to visit the two enterprises and assist in technology transfer, monitoring activities and conduction of new MDI stability tests.

The costing submitted from technology providers includes the following important elements:

- ◆ cost of raw materials
- ◆ cost of packaging components
- ◆ cost of manufacturing stability batches
- ◆ cost of manufacturing placebo
- ◆ cost of travelling
- ◆ cost of legal fees - excl. Contractor's own costs
- ◆ cost of shipping, custom duties
- ◆ cost of specialty chemicals, solvents, columns
- ◆ cost of innovator samples
- ◆ cost of external labs work eg: micro testing
- ◆ cost of patenting fees including Contractor's fees related to paper work

It is clear from a review of the companies' technical capabilities in respect of formulation development and understanding of the increasing regulatory demands from the Ministry of Health, that both companies will require significant technical support in the development and successful registration and industrialization of HFA MDIs. Failure to obtain this support will expose the program to unacceptably high levels of risk of failure.

### **6.3.1. MosChimPharmPreparaty**

MosChimPharmPreparaty has invested in accessing a potential formulation for Salbutamol. The formulation approach has not been based on best practice and little has been understood about the physical stability of the formulation. Ethanol containing water has been used in the formulation which is known to result in instability in the formulation, however no work has been conducted on particle size distribution and emitted dose, which would have identified the issues. As a result time and money have been used up on a formulation which is not commercially viable.

The detailed formulation was reviewed and it is felt that the resulting product is unlikely to be acceptable for development. The product included the use of ethanol containing water (known to result in stability issues) and little if any testing has been done by either MosChimPharmPreparaty, or the technology provider to understand the physical stability of the product. Therefore, one technology transfer option offer received from on of the potential suppliers for MosChimPharmPreparaty will be also carefully considered by the project team.

There are two approaches which have been taken in previous UNIDO CFC to HFA MDI transition projects to access or develop the necessary technology.

- a) To access the necessary know-how, data and documentation from an established technology provider.
- b) To develop the technology locally with support from international consultants.

Option a) has been the most successful, but has been the most expensive costs in the range of \$600,000 to \$1,200,000 per formulation per beneficiary, based on UNIDO knowledge of international prices). The high cost has typically been driven by the requirements of the initial Terms of Reference, requiring significant data generation.

Option b) represents a lower cost however with the capabilities and competencies of the local companies to develop and commercialise a product, which should be technically acceptable.

It was decided to apply the second approach due to lack of international funds from GEF to conclude a contract with one of famous pharmaceutical laboratories. The two companies need to contribute to this process through conclusion of a contract with any pharmaceutical laboratory known to them (in this case with State Pharmaceutical Center, Kharkov, the Ukraine), which agrees to develop/formulate a new MDI product for the two Russian MDI companies.

Preliminary discussions with some potential providers have indicated that it may be possible to obtain the required data packages and technical support, to fast track Salbutamol in both companies for as little as US\$ 100,000. This is on the basis that the data already generated (for such aspects as pilot batch stability) can be used as the core of the documentation package. It is advisable to set a limit on the budget for this activity at a maximum of US\$ 100,000 to cover both enterprises. However, it is difficult to say in this case that a new design will not infringe the intellectual rights of the owner of the already tested MDI.

Based on successful technology transfers completed the following would be reasonable to be considered as provided for the budget set above. Technology transfer will be provided through the development of suitable replacement HFA MDI and the transfer of all know-how required to manufacture and test same as well as the selection of all materials and primary packaging components (valve, canister and actuator), excluding the secondary packaging components (carton, package insert etc.) including procurement of materials, components etc. for the formulation development and manufacture of up to three pilot batches for each formulation together with a reference placebo batch (minimum placebo 500 MDIs) against contribution from the two companies (US\$ 500,000).

It will be important to establish clearly defined Terms of reference for the technical support element of the project, to ensure a successful outcome.

The above deliverables can be converted in to a request for proposal (RFP) and provided to technology providers for quotation. It is unlikely that technology providers who have not already undertaken successful technology transfer programs would be likely to:

- a) Provide the degree of technical assistance required to minimise the risk to the program.
- b) Offer the support within the time-frame that the project requires.
- c) Achieve the levels of cost indicated.

Final conversion of CFC based MDI Salbutamol 200 dose, 100 µg/ dose label claim of Salbutamol Base (equivalent) at MosChimPharmPreparaty and the valve from a selected producer, for example VARI, Italy and Salbutamol Sulphate at Altayvitaminy and the valve and/ or specified in an acceptable manner as the Dose ex mouthpiece, if agreed will be performed.

### 6.3.2. Altayvitaminy

The Product has to be developed is Salbutamol 200 dose, 100 µg/ dose label claim.

All of the above to be suitable here for manufacture using a pressure filling process at Altayvitaminy.

NOTE: In the event that for any reason formulation of the above Active Pharmaceutical Ingredients (API) presents a problem. The proposal of an alternate API, with a rationale would be welcome for discussion. Since the MDI formulation processes are similar in their character the deliverables and key programme steps will be similar ones for the two Russian enterprises.

#### The Deliverables

- A full manufacturing product specification detailing all active components, excipients and packaging components, in addition full performance specifications and test methods will be disclosed
- Selection and rationale for the selection of the packaging components
- A report summarizing any intellectual property considerations that the proposed approach may have for the client.
- Formulation data package containing all process steps, sequences, temperatures etc.
- A report demonstrating scalability of the formulation package, up to a minimum of a 5,000 canister single manufactured batch.
- A limited stability study confirming acceptable stability performance (compliance with agreed specification) for a minimum of 6 months at 40C/ 75 RH.
- Fully detailed analytical methods required for manufacture and release of the product and associated training etc. to support technology transfer.
- Assistance in the verification of local implementation of analytical methods (supply of reference standards and samples, second site analysis).
- On-site support during the manufacture of up to three verification and/ or registration batches of the formulation).
- Chemistry, Manufacturing and Controls (CMC) data package from in-house activities, to support local market authorization filing by client.
- Support to the client with applications for clinical trial notifications, new drug applications or applications for marketing approval by the Russian regulatory body (RosSDravnadzor) for the CFC-free product Salbutamol.

#### Key programme steps

- Agree performance based product specifications for two different MDI Salbutamol developed product, between, Client/ Provider/ UNIDO. The objective is to replace the current CFC marketed product with an HFA equivalent product, that will meet the current regulatory requirements of the RF Health authority.
- Selection of all materials and primary packaging components (valve, canister and actuator), not the secondary packaging components (carton, package insert etc.). The selection process and evaluation **must** take in to consideration local and/ or current suppliers that may offer a more cost competitive product.

- Package and formulation development supported by short term performance data. Package to be reviewed with client/ UNIDO for acceptability prior to undertaking stability phase.
- Subject to agreement generation of a minimum of 6 months 40C 75RH un-protected stability/performance data on the selected package/ formulation. Full stability test data package to be reviewed with client/ UNIDO for acceptability.
- Generation of all required documentation and reports, technology transfer of all analytical and manufacturing methods.
- Verification of successful technology transfer of each product to client manufacturing facility. Including verification of analytical method transfer, assistance and training on-site of analytical and manufacturing personnel.
- Manufacture of Registration/ Stability batches (3) of the product(s).
- Submission to the RF Health Authorities for marketing approval.
- Market Launch of the new HFA formulation.

### Project Milestones

It is normal for this type of project for payment to be linked to clearly defined and measurable milestones. For example:

- Preparation and completion of the formal Work Plan for the formulation development of the HFA-MDI product, to include agreed and signed of product performance specifications, agreed and signed off test protocols and a detailed and signed off project plan.
- Development of the 2 Salbutamol HFA-MDI formulations, evidenced by formal signed and accepted test reports demonstrating compliance of the trial formulation batches to the agreed product performance specification, together with a summary report detailing formulation details, manufacturing steps and analytical methods developed.
- Successful completion of the production of batches for each of the HFA formulations evidenced by a summary report capturing the compliance of the product release samples to the agreed product release criteria, also evidence of the successful completion of training of key personnel with respect to formulation and analytical aspects of the formulations.
- Successful completion of the stability and full performance testing of the production batches for each of the HFA formulations evidenced by a summary report capturing the compliance of the products to the agreed stability and performance criteria.
- Submission of registration data to the Health Authorities, as evidenced by the submission of one application for marketing approval of the HFA formulations.
- Approval of one HFA formulated product by Rosdraznadzor including the presentation of a report summarizing the approvals.

If possible in any proposal consideration should be given in structuring the financial aspects of the proposal, such that clear links between the costs and these or similar milestones can be identified. This would significantly help in the generation of any subsequent contract.

## 7. Registration

Registration of the drugs in the RF is fully responsibility of Ministry of Health and Social Development (MOH) through its agency called RosSDravnadzor.

The process of registration is consisting of several steps including:

- ◆ Completion of all applicable forms.
- ◆ Submission of a suitable registration data package.
- ◆ Generation of suitable stability data (ICH Q1F Stability Data Package for Registration Applications in Climatic Zones III), on product that is representative of production.
- ◆ Bio-equivalence studies (if appropriate).
- ◆ Clinical trials (data if appropriate)
- ◆ Supporting samples.

Historically this process may have taken nearly 2 years to get approval for registration, from initial submission. As with many other international regulatory bodies RosSDravnadzor have implemented a streamlining programme. The initial objective is to reduce the approval times to around 6 months from full submission. Bearing in mind the international nature of this project RosSDravnadzor has already agreed to register this project within 3-6 months. Therefore, as soon as the first pilot production of the three batches is completed, all the documents and samples will be given to RosSDravnadzor for registration before the start of mass production at the two Russian MDI enterprises.

In October 2005 the technical committee of RosSDravnadzor finalized a decision to give Russian companies using CFC gas in pharmaceutical/ medical products a permission period until 2013 to replace the use of CFC with another substance. Any new propellant used must undergo for toxicity and safety tests, or have suitable data available from the suppliers to demonstrate its safety. Before CFC-free MDIs can be prescribed to patients they need to receive marketing authorization from RosSDravnadzor. Such authorization is only granted when the competent authority is satisfied that the proposed alternative product is safe and effective.

The government will review the license applications of non-CFC alternatives as fast as possible and if a non-CFC alternative contains the same dosage of the same drug substance, under the same administration route as the effective CFC MDI, then specified parts of the documents required for the application may be omitted. Data and documents originating in foreign countries can also be used for license application.

### 7.1. Preparation of Technical Dossier Required for non-CFC MDI Registration

On the basis of preliminary screening tests, the aerosol producer shall determine the substitution route according to the specific conditions (such as the properties and cost of alternative product), and apply for approval of modification of the medical excipient according to the Law of Drug Administration of the RF, the Regulations on Drug Registration, and the use requirement of the substitute. According to the Regulations on Drug Registration, different sets of technical documents shall be submitted corresponding to the following two cases of modification of medicinal adjuvant:

- a) the excipient was already approved in the RF for medical applications;

b) new medicinal excipient to be used first time in the RF (to register as new medicinal adjuvant, and determine the application type according to the actual conditions of the aerosol producers).

Table below lists the content of the dossier for application for change of excipient to a new one, already within the National Standards.

Technical Documents on Registration Application for Changing the Adjuvant of Medical Aerosol to a new one, already within the National Standard.

<b>Modification Item</b>	<b>Document Required</b>
Excipient of medical requirement approved for other products	1. Copy of drug approval certification documents and their appendix
	2. Certification documents
	3. Sample of revised <i>Package Insert</i> enclosed with detailed revision illustrations
	4. Sample of revised package/ label enclosed with detailed revision illustrations
	5. Documents of pharmacological research
	6. Real sample of drug
	7. Research documents & literature of genital toxicity research
	8. Research documents & literature of carcinogenesis research
	9. Domestic and relevant foreign overview of clinical trial documents
	10. Plan & scheme of clinical trial
	11. Clinical researcher manual
	12. Sample of Informed Consent, and approval document of Ethics Committee.
	13. Clinical Trial Report

Another Table below lists the content of dossier for Drug Registration Application for the Use of New Excipients.

Technical Documents required for Registration Application for Modifying the Adjuvant of Medical Aerosol

<b>Modification Item</b>	<b>Document Required</b>
New medicinal adjuvant	1. Name & naming basis of medicinal adjuvant
	2. Certification documents
	3. Objective & basis of topic establishment
	4. Summary & assessment of main research results
	5. Sample of <i>Package Insert</i> , drafting illustrations, and latest reference
	6. Design sample of package & label
	7. Overview of pharmacological research documents
	8. Research documents & literature of production process
	9. Research documents & literature verifying chemical structure or compositions
	10. Research documents & literature of quality research work
	11. Research documents & literature of drug-related compatibility
	12. Standard draft and drafting illustrations, with standard product or control product
	13. Inspection Report on 3 continuous batches of samples

	14. Research documents & literature of stability research
	15. Selection basis & quality standard of packing materials and containers in direct contact with medicinal adjuvant
	16. Overview of pharmacological & toxicological research documents
	17. Research documents & literature of pharmaco-dynamics influence on to-be-applied drug
	18. Research documents & literature of general pharmacological research
	19. Research documents & literature of acute toxicological research
	20. Research documents & literature of long-term toxicological research
	21. Research documents & literature of main local/systemic administration - related special safety test, such as allergy (local, systemic, and light), hemolysis, and local irritability (blood vessel, mucosa, muscle)
	22. Research documents & literature of mutagenesis research
	23. Research documents & literature of genital toxicity research
	24. Research documents & literature of carcinogenesis research
	25. Domestic and foreign relevant overview of clinical trial documents
	26. Plan & scheme of clinical trial
	27. Clinical researcher manual
	28. Sample of Informed Consent, and approval document of Ethics Committee.
	29. Clinical Trial Report

In accordance with the relevant regulations, each manufacturer has to make registration and get its license for their new MDI aerosol product based on its formulation and production process, though some products may also be produced by multiple manufacturers at Roszdravnadzor.

## 7.2. Good Manufacturing Practice (GMP)

Good Manufacturing Practice (GMP) is a core principle underpinning the manufacture of safe and effective medicines throughout the world.

Russia's service for the supervision of healthcare and social development (Roszdravnadzor) has prepared a plan that aims to complete good manufacturing practice (GMP) certification of all drug manufacturers Roszdravnadzor presented the draft GMP implementation plan at a 19 September 2007 meeting with the Ministry of Health and Social Development care and Social Development (MOHSD), the pharmaceutical industry and healthcare experts, summarized in the Information statement for Roszdravnadzor open hearings "On the Roszdravnadzor action plan concerning implementation of GMP standards in the pharmaceutical industry".

According to Roszdravnadzor, the majority of domestic pharmaceutical companies in Russia founded during the Soviet era or in the early 1990s have not yet started modernisation procedures that would make their drug manufacturing processes GMP compliant. Standardising the regulatory requirements for domestic and foreign drug producers is an essential part of the GMP certification process, since drugs registered in the country come from 1,264 factories located outside the Russian Federation. Thus, as well as inspecting domestic manufacturers, Roszdravnadzor has plans to inspect all foreign drug manufacturing sites. It is estimated this will require 407 additional inspectors and cost an estimated \$1.5-2 billion for staff training and implementation of new manufacturing procedures, among other things.

It is estimated that about one hundred stable enterprises in Russia provide 90% of the Russian pharmaceutical market in the country, but only 20% appear to be responding to the new GMP requirements. Further about 600 enterprises produce the 10% of the remaining volume and work with little commitment to the principles of GMP. It is improbable that many of these enterprises would be prepared to make the investment in equipment and resources to transition in to a position where they could meet GMP requirements.

In early 2010, following a majority vote of 393-1 in the lower house of the Duma - Russia's Parliament - Russia's new pharmaceutical bill was passed and moved forward for approval to the upper house and then to the President. And became law in September 2010.

The bill focus was to replace the existing 12-year-old pharmaceutical law. After much debate, 45 of the originally proposed 312 amendments have been included in the bill. The most controversial plans, such as the suggestion that additional clinical trials for innovative drugs must be conducted in Russia, were dropped.

The bills main aims were to improve regulation in the market, to ensure the country's pharmaceutical industry meets international production standards, to stimulate the domestic industry, to protect the market from counterfeit pharmaceuticals and guarantee affordable prices for consumers, as part of the government's wider modernisation agenda.

The bill will now standardise and stabilise medicine prices, and the government is to set a maximum price on 500 drugs, including those for tuberculosis and diabetes.

Diana Mikhailova, head of the Duma Committee on Pharmaceutical Market Development, commented at the time that "The main aim of the law is that we have quality medicine made by domestic producers," she added.

Under the bill, registration fees for new drugs in Russia will be cut from RUB 670,000 to RUB 300,000, a move that was welcomed by both domestic and international companies. In addition, the registration process should take no more than 210 days, considerably less than the current time of up to 18 months, which could see new drugs launch more quickly.

One key aspect of the bill states that by January 1, 2014, every pharmaceutical company operating in Russia must comply with European Good Manufacturing Practice (GMP) standards, and as imports currently account for around 75 per cent of Russia's pharmaceutical market, it is hoped that this will support the development of competitive domestic drug manufacturing.

According to Russia's Health Minister, Tatyana Golikova, in 2010 only 30 of the 400 pharma companies operating in the country are GMP compliant. The date for compliance has been extended from that proposed in the original version of the bill, which gave a 2012 deadline. Mikhailova has said that the state will assist in the transition to GMP to ensure medicines remain available to consumers during this period. However, analysts estimate that the costs to upgrade could run into billions of dollars.

### **7.3. Beneficiary Counterpart Funding**

There is significant investment required on the part of both the beneficiaries. Both companies have prepared an anticipated investment profile. The two beneficiaries have prepared cost estimates for the funding and investment that will be required on their part to complete the project. This is reflected in the table below (all Values are in \$000's).

Item	Altayvitaminy	Moschimpharm preparaty	Optional
Difference in actual cost of equipment and allocated amount as per company (see table of project equipment)	556	224	
<b>Preparation of normative and technical documentations:</b>			
Technology costs for preliminary in house development	14		
Technology costs in preliminary external development/ access		25	
Formulation optimization, Screening and pilot scale stability.	40	100	
Development of normative and technical documentation incl. draft of the enterprise pharmacopoeial article	15	15	
<b>Measuring equipment</b>			
Procurement of equipment to quality control testing/ release etc.	149		
Procurement of equipment for Laboratory scale manufacture (optimization, testing QC etc.)		364	
<b>Registration</b>	0	0	
Examination in Rosszdravnadzor	15	15	
Clinical tests	35	35	
Registration in MinZdravSotsRazvitiya (Ministry of Health and Social Development)	20	20	
<b>Batches production</b>			
Formulation Industrialization on Commercial line and manufacture of three stability/ registration batches Labour and Materials	65	65	
Pre-tests of the three stability batches and receipt of MinZdravSotsRazvitiya's (Ministry of Health and Social Development) permission for large-scale MDI production	20	20	
<b>Project management and engineering</b>			
Project Management (1 FTE)	50	50	
Engineering (3 FTE)	150	150	
Manufacturing (4 FTE)	160	160	
Laboratory (3 FTE)	150	150	
Office facilities, equipment and communications	25	25	
Project travel	25	25	
Development of MDI manufacture project meeting the GMP- requirements	50	50	
Dismantling of two existing aerosol lines	36		
<b>Auxiliary equipment</b>			

Procurement of equipment for production and use of water purified, compressed oil-free air, ventilation and air conditioning, power supply x 2			1660
Procurement of equipment for washing station, tank- and pipe-line chilling system	605	767	
Procurement of automatic in-line Check Weigher x 2			210
Procurement of automatic packing machine x 2			500
Clean room Construction work (GMP) x 2			160
Installation work and commissioning x 2			2600
IQ/OQ/ PQ for manufacturing equipment	100	100	
PQ and associated documentation for large-scale production	72	72	
Procurement and installation of functional testing and labelling equipment	408	408	
Total (two companies contribution to the project)	<b>2800</b>	<b>2800</b>	5130
Total including optional equipment and auxiliaries	<b>5,600,000</b>		
Grand Total:	<b>10,730,000</b>		

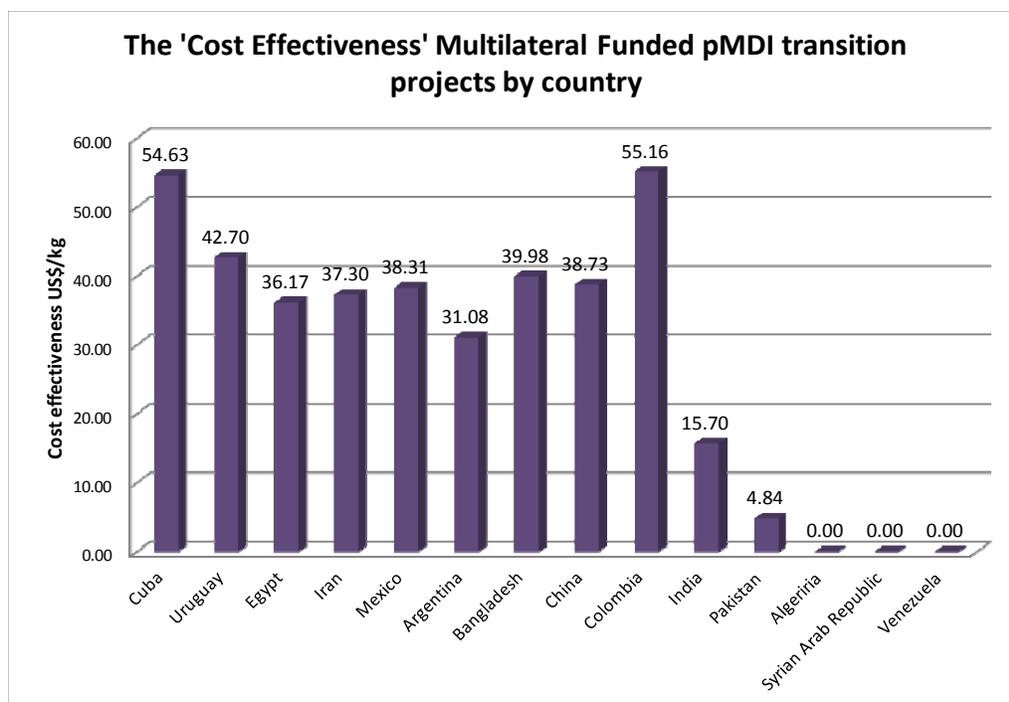
As shown in the table above, the counterparts (Altayvitaminy and Moschimpharmpreparaty) already agreed by the companies to provide funding of US\$ 5.6 million.

(Altayvitaminy and Moschimpharmpreparaty) agreed will be US\$ 5.6 million in kind. However, two counterparts' joint additional contribution to the project can be the US\$ 10.73 million. This amount additional and auxiliary equipment and services above Table, which required to ensure that the manufacturing operation meets the norms of current Good Manufacturing Practices. Although not an objective of this project, the two enterprises have to look at this issue in the future.

## 8. Environmental Impact

### 8.1. Ozone Depletion

Currently the Essential Use nomination for the Russian federation is 212 tonnes and based on the investment required to ensure that the transition project occurs (US\$ 2,550,000 –GEF contribution) the project results in a cost effectiveness of \$ 12.03/ kg of CFC use eliminated. Referring to the table below associated with the cost-effectiveness of the MDI projects being funded by the Montreal Protocol Multilateral Fund and with the exception of Pakistan where there was significant international stake-holding the cost effectiveness of the project for the RF would be better than all of the projects approved for Multilateral Fund assistance.



## 8.2. Global Warming

### 8.2.1. Replacement of current CFC products

In addition to Ozone Depletion, CFC propellants are significant Greenhouse gases. The following table is reproduced from Forster, and others, 2007: Changes in Atmospheric Constituents and in Radiative Forcing. In: Climate Change 2007: The Physical Science Basis. Contribution of Working Group I to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change.

Industrial Designation or Common Name (years)	Chemical Formula	Lifetime (years)	Radiative Efficiency ( $W\ m^{-2}\ ppb^{-1}$ )	Global Warming Potential for Given Time Horizon			
				SAR <sup>a</sup> (100-yr)	20-yr	100-yr	500-yr
Carbon dioxide	CO <sub>2</sub>	See below <sup>a</sup>	$1.4 \times 10^{-5}$	1	1	1	1
Methane <sup>c</sup>	CH <sub>4</sub>	12 <sup>c</sup>	$3.7 \times 10^{-4}$	21	72	25	7.6
Nitrous oxide	N <sub>2</sub> O	114	$3.03 \times 10^{-3}$	310	289	298	153
<i>Substances controlled by the Montreal Protocol</i>							
CFC-11	CCl <sub>3</sub> F	45	0.25	3,800	6,730	4,750	1,620
CFC-12	CCl <sub>2</sub> F <sub>2</sub>	100	0.32	8,100	11,000	10,900	5,200
CFC-13	CClF <sub>3</sub>	640	0.25		10,800	14,400	16,400
CFC-113	CCl <sub>2</sub> FCClF <sub>2</sub>	85	0.3	4,800	6,540	6,130	2,700
CFC-114	CClF <sub>2</sub> CClF <sub>2</sub>	300	0.31		8,040	10,000	8,730
CFC-115	CClF <sub>2</sub> CF <sub>3</sub>	1,700	0.18		5,310	7,370	9,990
<i>Hydrofluorocarbons</i>							
HFC-23	CHF <sub>3</sub>	270	0.19	11,700	12,000	14,800	12,200
HFC-32	CH <sub>2</sub> F <sub>2</sub>	4.9	0.11	650	2,330	675	205
HFC-125	CHF <sub>2</sub> CF <sub>3</sub>	29	0.23	2,800	6,350	3,500	1,100
HFC-134a	CH <sub>2</sub> FCF <sub>3</sub>	14	0.16	1,300	3,830	1,430	435
HFC-143a	CH <sub>3</sub> CF <sub>3</sub>	52	0.13	3,800	5,890	4,470	1,590
HFC-152a	CH <sub>3</sub> CHF <sub>2</sub>	1.4	0.09	140	437	124	38
HFC-227ea	CF <sub>3</sub> CHFCF <sub>3</sub>	34.2	0.26	2,900	5,310	3,220	1,040

Currently although the domestic manufactured CFC MDIs in the RF are only labelled to deliver 90 doses, they contain a significant amount of propellant. This is due to;

- a) The fact that they employ metering valves with a delivered volume of 100 $\mu$ l.
- b) The overage in the canisters 30 -35 “puffs” is consistent with industry practice but represents a high percentage as the MDIs are only labelled for 90 doses (as opposed to 200).

For 2010 the amounts of CFC consumed by the two enterprises in the RF were:

CFC	CFC Consumption tones	
	Moschimpharmpreparaty	Altayvitaminy
CFC-11	21.2	44.24
CFC-12	84.8	61.76

Applying this consumption to the equivalent CO<sub>2</sub> emission data known from many sources of information, the equivalent CO<sub>2</sub> impact (assuming constant 2010 usage levels) can be determined.

CFC	CO <sub>2e</sub>		CO <sub>2e</sub> (actual 2010)	
	20 Year	100 year	20 Year	100 year
CFC-11	6,730	4,750	440,411	310,840
CFC-12	11,000	10,900	1,612,160	1,597,504
Total			2,052,571	1,908,344

This shows that the manufacture of around 12 million CFC MDIs has a GWP impact (100 year CO<sub>2e</sub>) of 1.7 Million tonnes. As the HFA formulations considered currently for the RF are based on the use of 50 $\mu$ l valves and contain in the range of 12% v/v ethanol, then the volume of HFA filled per canister is below that of the current CFC products (approximately 13 grams). Further the GWP of HFA 134a is much lower than that of either CFC.

Assuming the same number of MDIs as in the above table (12.00 million), the GWP figures for the proposed HFA MDIs would look like as presented in the table below:

CFC	CO <sub>2e</sub>		CO <sub>2e</sub> (156 MT as per MDI Numbers)	
	20 Year	100 year	20 Year	100 year
HFA 134a	3,830	1,430	597,480	223,080
Total			597,480	223,080

The above picture is a conservative model, as it is based on a 1:1 replacement of MDIs. However the current domestic CFC MDI is only labelled to deliver 90 doses. The proposed HFA replacement would be labelled to deliver 200 Doses. If a 1:1 dose replacement model was followed, then this would represent a reduction in CO<sub>2</sub> equivalent emissions in the RF (100 year CO<sub>2e</sub>) of 2.1 Million tonnes or around 95%. However the reality lies between these two positions, it is probable that not all patients will use their MDI to end of label claim, therefore the equivalence model should lie between the above two positions. With either model considered the reduction in 100 year CO<sub>2e</sub> emissions is very significant.

This represents a reduction in CO<sub>2</sub> equivalent emissions in the RF (100 year CO<sub>2e</sub>) of 1,685,264 tonnes or around 88%.

## 8.2.2. In Comparison to Imported HFA MDIs

### 8.2.2.1 HFA propellant

The two leading HFA Salbutamol products imported in to the Russian Federation are based on an HFA suspension, which necessitates the use of larger amounts of HFA propellant, a canister with a thicker wall (more Aluminium) and an applied internal coating (requiring baking).

In addition to the cost savings associated with the use of a 50µl metering valve (as opposed to the current 63µl valve) and the replacement of a proportion of the HFA propellant with ethanol, the mass of HFA (a known Greenhouse gas) emitted to the atmosphere is reduced. Assuming that both the current HFA MDIs and those to be formulated in the future contain 240 actuations (200 labelled and 40 overage industry norm), then for the manufacture of 12,000,000 MDIs per annum, client would use 64 tonnes less HFA, if applying, for example for the purpose of calculations, one of the potential suppliers developed products (valve, canister).

The following is taken from the Final Report on U.S. High Global Warming Potential (High GWP) Emissions 1990-2010: Inventories, Projections, and Opportunities for Reductions. EPA High Global Warming Potential Gases. <http://www.epa.gov/highgwp/projections.html>.

“...HFCs and PFCs are powerful greenhouse gases. In order to achieve climate protection, it is important to **increase the efficiency of their** use, abate emissions, or find substitutes that are environmentally benign.”

Based on GWP values and lifetimes from 2007 IPCC AR4 p212, HFA 134a has the following GWP impacts

CFC	CO <sub>2e</sub>		CO <sub>2e</sub> (56 MT)	
	20 Year	100 year	20 Year	100 year
HFA 134a	3,830	1,430	214,480	80,080
	Total		214,480	80,080

### 8.2.2.2 Canister

The canister used in many HFA suspension formulations being imported has a thicker wall and is internally coated. Both of these factors increase the amount of energy (and hence liberation of CO<sub>2</sub>). It is possible to make some very basic calculations in this regard.

Additional Aluminum (approximately 25% more per canister), which translates in to 1.26 grms per canister. For a usage of 12,000,000 cans per annum, this translates in to an extra 15 tonnes of Aluminum. It takes four tonnes of bauxite to make two tonnes of alumina, which makes one tonne of aluminium, consuming around 15,000 kwh electricity equivalent to around 12 tonnes of CO<sub>2</sub>. Therefore the CO<sub>2</sub> emissions which would be saved in transferring to the V.A.R.I. & Co formulation approach, resulting from the use of less aluminium in the canisters is in the range of 180 tonnes. This is not generated in the Russian Federation but is liberated further up the supply chain.

Little data is published on the efficiency of the baking operation related to the application of the internal coating of the canisters. However a conservative estimate would be 5 kWh per 1,000 canisters. Therefore for 12,000,000 canisters per year, this would equate to a further 30,000 kWh (48 tonnes of CO<sub>2</sub>) saved using an HFA MDI formulation containing ethanol. The total direct reduction in CO<sub>2</sub> emissions based on the above calculations as a result of transferring to a domestically produced HFA/ ethanol formulation, is in the region of 228 tonnes, when compared to the imported HFA only suspension products.

Assuming that both the current HFA MDIs and those to be formulated in the future contain 240 actuations (200 labelled and 40 overage industry norm), then for the manufacture of 12,000,000 MDIs per annum, client would use 56 tonnes less HFA.

## **9. Financing Plan**

Initial approval from the GEF will include the funds necessary to cover the incremental capital costs, partial project equipment. The project is planned to be completed by June 2013 within 2 years period of time.

## **10. Project Impact**

This project will eliminate the use of 212 ODP tonnes per year (2010).

## **11. Project Implementation**

### **11.1 Management**

While the CFC MDI replacement technology will be sourced from appropriate centres of expertise using funds requested under the project, UNIDO 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 "Site Acceptance Test Trials (SAT)".

Any construction work and services required to accommodate and operate the equipment for the new CFC Free MDI aerosol technology will be carried out by the beneficiary enterprises. The relevant details are not reflected in the project document. The specifications for any construction work will be coordinated by the beneficiary enterprise 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 UNIDO project staff/ international expert(s).

## 11.2 Tentative Project Schedule

A preliminary project schedule has been generated based on feedback received from similar programmes from the past. **The top-level** plan is presented in the table below.

From GEF approval of the project to the launch of the first non CFC MDI is in the frame of 24 months. There will be a staggering effect for subsequent products as similar resources e.g. manufacturing equipment; personnel will be required for each formulation, registration. It must be underlined that these are preliminary estimates and would need to be reviewed by following appointment of the providers.

This means that the final re-formulated product would be launched potentially 3 – 4 months after the first product. The above timings are based on the assumption that by the time of submission the MOH/ Roszdravnadzor will be able to approve the new products quite rapidly. If this is not the case then it will have a direct impact on the programme timing. With respect to the project the launch of the MDIs is not the end of the story, there will be the need for completion of documents and associated activities and generation of a final report. Therefore an overall project duration of 30 months is realistic, but as emphasized, the above is depending on the approval timings by the Russian authorities.

N	Task name	2011	2012				2013				2014		
		4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q
1	Submission of the MDI project to GEF												
2	Approval of the MDI project												
3	Project document signature by two counterparts												
4	Implementation appraisal												
5	Signature of technology transfer contract												
6	Implementation of Technology Transfer Contract including 6 months stability tests												
7	New MDI development at two counterparts												
8	Project equipment bids requested												
9	Bid analyses, vendor selection												
10	Project equipment manufacture												
11	Equipment installation and commissioning												
12	Conduction of pilot equipment trials												
13	Purchase of project equipment by counterparts												
14	Conduction of pilot trials the filling lines												
15	Pilot batches manufacture (1500 pcs)												
16	Three commercial batches manufacture												
17	Conduction of 6 months stability tests of new MDI												
18	Registration of new MDI at Roszdravnadzor												

**Figure 12. Showing preliminary top level plan for the project**

Any construction work and services required to accommodate and operate the equipment for the new CFC Free MDI aerosol technology will be carried out by the beneficiary enterprises. The relevant details are not reflected in the project document. The specifications for any construction work will be coordinated by the beneficiary enterprise 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 UNIDO project staff/ international expert (s).

### 11.3 Milestones for Monitoring Project Implementation

Based on the above project schedule the key milestones are reproduced below.

TASK	MONTH*
(1) Project document submitted to beneficiary	1-2
(2) Project document signature	2-3
(3) Implementation Appraisal	3-4
(4) Signature of Contract for CFC-free MDI Technology Transfer	5
(5) Equipment Bid Documents prepared and Bids requested	5-6
(6) Bids Analysis, Vendor Selection, & Contracts Awarded	6-7
(7) Commence MDI Transition Strategy Activities	10
(8) MDI Manufacturing Equipment Delivered, Installed	8-12
(9) Commence Production of CFC-free MDIs on manufacturing equipment for Stability Testing, Clinical Trials, Registration, & Approval	13-18
(10) CFC-free MDI Approval	24
(11) Start of Commercial CFC-free MDI manufacture	24 >
(12) Post Market Surveillance Data Collection	26 - >
(13) Verification & Certification of Project Completion	30
(14) Confirmation of Destruction/Disablement of baseline CFC MDI equipment replaced with GEF funding	30
(15) Submission of Project Completion Report	30

\* As measured from project approval

## 12. Risk, Sustainability and Replicability

### 12.1 Risk

Assuming that the enterprises manufacturing CFC MDIs receive no financial assistance and as a result find it too commercially challenging to convert their products to HFA MDIs in the shorter term or at any point, then there are a number of potential risks which may be envisioned.

There is already a significant increase in the cost of pharmaceutical grade CFC propellant worldwide. As the global phase out of CFC in pharmaceutical MDIs is reduced the economies associated with scale manufacture will disappear and there is an expectation of very significant increases in the costs of CFC propellants in the future. As in a typical Salbutamol the propellant may account for 30-40% of the total cost of the MDI, then any increase in the cost of propellant will impact in the cost of the MDI.

Further by becoming totally dependant on an import based strategy for MDIs to support Russian patients. The logistics, supply chain and buffer stock issues mean that the risk of potential shortage within the national distribution chain will carry significantly higher levels of risk. The result of this would be patients who are dependant on the regular availability of essential medication, may be placed at risk. As the global phase out of CFC in pharmaceutical MDIs is reduced it is widely acknowledged that management of the supply of pharmaceutical grade CFC will be via very rigidly administered essential use nomination allowances. This will lead to significant limits on the availability of CFCs and no ability for companies to increase production to meet potentially increasing market needs. In the event that manufacture of MDIs ceased in the Russian Federation, then there is a current demand for MDIs in the region of 15 million per annum. If Russian patients are not to suffer shortages of essential medication then this quantity would need to be sourced from international companies. 15 million per annum is a significant quantity and may well exceed the current "spare" manufacturing capacity of the companies who may be interested in importing products into Russia.

Of equal importance to cost and availability of the medication to the patient is quality. In some circumstances an MDI may be a life saving medicine. As a result it is absolutely essential that any patient can rely on the quality and efficacy of the product in their hand. This is clearly recognized in the Russian Federation as is evidenced by the programme for the implementation of GMP.

It is evident that there is an increasing demand for MDIs in the Russian Federation, the prohibitive costs associated with an import only strategy may result in significant pressure to extend the period of essential use nomination (and hence use of CFC), so as not to endanger the lives of asthmatic patients. The potential market pressures that may result from lack of affordable MDIs, increases the opportunity for the ever increasing problems of counterfeiting occurring in the pharmaceutical industry. There is a risk that such counterfeit MDIs may be manufactured from illegal or sub standard stocks of CFCs, continuing the use of CFCs and exposing the patients to significant health risks.

The project must consider installing or upgrading the lab equipment to make sure both have adequate facilities for monitoring the quality of the HFA MDIs are available. The stability tests to be conducted at the both enterprises would demand some specific test equipment, which need to be procured or rented by the two Beneficiaries.

One of the key barriers to project implementation is the scale and complexity of the CFC production and consumption situation in the Russian Federation. Geographically the Russian Federation is the largest country in the world. Implementation of legislative frameworks required enactment across 9 federal states.

There is a risk that the number and variety of stakeholders to be actively engaged will result in lower than predicted speed of implementation or lower than anticipated replication across the Federation.

The lack of local institutional infrastructure to address the main CFC phase out issues must therefore be a priority in the initial stages of the project to ensure that as the investment and technology components are developed the institutional capacity to sustain and replicate activity across the Federation is in place. For technology transfer the both companies have to apply to the one pharmaceutical institution in the Ukraine. Time shows whether this Institute will successfully solve all the tasks associated with the technology transfer. There is a risk and it may delay the project implementation.

A number of elements of the programme are based on initial discussions with potential counterparts and technology suppliers. Whilst potential suppliers have agreed in principle to collaboration with the project, there is a risk that when the full details are negotiated there may be logistical or commercial reasons that would prevent a technology supplier or CFC/HFA supplier from collaborating. However there is more than one potential supplier for the majority of applications and therefore this risk can be minimised.

## **12.2 Sustainability**

The direct full phase out of CFCs will be achieved through the implementation of this capital investment project within the 2 years duration of the project. This project will provide a significant boost to the technical capabilities and awareness of the counterpart companies and will also achieve a significant proportion of the required phase out as counterparts will in general be the biggest consumers of CFCs.

A prerequisite for receiving assistance through the project will be to allow reasonable access and knowledge sharing (subject to appropriate commercial confidentiality) for other companies to gain an understanding of how to achieve economical conversion to non-CFC alternatives.

The principal activities of this programme are effectively self sustaining as they are based on the conversion of ongoing commercially viable enterprises. However given the range of scale and scope of CFC consuming companies, it is important to ensure that the appropriate range of technology options is made available so that the barriers to take up are minimised. For that reason the project will ensure that wherever possible low cost solutions are properly adapted and promulgated to small and medium enterprises.

The final phase out of all CFCs in the MDI sector requires longer term commitment and activity. The sustainability of the outputs of this programme will depend on the quality and effectiveness of the institutional capacity that is provided through the project. Significant emphasis has therefore been placed on establishing and maintaining an efficient and effective communications network for cross-functional stakeholders which will allow free access to information and technological know-how generated by technology transfer and implementation of investment projects in the RF. Furthermore the Ministry of Environment and Natural Resources fully endorses and embraces the knowledge sharing and technology transfer approach and is committed to providing sustained institutional support to facilitate the final CFC phase out in the RF and ongoing reduction of GHG emissions both directly and through the initiative and activities sponsored by Government and non-government organizations.

## **12.3. Replicability**

The project will provide visible demonstrations of the most appropriate technology for the phase out of CFCs in the MDI sector in the Russian Federation. Significant communication and information dissemination will contribute to the widespread knowledge and understanding of how this investment project can be replicated in similar enterprises, if any.

## **SECTION B**

### **Reasons for UNIDO Assistance**

The project is consistent with the country's priorities and is designed to build on the strengthened national monitoring and legislative system established for the implementation of CFC phase-out completed in 2000. The total phase of CFCs in the MDI sector is to be achieved by end of 2012.

The programme is based on GEF-5 Strategic program: Phasing out CFCs and Strengthening Capacities and Institutions.

## **SECTION C**

### **The Project Objectives**

The objectives of this project are:

- (a) to phase-out the consumption of 212 ODP tones of CFC-11 and CFC- 12 (2010)used in the manufacture of Aerosol Metered-Dose Inhalers (MDIs) in the Russian Federation through appropriate technology transfer and
- (b) to manage the transition from CFC- based MDIs to CFC-free MDIs in the country. The primary objective is the direct phase out of 212 ODP tonnes of CFCs (2010) in the medical aerosol sector in the Russian Federation.

The secondary objective is to reduce future GHG emissions by approx.1.9 MMT CO<sub>2</sub> t/equivalent, by introducing, through technology transfer a lower GHG propellant, HFC-134a. The two MDI companies in the RF will require technology transfer from one, or more, established multinational enterprises that have experience in the development and manufacture of MDIs using CFC-free technologies, and who have the right to transfer such technology to the Russian Federation (RF) 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 within the domestic market.

This proposal addresses the requirements for conversion of a manufacturing facility currently using CFCs to manufacture MDIs to one only using HFC -134a.

### **The UNIDO Approach**

The Government of the Russian Federation has requested UNIDO in 2009 to provide technical assistance to the two enterprises in converting CFC-based production of the MDIs into CFC-free one. UNIDO has been involved in the MDI conversion since 2006 when the first UNIDO project in the MDI sector was approved for Egypt. Then it was followed by the projects in China, Mexico and Iran. The first attempt was to negotiate with the GEF the return of already released funds by the WB. Although the GEF confirmed the return of funds, however, the unspent funds were already returned to the donor countries and any request for additional funding from the GEF needs to go through the established procedures. A project is urgently needed by the both companies to be equipped with new CFC-free equipment, which allows the use of HCF-134a propellant in the MDI production. The RF, moreover, applied to the Meeting of the Parties of the

Montreal Protocol in 2009 and 2010 for Essential Use Nomination of CFCs for the MDI production in 2010-2011.

There are three main barriers to achieving CFC phase-out and developing long term strategies to minimize the climate impact of alternative technologies in the foam and refrigeration and air conditioning sectors:

- i) insufficient institutional capacity at the two Russian enterprises
- ii) lack of knowledge of and local availability of suitable alternative technologies
- iii) Insufficient market drivers for environmentally friendly equipment and products.

This project represents the first comprehensive international effort to consider the entire scope of work required to achieve the total CFC phase-out in the RF and minimise climate impact taking into consideration both Montreal and Kyoto Protocols as well as National environmental policy and targets. The project is made up of a number of key work streams:

1. Technical assistance in converting a CFC-based MDI production to HFA –based MDI
2. Phase out of CFC consumption -212 MT (2010) in the Medical aerosol (MDI) sector
3. Technology transfer in developing a new HFA –based MDI
4. New developed MDIs registered at the Ministry of Health and Social Development.
5. Project management, monitoring and evaluation (2 years)

The work streams 2 and 3 respond specifically to the Strategic Programme on Technology Transfer and Climate change.

### **Rationale for GEF Intervention**

The Russian Federation, as the only CFC consumer in the MDI sector among the CEIT countries, requires further incremental technical and financial assistance of the GEF in strengthening of its institutional capacities and receiving practical experience on sustainable CFC phase-out obligations, specifically in the MDI sector.

The technology selected on the basis of the least costly and technically acceptable to phase-out CFCs will not necessarily be a technology, which provides the overall highest climate benefit. For example, a technology solution with HFA 134a propellant, which is only available technological solution applied in the pressurised MDIs have a GWP of 1300 and which is considerably lower than presently used CFCs.

The Russian Federation has demonstrated a significant commitment to the elimination of the use of Ozone Depleting Substances (ODS) in a number of industrial sectors. With the assistance of significant grants from the Global Environmental Facility (GEF) CFC manufacture has ceased in Russia and the use of CFC has been dramatically reduced. However the issues associated with the use of CFCs in MDIs were effectively deferred. It became evident that without some intervention in the form of financial assistance, it is most probable that the MDI projects would either continue to slip, or that the enterprises may be placed in a position where they have to consider ceasing manufacture of MDIs, as they are no longer commercially viable or the approved materials (CFCs) are no longer available. A number of reasons for the slippage in the programme for the development of HFAs have been cited, including

- Lack of funding from the procurement of equipment required to develop the new MDI formulations.
- Lack of funding for the procurement of new industrial scale equipment to produce stability batches etc. This equipment will also facilitate the adoption of GMP ways of working with respect to MDI manufacture.
- Significant personnel changes within the two companies that resulted in the loss of continuity and experience.
- A general lack of experience relating to the demands of developing a new type of a MDI with HFC-134a propellant (an HFA MD).
- Competing priorities for limited resources. The resources in place have commitments to existing production, manufacturing systems improvement e.g. Good Manufacturing Practices (GMP) and product development.

## SECTION D INPUTS

### D.1 Counterparts inputs

The GEF, as the financial mechanism will provide a proposed budget of US\$ 2,550,000 incremental cost funding for the project. The two Russian enterprises will commit US\$ 5,600,000 in kind contribution to the project. Additional amount of US\$ 5,130,000 in kind 000 (Phase II of the project) may be also contributed by the two counterparts to introduce GMP practices in production bringing the counterpart contribution to the total amount of US\$ 10,730,000. No Incremental Operating Costs (IOC) are considered in this project. They will be also covered by the counterpart companies.

### D.2 UNIDO Inputs

UNIDO has provided a contribution of US\$ 50,000 along with a GEF contribution of US\$ 50,000 for preparation of this project proposal.

## SECTION E BUDGET

### E.1 Project Budget

	<b>Project Preparation*</b>	<b>Project</b>	<b>Agency Fee</b>	<b>Total</b>
GEF	50,000	2,550,000	255,000	2,805,000
UNIDO	50,000			
Co-financing		5,600,000		5,600,000
Total	100,000	8,150,000	255,000	8,405,000

GEF Agency	Focal Area	Country Name	(in USD)		
			Project (a)	Agency Fee (b) <sup>2</sup>	Total c=a+b
UNIDO	ODS	Russian Federation	2,550,000	255,000	2,805,000
<b>Total GEF Resources</b>			<b>2,550,000</b>	<b>255,000</b>	<b>2,805,000</b>

UNIDO BL format

	GEF outputs	Budget lines	Description	Year 1	Year 2	Total
1	Technical assistance	11 50	International Experts	20,000	20,000	40,000
		15 00	Project Travel	5,000	5,000	10,000
			Sub-total			50,000
2	Phase out of CFC consumption	45 00	Equipment	2,300,000	0	2,300,000
			Sub-total			2,300,000
3	Technology transfer	21 00	Subcontract	70,000	30,000	100,000
			Sub-total			100,000
4	New MDI registered	11 50	International Experts		20,000	20,000
		21 00	Subcontract		30,000	30,000
			Sub-total			50,000
5	Project management	11 50	International Experts	15,000	10,000	25,000
		81 00	Monitoring and Evaluation		10,000	10,000
		15 00	Project Travel	10,000	5,000	15,000
			Sub-total			50,000
	<b>Total GEF funding</b>					<b>2,550,000</b>

## SECTION F

### Monitoring, evaluation, reporting and lessons learned

The Ministry of Natural Resources and Environment is responsible for the total CFC phase out in the RF and it has been involved in execution of the ODS Phase-out Programme of the RF. The Ministry of Health and Population is on-line Ministry to which the two Russian MDI enterprises are subordinated. This Ministry will be responsible for the final conversion of CFC-based MDI production to CFC-free MDI production at the two Russian enterprises, subject of this project, and for all necessary arrangements associated with control and monitoring of CFC-free MDI imports into the country.

A Project Steering Committee (PSC) will be formed at the inception stage of the project, the PSC, which will meet twice a year and be responsible for the overall strategic and policy guidance of the Project. A detailed schedule of project reviews will be developed by the project management team, in consultation with project implementation partners and representatives of the participating communities (for example, Russian Lung Association, etc.), during the early stages of project initiation. Such a schedule will include tentative timeframes for PSC meetings, and monitoring and evaluation of the Project activities by the PSC.

A detailed schedule of project reviews will be developed by the project management team, in consultation with project implementation partners and representatives of the participating communities (for example, Russian Lung Association, etc.), during the early stages of project initiation. Such a schedule will include tentative timeframes for PSC meetings, and monitoring and evaluation of the Project activities by the PSC. In order to use efficiently funds, it is suggested that this UNIDO CFC Phase out Project in the MDI sector can be also monitored by the Project Monitoring Unit (PMU) established for the HCFC Phase out Project in the Russian Federation, especially in organizing annual PSC meetings. The UNIDO office in Moscow will be a coordinator of the whole GEF programme in the RF including the monitoring this project implementation.



**Figure13. Project management structure**

The project management structure is given in Figure 13 above. The project will be subject to GEF Monitoring and Evaluation rules and practices of the GEF and UNIDO. The project management team and the UNIDO focal point will develop criteria for participatory monitoring of the project activities. Appropriate participatory mechanism and methodology for performance monitoring and evaluation will be established at the outset of the project. Evaluation activities will be based on the Logical Framework Matrix and the funds will be allocated for this purpose in the amount of US\$ 10,000 under the project management costs.

The overall M&E format for the project will follow the instructions and guidelines of the GEF M&E unit. In accordance with the GEF requirements, Quarterly Progress Reports will also be provided to GEF during the course of the project implementation. The M&E planned activities are presented in table below.

<b>M&amp;E Activities</b>		
<b>Type of M&amp;E activity</b>	<b>Responsible Parties</b>	<b>Time frame</b>
Inception Report	Project Management Team	No later than 4 months after project starts
Steering Committee Meetings	NPM UNIDO PM	Subsequently twice a year
Quarterly progress reports	UNIDO PM	Every three months
APR and PIR	NPM	Annually
Mid-term Review	UNIDO PM	At the mid-point of project implementation or after one year of the start of the project.
Terminal Project Evaluation and Report	Project Management Team UNIDO PM and M&E Branch	At the end of project implementation
Lessons learned	Project Management Team	At the end of project implementation
Visits to field sites	UNIDO PM Government representatives (UNIDO staff travel costs to be charged to agency fees)	Minimum yearly

### Project Inception Report

The inception report prepared by the project team will take place no later than four months after the project start-up. The report will include a detailed annual work plan with clear indicators and corresponding means of verification for the first year of the project, fine tuning of Terms of Reference (TOR) for project professionals, TOR for sub-contractual services, progress to date on project establishment and start up activities, amendments to project activities/approaches, if any, and it will be submitted to GEF.

### The Annual Project Report /Project Implementation Report

The Annual Project Report /Project Implementation Report in a prescribed format will be prepared and submitted annually by the project management as per guidelines set for the same. The Annual Project Report /Project Implementation Report will inform the annual review meeting (ARM) of the project, which will be held in conjunction with the annual Steering Committee meetings and should therefore be circulated to PSC participants well in advance. The final Annual Project Report /Project Implementation Report will be submitted to GEF as per standard procedures.

The independent mid-term project evaluation would focus on preparation of the MDI Salbutamol production at the two Russian enterprises with a new propellant HFC 134a including the technology transfer for the new product, equipment procurement and its installation. The final evaluation will focus on the results of the 6 months stability tests and clinical tests of the new MDI-Salbutamol product and its registration at the health authorities concerned.

Recommendations for follow-up activities would be included in each of these review processes.

While the CFC MDI replacement technology will be sourced from appropriate centres of expertise using funds requested under the project, UNIDO 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 labeled 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 "Site Acceptance Test Trials (SAT)".

## **SECTION G**

### **Legal Context**

**Production, consumption, circulation, export and import of ODSs in the Russian Federation are regulated by the following legislation:**

- Federal law of 04.05.1999 No. 96-FZ "About protection of atmospheric air". Article 16 of the law "It is prohibited to design, to place and to construct any object of economic or other activity, functioning of which may lead to unfavorable changes of climate or ozone layer."
- Federal Law of 10.01.2002 No.7-FZ "About Environmental Protection". In the Article 1 of this Law the ozone layer of atmosphere is referred as the main components of the natural environment, while by Article 4 – as the main targets of environmental protection from pollution, depletion, degradation, damage, destruction and other negative effects of economic or other activities. The Article 54 "Protection of the Ozone Layer" stipulates that the "protection of the ozone layer of the atmosphere of environmentally hazardous changes is effected through the regulation of production and use of substances that deplete the ozone layer of the atmosphere, in accordance with international treaties of

the Russian Federation, the generally recognized principles and norms of international law as well as the laws of the Russian Federation“.

- Resolution of the Government of the Russian Federation of 03.07.1992 No. 378 “About measures to enforce the obligations of the Russian Federation under the Vienna Convention for the Protection of the Ozone Layer and the Montreal Protocol on Substances that Deplete the Ozone Layer” it was decided to develop a state program for the production of ozone-safe freons and the assessment of funding required to conduct appropriate research and development.
- Resolution of the Council of Ministers - the Government of the Russian Federation dated 30.08.1993 No. 875 “About Approval of Regulations on Inter-Agency Commission for the Ozone Layer Protection under the Ministry of Environment and Natural Resources of the Russian Federation and the personal composition of the Commission” under the Ministry of Environment and Natural Resources of the Russian Federation an Inter-Agency Commission for the Ozone Layer Protection (hereinafter - the IAC) was established in order to organize and coordinate efforts to implement the program, as well as the actions of ministries, agencies, management, organizations and others to implement the international obligations of the Russian Federation in the field of the ozone layer protection.
- Resolution of the Council of Ministers - the Government of the Russian Federation dated 18.05.1994 No. 496 “About the Government Action Plan on Environmental Protection in 1994 – 1995” the Ministry of Environment and Natural Resources of the Russian Federation was entrusted with the participation of other ministries and departments to develop and submit to the Government of the Russian Federation of a Federal Target Program “The production of ozone-safe freons” in August 1994. In the absence of funding from the federal budget conversion program developed by Russian industry to ozone-safe substances and technologies was not adopted.
- Resolution of the Government of the Russian Federation of 24.05.1995 No. 526 “About the priority measures to implement the Vienna Convention for the Protection of the Ozone Layer and the Montreal Protocol on Substances that Deplete the Ozone Layer” Priority actions have been approved to comply with international obligations of the Russian Federation in the field of the ozone layer protection by 1995 - 1996. At the same time, the import and export of ODS and ODS-based products were banned to countries which are not-parties of the Montreal Protocol on Substances that Deplete the Ozone Layer. From 01.01.1996 compulsory licensing of imports and exports of ODS and ODS-based products in the countries that are Parties to the Montreal Protocol on Substances that Deplete the Ozone Layer was introduced.
- Resolution of the Government of the Russian Federation of 08.05.1996 No. 563 “About the regulation of import into the Russian Federation and export from the Russian Federation of ozone depleting substances and products containing them” the regulation of imports and exports of ODS and products based on ODS in the Russian Federation was approved.
- Resolution of the Government of the Russian Federation of 05.05.1999 No. 290 “About strengthening measures of state regulation of production of ozone-depleting substances in the Russian Federation” it has been established that starting from 01.08.1999 ODS production is carried out in accordance with the quotas approved by the State Committee of the Russian Federation on Environment Protection, together with the Ministry of Economy of the Russian Federation, and based on the calculated levels, timing and other requirements of the Montreal Protocol on Substances that Deplete the

Ozone Layer. The same decision also prohibits creation on the territory of the Russian Federation of new capacities for production of ODS after 01.07.2000.

- Based on the Order of the Government of the Russian Federation dated 26.11.1999 No. 1980-r the State Committee on Environment Protection of the Russian Federation has approved the list of urgent measures to gradually reduce the production and consumption of ozone depleting substances in the Russian Federation in 1999-2000.
- Resolution of the Government of the Russian Federation dated 09.12.1999 No. 1368 "About strengthening measures of state regulation of importation to the Russian Federation and the removal of the Russian Federation of the ozone depleting substances and products containing them", it was determined that since 01.03.2000 import of ODS in the Russian Federation and the export from the Russian Federation will be allowed only in the following cases:
  - Used as feedstock in chemical production;
  - For the main (critical) applications under the Montreal Protocol on Substances that Deplete the Ozone Layer;
  - In transit between the Parties to Montreal Protocol on Substances that Deplete the Ozone Layer.
- Resolution of the Government of the Russian Federation of 26.09.2000 No. 728 "About the Agreement between the Russian Federation and the International Bank for Reconstruction and Development Grant to fund Project "Special Initiative on Ozone Depleting Substances Production Closure in the Russian Federation". The signing of the Agreement between the Russian Federation and the International Bank for Reconstruction and Development of the grant for the Project "Special Initiative on ODS Production Closure in the Russian Federation" had been agreed.
- Resolution of the Government of the Russian Federation dated 19.12.2000 No. 1000 "About the refinement of the term of government to regulate the production of ozone depleting substances in the Russian Federation" has shifted some dates provided by decision of the Government of the Russian Federation dated 05.05.1999 No. 290, i.e. deadline at which the production of ODS in the Russian Federation is authorized only for use as feedstock in the production of other chemical products or for special occasions, the Montreal Protocol on Substances that Deplete the Ozone Layer was changed to 20.12.2000.
- Resolution of the Government of the Russian Federation of 27.08.2005 No. 539 "About adoption by the Russian Federation amendments to the Montreal Protocol on Substances that Deplete the Ozone Layer". The Russian Federation adopted the Copenhagen, Montreal and Beijing Amendments to the Montreal Protocol on Substances that Deplete the Ozone Layer.
- Resolution of the Government of the Russian Federation of 20.08.2009 No. 678 "About measures of the state regulation of import into the Russian Federation and export from the Russian Federation of ozone depleting substances".

The above resolutions and orders of the Government of the Russian Federation served a basis for the implementation in Russia of measures, allowed to return to a regime of compliance with the Montreal Protocol on Substances that Deplete the Ozone Layer in 2001.