EXPERT GROUP MEETING
ON
ELIMINATION OF CFCs CONTAINED IN
AEROSOL METERED DOSE INHALERS (MDI)
IN THE COMMONWEALTH OF INDEPENDENT STATES (CIS)
4-5 OCTOBER 2011

GEF/UNIDO PROJECT
Phase-out of CFC consumption in the Manufacture of Aerosol
Metered-Dose Inhalers (MDIs) in the Russian Federation
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The Global Problem

Hole in ozone layer (ozone depletion) is increasing

♦ Leads to increase in UV-B radiation-skin cancer, crop damage, marine phytoplankton decrease

Caused by ozone depleting substances that contain chlorine/bromine e.g. chlorofluorocarbons (CFCs)

♦ Most CFC use is for commercial and manufacturing (e.g. aerosols, air-conditioning, refrigeration, foam manufacture)

CFCs also in propellants of metered dose inhalers (MDIs) for asthma & COPD

♦ MDI CFC use has always been small

♦ Globally about 1–5% of total CFC use
The Global Solution

Montreal Protocol on Substances that Deplete the Ozone Layer, international treaty, 1987
Signed by 194 countries
Aims to control ozone depleting substances
Set phase-out schedule for CFC production and consumption worldwide
Global adoption and implementation, real international co-operation and progress
Final phase-out date set, January 1, 2010
PHASE-OUT SCHEDULE FOR DEVELOPING (Art. 5) COUNTRIES

1 July 1999: Freeze of CFCs at 1995-1997 average level
1 January 2002: Freeze of Halons at 1995-1997 average level
              Freeze of MeBr at 1995-1998 average
1 January 2005: 85% reduction of CTC from 1998-2000 level
                 50% reduction of CFCs and Halons from 1995-1997 level
                 30% reduction of TCA from 1998-2000 level
                 20% reduction of MeBr from 1995-1998 level
1 January 2007: 85% reduction of CFCs from 1995-1997 level
1 January 2010: Total phase-out of CFCs, CTC and Halons
                 70% reduction of TCA from 1998-2000 level
1 January 2015: Total phase out of MeBr and TCA
The Global Reality

- Even with successful implementation, ozone depletion will continue for some time
- Earlier CFCs continue to rise to stratosphere
- CFCs remain for 50-100 years
- Ozone layer will return to normal about 2050
- Transition to CFC-free MDIs varies between
  - Developed and developing countries
  - MDI manufacturing and importing countries
Montreal Protocol Achievements (Phase I)

Over the past 20 years global implementation of the Montreal Protocol has reduced the production and consumption of ODSs by more than 97%

Implementation of the protocol has also eliminated at base 11 billion tones of CO$_2$ equivalents

CFCs and Halons have been deployed over the past 50 years or more in various forms and in various types of user applications; such as refrigerators, air conditioners, fire extinguishers, and foam related products contain significant mount of ODSs being referred to as “ozone –depleting substance banks”

No legislation or other incentives requiring the capture or destruction of these substances in these banks
Montreal Protocol, UNFCCC and its Kyoto Protocol
The Montreal Protocol & the Kyoto Protocol

Production & Consumption are regulated under the Montreal Protocol

Ozone Depleting Substances

- CFCs
- HCFCs
- HFCs
- Halons
- etc.

Emission is regulated under the Kyoto Protocol

Greenhouse Gases

- CO₂
- CH₄
- N₂O
- PFCs
- SF₆
<table>
<thead>
<tr>
<th>Substance</th>
<th>Example</th>
<th>ODP (Ozone Depleting Potential)</th>
<th>GWP (Global Warming Potential)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFC</td>
<td>CFC 11</td>
<td>1.0</td>
<td>4,750</td>
</tr>
<tr>
<td></td>
<td>CFC 12</td>
<td>1.0</td>
<td>10,900</td>
</tr>
<tr>
<td>Halon</td>
<td>Halon 1211</td>
<td>3.0</td>
<td>1,890</td>
</tr>
<tr>
<td></td>
<td>Halon 1301</td>
<td>10.0</td>
<td>7,140</td>
</tr>
<tr>
<td>HCFC</td>
<td>HCFC 22</td>
<td>0.055</td>
<td>1,810</td>
</tr>
<tr>
<td></td>
<td>HCFC 141b</td>
<td>0.11</td>
<td>725</td>
</tr>
<tr>
<td></td>
<td>HCFC 142b</td>
<td>0.065</td>
<td>2,310</td>
</tr>
<tr>
<td>HFC</td>
<td>HFC 134a</td>
<td>0</td>
<td>1,430</td>
</tr>
<tr>
<td></td>
<td>(R407C)</td>
<td>0</td>
<td>1,774</td>
</tr>
<tr>
<td></td>
<td>(R410A)</td>
<td>0</td>
<td>2,088</td>
</tr>
</tbody>
</table>
CFC Phase out Programme in the RF Consumption Sector

The GEF/WB project to reduce the ODS consumption in the RF – Phase 1

- Project budget – US$ 60,0 million
- The project was prepared by the WB in 1996
- The project was completed - 1 July 2004
- Number of enterprises converted – 36
- Industrial sectors: refrigeration (80%), aerosols (100%), foam (80%) and servicing sector, no MDIs, no halons
CFC Phase out Programme in the RF Production Sector

The GEF/WB/Donor countries ODS phase out project in the RF as a Special Initiative– Phase 2

- Project budget – US$ 26.2 million (spent US$ 24.7)
- Project start – 2000
- Project completion – 2002
- Number of converted/closed enterprisers – 7
  by 12 by Dec. 2000
- Donors (USA – US$ 5.0 million, Japan – US$ 2.0 million, Finland – US$ 1.0 million, Italy – US$ 0.25 million, etc.
- The amount of US$ 2.3 million was not spent and allocated to the MDI sector (two MDI producers)
- This amount of US$ 2.3 was returned back to the WB/ GEF/ Donors
What are MDIs?

MDIs are small aerosols that deliver a dose of medication into the patient’s airways by inhalation.

Until recently, the MDI propellant contained CFCs.

Dry powder inhalers (DPIs) are also available:
- Have been used for a long time
- Contain no propellant

Not all patients can use DPIs.

Patient preference is important so MDIs and DPIs both need to be available.
Global Needs

♦ MDIs and DPIs needed to treat asthma (300 million people) and COPD (600 million people) worldwide
   - Available in developed and developing countries
   - Increasing use in developing and developed countries because the most effective treatment

♦ Necessary to develop efficacious, cost-effective and safe CFC-free alternatives
   - Pharmaceutical industry investment (US$ 2.0 billion) to develop CFC-free propellant over past 20 years
   - CFC-free MDIs contain hydrofluoroalkanes
Patient Health

♦ Patients need ongoing access to safe, efficacious and affordable inhalers
  - Absolute goal of phase-out

♦ DPIs are available in most countries
  - Cost may be an issue

♦ Transition from CFC-containing MDIs to CFC-free MDIs must be seamless

♦ Supply must be ensured at affordable price

♦ Doctors and patients must understand the reason for CFC-free transition

♦ Patients must remain confident in their medication
CFC production in the RF

Two producers of medical aerosols continue to operate, (Federal State Enterprise «MosChimPharmPreparaty», Moscow and «Altayvitaminy Ltd.», Altay Region in the RF and were reported to consume 240 MT of CFC-11/12 mixture in 2009.

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 for 2010 and received a quota of 105 MT in 2011. These two MDI producers are still consuming CFC-11 (solvent) and CFC-12 (propellant) for the production of the asthma rescue medicine – Salbutamol against ASTMA
Why is the GEF/UNIDO project important?

♦ Local CFC manufacture of MDI’s is not necessary to support the Russian domestic market. Imported non-CFC products are already approved in the Russian Federation and many competitive products are available from international companies.

♦ Support for local enterprises has both economic and patient support benefits.
## Market prices and market shares for both domestic and imported MDIs

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Manufacturer</th>
<th>Country</th>
<th>Packer</th>
<th>Стра на</th>
<th>Registration number</th>
<th>Registration date</th>
<th>Form</th>
<th>Registered price</th>
<th>Currency</th>
<th>Registered price in roubles</th>
<th>Wholesale price min-max</th>
<th>Retail price min-max</th>
<th>Sales (cans)</th>
<th>Weighted average registered price in roubles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthalin</td>
<td>Cipla Ltd</td>
<td>India</td>
<td>~</td>
<td>~</td>
<td>N015251/04</td>
<td>13.08.2008</td>
<td>MDI 0.1 mg/dose, 200 doses, 15 g.</td>
<td>2.29</td>
<td>USD</td>
<td>69.26</td>
<td>64.9</td>
<td>91-111</td>
<td>230,713</td>
<td>113.51</td>
</tr>
<tr>
<td>Ventolin</td>
<td>GlaxoSmithKline</td>
<td>Poland</td>
<td>GlaxoSmthKline Poland</td>
<td>ПН014212/01</td>
<td>01.06.2010</td>
<td>MDI 0.1 mg/dose, 200 doses,</td>
<td>107.41</td>
<td>roubles</td>
<td>107.41</td>
<td>106,27-126,96</td>
<td>121-168</td>
<td>1,848,369</td>
<td>no information</td>
<td></td>
</tr>
<tr>
<td>Salamol Eco</td>
<td>Norton Waterford</td>
<td>Ireland</td>
<td>IWAX</td>
<td>Czech Republic</td>
<td>ПН013290/01</td>
<td>24.12.2009</td>
<td>MDI 0.1 mg/dose, 200 doses,</td>
<td>98.5</td>
<td>roubles</td>
<td>98.50</td>
<td>81,37-116,50</td>
<td>94-373</td>
<td>693,238</td>
<td>no information</td>
</tr>
<tr>
<td>Salamol Eco Easy Breathe</td>
<td>Norton Waterford</td>
<td>Ireland</td>
<td>~</td>
<td>~</td>
<td>ПН014097/01</td>
<td>17.04.2007</td>
<td>MDI 0.1 mg/dose, 200 doses,</td>
<td>255.76</td>
<td>roubles</td>
<td>255.76</td>
<td>248,13-269,58, 526,08</td>
<td>108-362</td>
<td>224,121</td>
<td>no information</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>ZAO Altayvitaminy</td>
<td>Russia</td>
<td>~</td>
<td>~</td>
<td>Р N001105/01-2002</td>
<td>05.03.2009</td>
<td>MDI 0.1 mg/dose, 90 doses, 12 ml</td>
<td>43.89</td>
<td>roubles</td>
<td>43.89</td>
<td>34,00-97,69</td>
<td>45-115</td>
<td>4,944,320</td>
<td>4,530,662</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>Moschemfarmprparary im. Semashko</td>
<td>Russia</td>
<td>~</td>
<td>~</td>
<td>ЛС-001925</td>
<td>29.12.2006</td>
<td>MDI 0.1 mg/dose, 90 doses, 12 ml</td>
<td>57.58</td>
<td>roubles</td>
<td>57.58</td>
<td>62,97-75,59</td>
<td>39-115</td>
<td>7,781,436</td>
<td>6,646,224</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>ZAO Binnopharm</td>
<td>Russia</td>
<td>~</td>
<td>~</td>
<td>ЛСР-006937/10</td>
<td>21.07.2010</td>
<td>MDI 0.1 mg/dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15,722,197</td>
<td></td>
</tr>
</tbody>
</table>
MDI Salbutamol 99 dose, 100 µg/ dose produced at Moschimpharmpreparaty, Moscow and Altayvitaminy, Biysk
Installed filling machines at Moschimpharmpreparaty and Altayvitaminy.
A typical MDI showing the basic construction of the system

- **Canister**
- **Formulation comprising**
  - Propellant(s)
  - Excipient(s)
  - Co-solvent(s)
  - Active ingredient(s)
- **Metering valve**
- **Actuator/ mouthpiece**
Main components of a MDI

- 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 aluminum or stainless steel and sometimes internally coated
- The actuator/mouthpiece: holds the canister and through which the patient inhales the dose.
HFAs have proved to be “safer” than the CFCs

<table>
<thead>
<tr>
<th>Toxicity test</th>
<th>HFA 134 a</th>
<th>HFA 227ea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended workplace guide value</td>
<td>1,000 ml/m³</td>
<td>1,000 ml/m³</td>
</tr>
<tr>
<td>Acute inhalation toxicity</td>
<td>500,000 ppm</td>
<td>800,000 ppm</td>
</tr>
<tr>
<td>Cardiac sensitisation LOAEL</td>
<td>80,000 ppm</td>
<td>100,000 ppm</td>
</tr>
<tr>
<td>Effects on: pulse, blood pressure, ECG, lung function in human volunteers</td>
<td>No adverse effects after exposure levels up to 8,000 ppm</td>
<td>No adverse effects after exposure levels up to 8,000 ppm</td>
</tr>
<tr>
<td>Reverse mutation assay</td>
<td>Non-mutagenic</td>
<td>Non-mutagenic</td>
</tr>
<tr>
<td>Carcinogenitcity</td>
<td>Non-carcinogenic</td>
<td>Non-carcinogenic</td>
</tr>
</tbody>
</table>
Project objectives

The objectives of this project are:

(a) through appropriate technology transfer, to phase-out the consumption of 241.1 ODP tones of CFC-11 and CFC-12 used in the manufacture of Aerosol Metered-Dose Inhalers (MDIs) in the Russian Federation (RF) 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 241.1 ODP tonnes of CFCs (2009) in the medical aerosol sector in the Russian Federation. The secondary objective is to reduce future GHG emissions by approx. 2.0 MMT CO2 t/equivalent, by introducing, through technology transfer a lower GHG propellant. 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 with CFC-free propellant (HFC-134a).
Project tasks to be solved

♦ The new inhaler is 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 appearances, dosage and taste these do not imply any reduction in the effectiveness of the medicines.
Criteria to be met before the phase out of CFC MDIs in the RF

- Any new CFC free inhaler is at least as safe as the previous ones;
- 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;
- Post-marketing surveillance data must confirm the safety of the alternative product(s);
- There should be sufficient types of alternative(s) available to meet the needs of different patient sub-groups.
Non-CFC (HFA) Metered Dose Inhalers

<table>
<thead>
<tr>
<th>How non-CFC MDIs are the same?</th>
<th>How non-CFC MDIs are different?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safe and effective for the same previously approved uses</td>
<td>Ozone-friendly and do less damage to the environment</td>
</tr>
<tr>
<td>Shape is similar</td>
<td>The spray will be probably be slightly different in smell and taste</td>
</tr>
<tr>
<td>Size is similar</td>
<td>The spray will probably feel less forceful and warmer</td>
</tr>
<tr>
<td>Convenient to use</td>
<td>The inhaler may need to be cleaned and cared for differently</td>
</tr>
</tbody>
</table>
Factors considered in MDI re-formulation

Replacement HFA product

- Basic Approach
  - Solution
  - Suspension

- Purging
  - None
  - Vacuum
  - Propellant in can
  - Propellant through valve

- Filling approach
  - Single stage
  - Two stage
    - Cold Fill

- Post fill clean
  - None
  - Vacuum
  - Propellant fill

- Surfactant
  - None
  - Oleic acid
  - Sorbitan tri-oleate
  - Lecithin
  - PEG
  - Novel

- Stabilizer
  - None
  - Water
  - Acetic Acid
  - Citric Acid
  - Other

- Predicate product
  - Own CFC
  - Brand CFC
  - Brand HFA
  - Other
  - None

- Packaging components
  - Existing supplier
  - Enhanced performance
  - Coated

- Formulation preparation
  - Make and fill
  - Time
  - Temperature
  - Homogenization

- Product Profile
  - Number of actuations
  - Canister size
  - Dose Volume
Which is the best approach for a particular MDI product?

Is the drug soluble in the chosen solvents to the level required for therapy?

What is the solubility of the drug when the temperature range is considered?

Is the proposed solvent likely to be tolerated?

Is it possible to produce solid particles of the desired size to suspend commercially?

Is the proposed solvent compatible with the components of the container closure system?

If the drug is in solution is it more susceptible to degradation?

Is it possible to create an aerosol from the resulting solution (viscosity, surface tension, etc.)?

What happens to any residue of the formulation following operation (if the solvent evaporates does the drug coat on to fine flow paths?)

What manufacturing equipment and processes are available?
Intellectual Property Rights

Various patents are/were approved prior, and during the initiation of the HFA change over. For example, 3M -Co patented the use of Co solvents, University of Virginia- Surfactants. Glaxo- Internal pressure exerted within the can, etc. Most of these have been challenged and overturned in Europe. These, patents however have not been challenged in the North America -due to the high costs of mounting such a legal case in that part of the world.

It is UNIDO's strategy to utilise technology that will not infringe patents in the EU.
Which reference product?

OR
Don’t have to look the same to be equivalent
PROJECT FOUR ELEMENTS

National strategy
Government

Technology Transfer
Beneficiary

Incremental Operating Costs
Beneficiary

Equipment
UNIDO
Registration by medical authorities

1. APPLICATION FOR REGISTRATION
2. COMPOSITION FORMULA CERTIFICATE
3. CERTIFICATE OF ANALYSIS OF FINISHED PRODUCT
4. CERTIFICATE OF ANALYSIS OF ACTIVE INGREDIENT
5. PHARMACOPEIAL MONOGRAPH OR ANY SPECIFICATION FOR ALL COMPONENTS INVOLVED IN THE PREPARATION
6. METHOD OF ANALYSIS OF FINISHED PRODUCTS IN DETAILS (identification tests, related or degradation determination, chemical assay or microbiological assay of active ingredient, determination of any preservative or antioxidant included in the formula)
7. SPECIFICATION OF FINISHED PRODUCT
8. MANUFACTURING PROCEDURE
9. STABILITY STUDIES AT REFRIGERATOR, ROOM TEMPERATURE 40 & 45°C AND 75% RH FOR SEVERAL INTERVALS OF TIME (0, 3, 6, 9, 12, 18, 20, 24)
10. STABILITY PROTOCOL AND STABILITY INDICATING ASSAY
11. INSERT AND LEAFLETS
12. BIOAVAILABILITY OR BIOEQUIVALENCE STUDIES
13. CLINICAL STUDIES OR TOXICOLOGICAL ABOUT FORMULATION
Project equipment
Project equipment con-d
Estimated cost of project components

1. Cost of equipment

Altayvitaminy
a) One Filling line with two Macromat 1245 (Pamasol) with double/ single filling stages and automatic valve loader- US$ 1,200,000
b) Vacuum mixing vessel 150 liter – US$ 300,000
c) Automatic can loader- US$ 100,000
d) Weigher- US$ 20,000
c) Other equipment items (can sorter) – US$ 100,000

Sub-total: US$ 1,720,000

MosChimPharm Preparaty
a) Two Filling lines, each with Macromat 1245 (Pamasol) double/ single filling stages and automatic valve loader- US$ 1,200,000
b) Two Vacuum mixing vessels 150 liter – US$ 300,000x2=US$ 600,000
c) Automatic can loader- US$ 100,000
d) Weigher- US$ 20,000
c) Other equipment items – US$ 100,000

Sub-total: US$ 2,020,000

Total (equipment): US$ 3,700,000- 4,000,000
Thank you