EXPERT GROUP MEETING
ON
ELIMINATION OF CFCs CONTAINED IN
AEROSOL METERED DOSE INHALERS (MDI)
IN THE COMMONWELATH 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

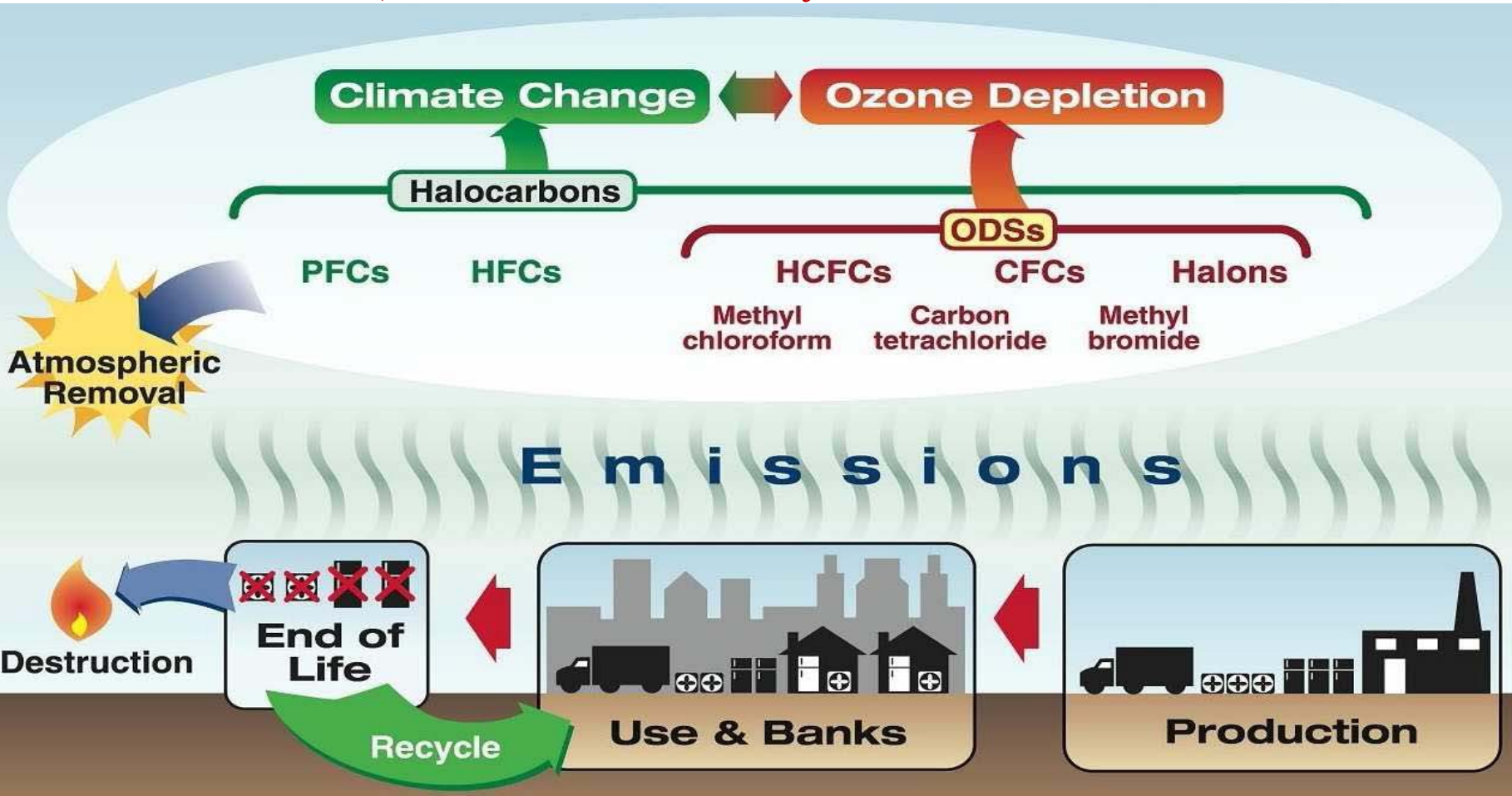
The Global Reality

- 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



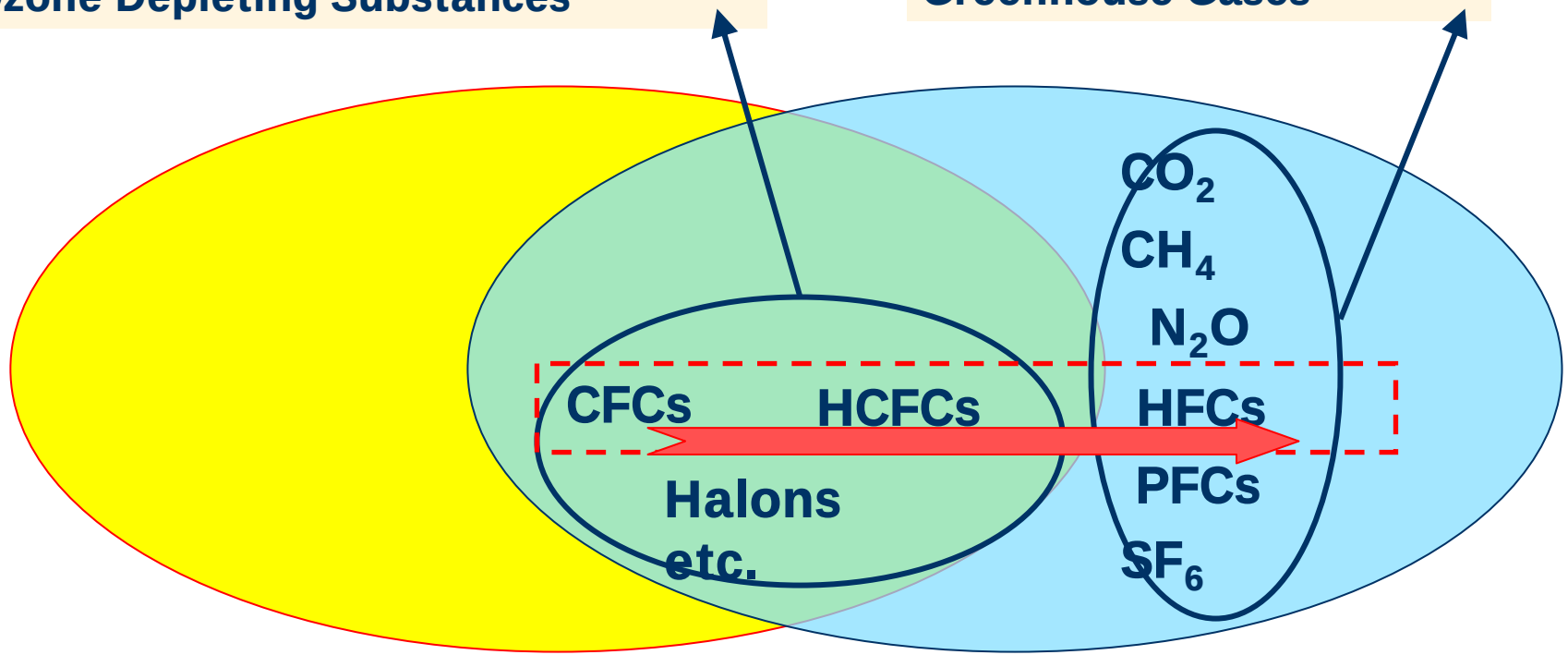
The Montreal Protocol & the Kyoto Protocol

Production & Consumption are regulated under the Montreal Protocol

Ozone Depleting Substances

Emission is regulated under the Kyoto Protocol

Greenhouse Gases



ODP & GWP

Substance	Example	ODP (Ozone Depleting Potential)	GWP (Global Warming Potential)
CFC	CFC 11	1.0	4,750
	CFC 12	1.0	10,900
Halon	Halon 1211	3.0	1,890
	Halon 1301	10.0	7,140
HCFC	HCFC 22	0.055	1,810
	HCFC 141b	0.11	725
	HCFC 142b	0.065	2,310
HFC	HFC 134a	0	1,430
	(R407C)	0	1,774
	(R410A)	0	2,088

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?

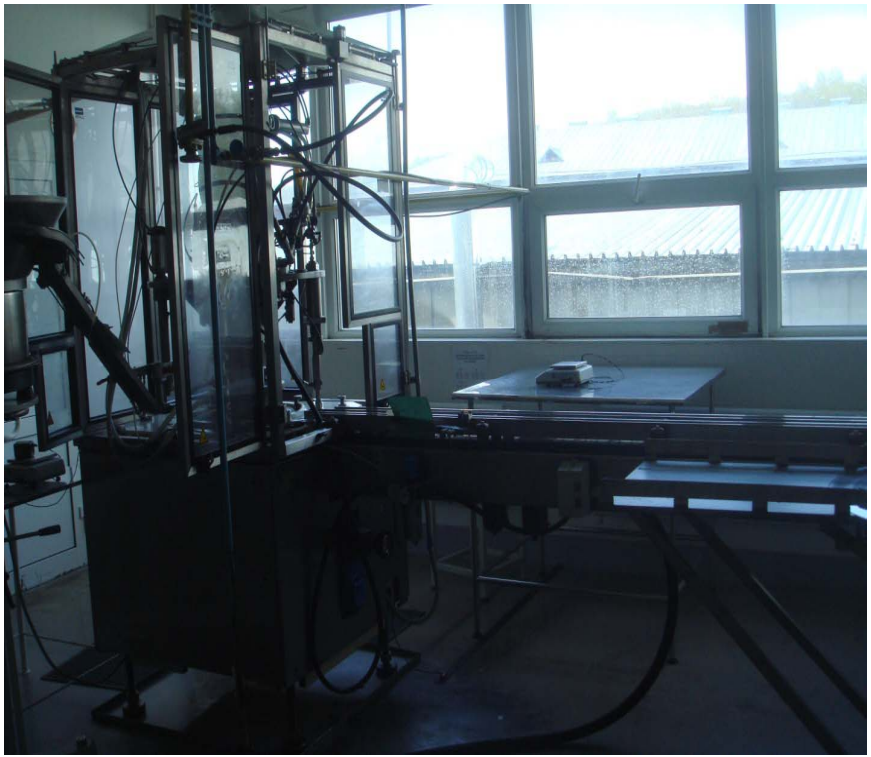
- Local CFC manufacture of MDI's is not necessary to support the Russian domestic market. Imported non-CFC products are already approved in the Russian Federation and many competitive products are available from international companies.
- Support for local enterprises has both economic and patient support benefits.

Market prices and market shares for both domestic and imported MDIs

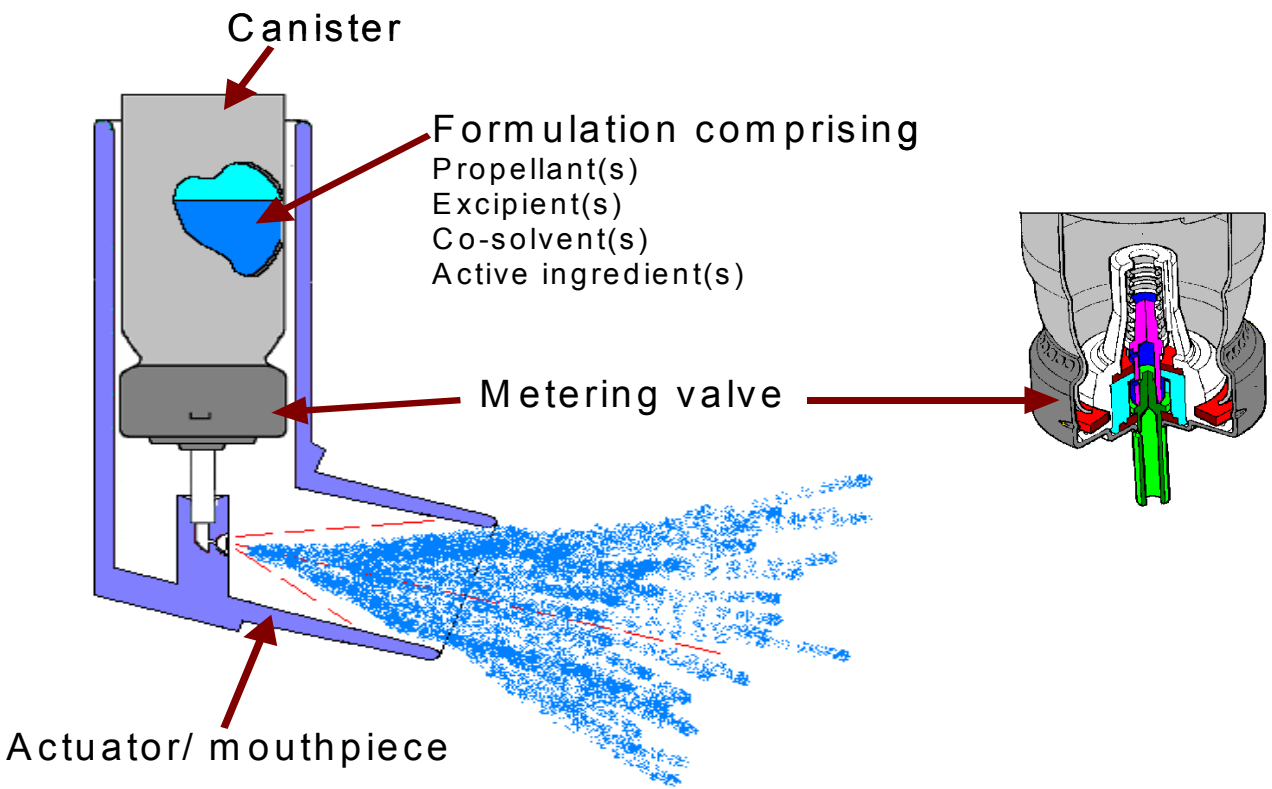
Brand name	Manufacturer	Country	Packer	Страна	Registration number	Registration date	Form	Registered price	Currency	Registered price in roubles	Wholesale price min-max	Retail price min-max	Sales (cans) 2008	Sales (cans) 2009	Weighted average registered price in roubles
Asthalin	Cipla Ltd	India	~	~	N015251/04	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	~	~	P 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	Moschemfarmpreparary 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 Binnopharn	Russia	~	~	ЛСР-006937/10	21.07.2010	MDI 0.1 mg/dose								
													15,722,197		

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



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

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

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.

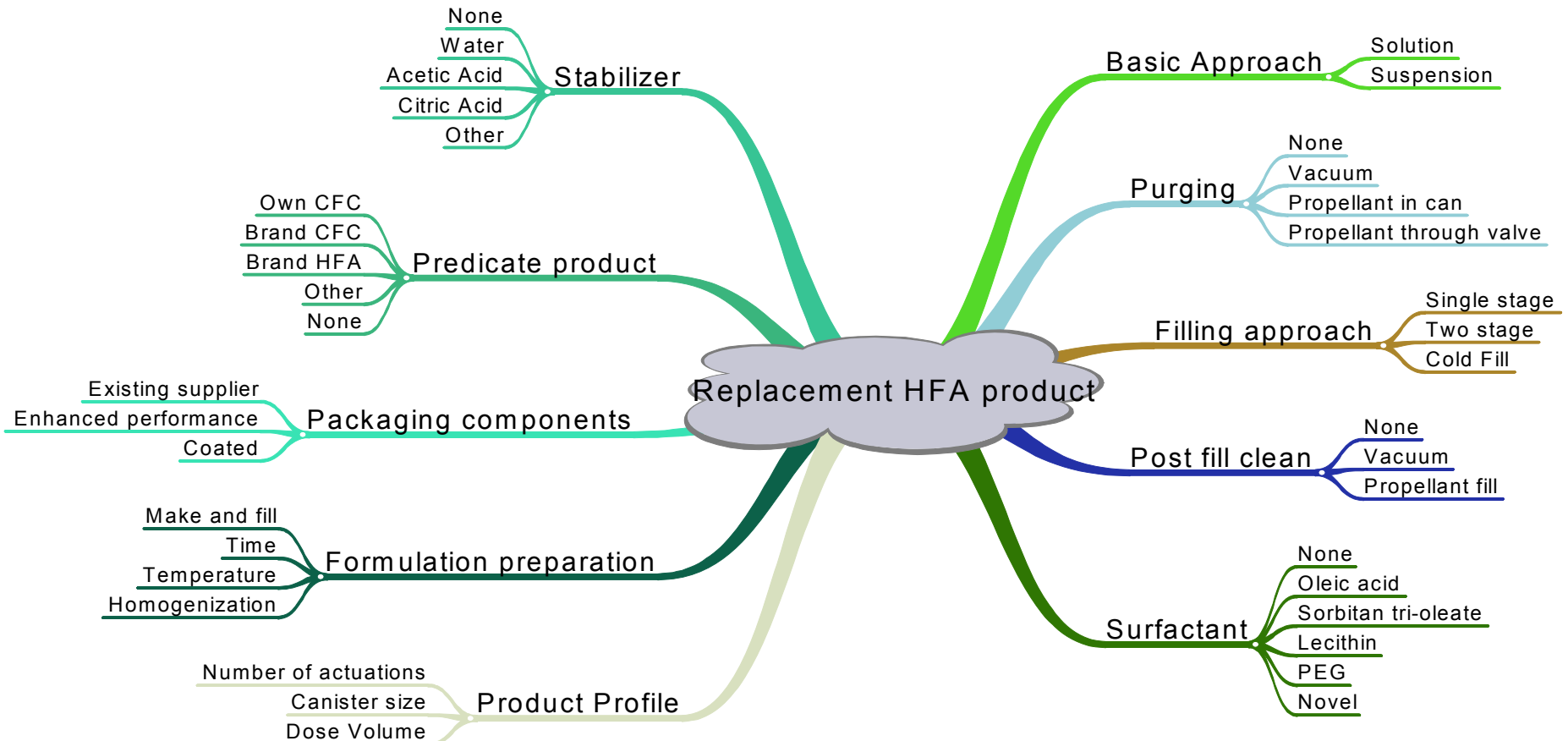
Criteria to be met before the phase out of CFC MDIs in the RF

- 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

How non-CFC MDIs are the same?	How non -CFC MDIs are different?
Safe and effective for the same previously approved uses	Ozone-friendly and do less damage to the environment
Shape is similar	The spray will be probably be slightly different in smell and taste
Size is similar	The spray will probably feel less forceful and warmer
Convenient to use	The inhaler may need to be cleaned and cared for differentely

Factors considered in MDI re-formulation



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.

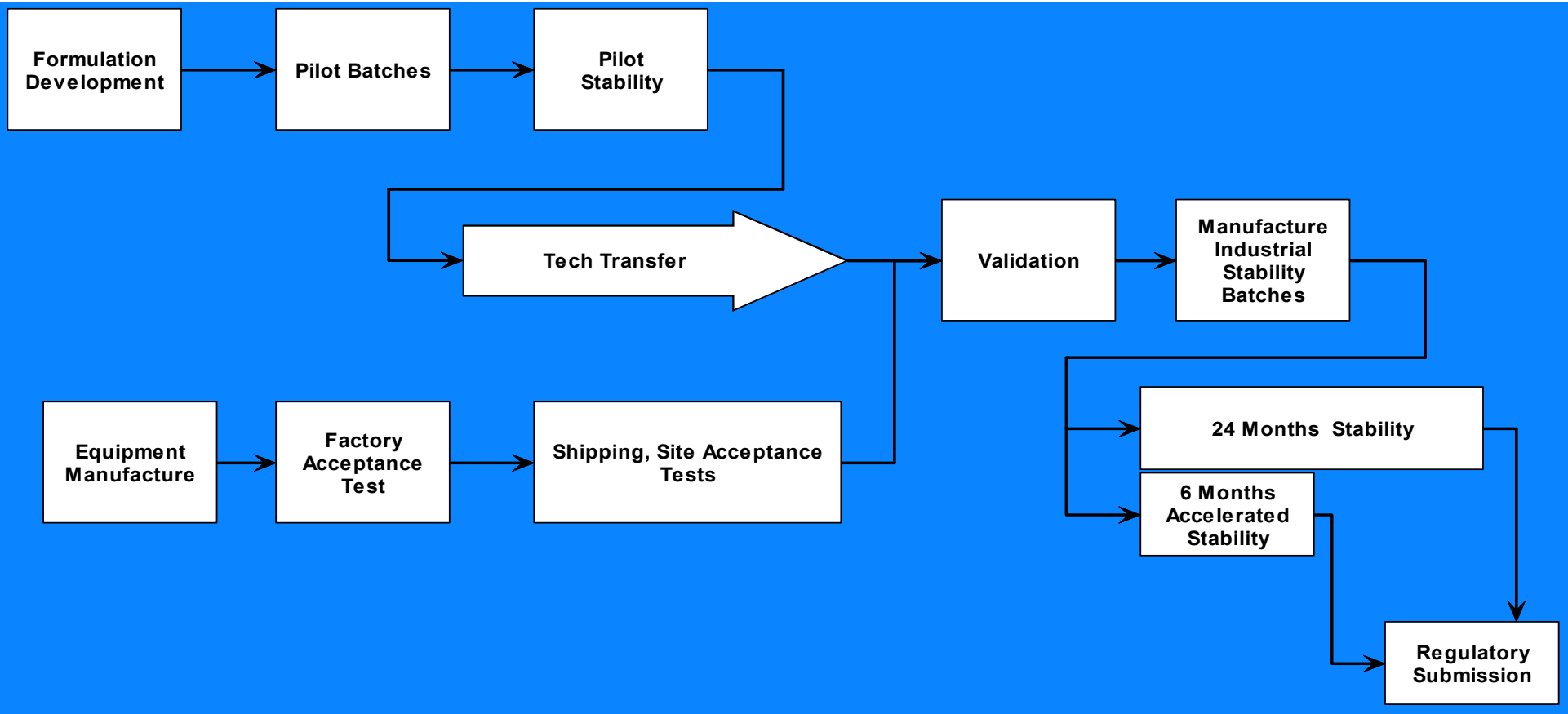
It is UNIDO's strategy to utilise technology that will not infringe patents in the EU.

Which reference product?

OR

Don’t have to look the same to be equivalent

Basic outline for provided technology
Project strategy



PROJECT FOUR ELEMENTS

National strategy
Government

Incremental
Operating Costs
Beneficiary

Technology Transfer
Beneficiary

Equipment
UNIDO

Registration by medical authorities

1. APLICATION 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 TEMEPERATURE 40 & 45^0 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