(*Translation from Russian*)

Ministry of Natural Resources of the Russian Federation
123995 Moscow, d-242, GSP-5
B. Gruzinskaya St. 4/6
Tel. (095) 254 1565
Fax : (095) 254 8283

12 November 2004

Ref.: BC-24-45/7789

Attn. : Ms. Megumi Seki (second transmission)

Dear Mr. Gonzalez,

The Ministry of Natural Resources of the Russian Federation has the honour to transmit 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.

Yours sincerely,

(*signed*) V.G. **Stepankov**
Deputy Minister of Natural Reources
of the Russian Federation

Mr. M. Gonzalez
Executive Secretary
Secretariat of the Vienna Convention on Protection of the Ozone Layer and
the Montreal Protocol on Substances that Deplete the Ozone Layer
P.O. Box 30552
Nairobi, Kenya

K0581783 130605

Ministry of Natural Resources of the Russian Federation

Ministry of Health and Social Development of the Russian Federation

Ministry of Industry and Energy of the Russian Federation

Federal Service for Environmental, Technological and Atomic Oversight

Foundation “Ozone-Depleting Substance Phase-out Investment Centre”

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

Moscow
2004

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

No.	Description of measure (area of activity – scientific research, design and testing; investments)	Executing bodies	Cost of measures in millions of roubles	Funding sources				
			Total	2005	2006	2007	Extra-budgetary sources	own resources
1	2	3	4	5	6	7	8	9
1.	Development of MDI composition for MDIs using HFC-227a as a propellant Scientific research, design and testing	Federal State enterprise N.A. Semashko Moscow Pharmaceuticals Co.	0.5	0.5				0.5
		Altaivitaminy Pvt. Ltd.	0.5	0.5				0.5
2.	Consultation with the State Applied Chemistry Centre and the B.P. Konstantinov chemical plant in Kirovo-Chepetsk on the technical instruction “Halon HFC-227a for the pharmaceutical industry” Scientific research, design and testing	Fiton holding company	0.1	0.1				0.1
3.	Orgnizing production of the halon HFC-227a in accordance with the technical instruction “Halon 227a for the pharmaceutical industry” Investments	B.P. Konstantinov chemical plant in Kirovo-Chepetsk	1.2		0.3	0.9		1.2
4.	Preparation of scientific, technical and regulatory documentation for the conduct of appraisals of the efficiency and safety of MDIs in the Federal State Scientific Centre for the Expert Appraisal of Medicinal Products and preclinical and clinical tests Scientific research, design and testing	Federal State enterprise N.A. Semashko Moscow Pharmaceuticals Co.	0.2	0.1	0.1	0.2		0.2
		Altaivitaminy Pvt. Ltd.	0.2	0.1	0.1			0.2
5.	Developing project documentation on the conversion of MDI manufacture to the ozone-friendly halon HFC-227a Scientific research, design and testing	Federal State enterprise N.A. Semashko Moscow Pharmaceuticals Co.	0.3	0.1	0.2	0.3		
		Altaivitaminy Pvt. Ltd.						

6.	Developing scientific and technical documentation regulating the use, repair and technical servicing of aerosol-filling operations with the use of the ozone-friendly halon HFC -227a	Federal State enterprise N.A. Semashko Moscow Pharmaceuticals Co.	0.3	0.1	0.2	0-3		
	Scientific research, design and testing	Altaivitaminy Pvt. Ltd.	0.3		0.1	0.2		0.3
7.*	Obtaining results of expert studies of project documentation conducted in regional offices of the Federal Service for Environmental, Technological and Atomic Oversight	Federal State enterprise N.A. Semashko Moscow Pharmaceuticals Co.	0-1			0.1		0.1
	Scientific research, design and testing	Altaivitaminy Pvt. Ltd.	0.1			0.1		0.1
7.	Conduct of subprojects for the conversion of MDIs to ozone-friendly halons**	Federal State enterprise N.A. Semashko Moscow Pharmaceuticals Co.	30.0		10.0	20.0	30.0	
	Investments	Altaivitaminy Pvt. Ltd.	20.0		8.0	12.0	20.0	
8.	Work to upgrade workshop facilities for storage of HFC-227a	Federal State enterprise N.A. Semashko Moscow Pharmaceuticals Co.						
	Investments	Altaivitaminy Pvt. Ltd.						
9.	Assembly and start-up work in aerosol filling shop	Federal State enterprise N.A. Semashko Moscow Pharmaceuticals Co.						
	Investments	Altaivitaminy Pvt. Ltd.						
10.	Running-in of equipment in operating conditions and trial run of filling lines	Federal State enterprise N.A. Semashko Moscow Pharmaceuticals Co.	0.5			0.5		0.5
	Investments	Altaivitaminy Pvt. Ltd.	0.5			0.5		0.5

* No. 7 is repeated in the Russian original [*translator's note*].

** Subject to the allocation to the Russian Federation of GEF funding and the signing of a corresponding agreement between the Russian Federation and the International Bank for Reconstruction and Development.

11.	Equipping of laboratory for quality control of HFC-227a and for finished product Investments	Federal State enterprise N.A. Semashko Moscow Pharmaceuticals Co.	0.5			0.5		0.5
		Altaivitaminy Pvt. Ltd.	0.5			0.50.5		
	Total		**57.7**	**1.5**	**19.1**	**37.1**	**50.0**	**7.7**

V.N. Tselikov

General Director,
ODS Production and Consumption
Phase-out Investment Centre

Explanatory note to 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

1. Introduction

In accordance with chapter 1, article 1, of the Federal Environmental Protection Act of 10 January 2002, No. 7-FZ (hereinunder referred to as "the Act"), the ozone layer of the atmosphere is one of the primary components of the natural environment, alongside the land, soil, surface and ground water, atmospheric air, plant and animal resources and other organisms, which in their totality ensure conditions propitious to the existence of life on Earth. Under article 4 of the Act, the ozone layer is included among fundamental elements of the natural environment to be accorded protection from pollution, depletion, degradation, damage, destruction and any other negative effect of economic or other activities. Article 53 of the Act, on protection of the ozone layer, states that "protection of the ozone layer of the atmosphere from environmentally hazardous changes shall be effected by regulating the production and use of substances which destroy the ozone layer, in accordance with the international treaties to which the Russian Federation is a party, with universally recognized principles and standards of international law and also with the law of the Russian Federation."

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 by 1 January 1996 and also to fulfil a number of other lesser obligations.

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. Since, to date, Russia lacks any technically or economically feasible alternatives enabling it to convert the production of metered-dose inhalers to ozone-friendly propellants, the consumption of CFC-11 and CFC-12 has continued to the present day in this sector of industry and will continue until 2008.

2. Demand for and actual use of metered-dose inhalers in the Russian Federation

Metered-dose inhalers are widely used in the prevention and treatment of a serious disease – bronchial asthma. Statistical records show that more than 100 million people in the world suffer from this disease. Despite the development and introduction of new effective medical anti-asthmatic treatments, over the last 10 years the incidence of the disease has grown by more than 50 per cent in many countries. 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. There are a number of factors responsible for this, most notably, the continuing problem of atmospheric pollution in industrial centres, viral infections of the respiratory tract, etc. As bronchial asthma infection rates grow, so too will the demand for treatment (tablets, capsules, injectable solutions and suspensions, sprays and other inhalation treatments).

Currently, inhalation treatment is the most effective treatment for bronchial asthma, with considerably lower systematic side-effects on the organism. Research has shown the effectiveness of metered-dose inhalers, manifested in improvements in external respiration, a reduction in the hypersensitivity of the bronchi, suppression of symptoms and a reduction in the frequency and severity of attacks. The prevention and treatment of bronchial asthma would be impossible without metered-dose inhalers.

The asthma inhalation treatments available on the Russian pharmaceutical market may be divided into two groups:

- Long-term anti-inflammatory prophylactic treatments;
- Emergency treatments (to arrest bronchial asthma attacks).

Demand in the Russian Federation for metered-dose inhalers in these two categories amounts to 18–20 million such inhalers per year.

Despite the fact that basic anti-inflammatory treatment has been defined as the fundamental treatment for bronchial asthma, the demand for anti-asthmatic drugs is following a somewhat different pattern. The overwhelming preference is for inhalation treatment intended to arrest bronchial asthma attacks – representing, in real terms, 88 per cent of demand – while only 12 per cent is constituted by demand for anti-inflammatory prophylactic treatments for […] ***(line missing in fax of original)*** – beclomethasone, budesonide, fluticasone, triamcinolone, formoterol, cromoglycic acid, salmeterol and others). Imported inhalers designed to suppress atatckes, manufactured under a range of trade names – fenoterol, ipratropium bromide, salbutamol, orciprenalin – make up 28 per cent of the market, while and locally made salbutamol-based inhalers, manufactured by the Altaivitaminy private company and the federal State enterprise N.A. Semashko Moscow Pharmaceuticals, make up 72 per cent. At the same time, the increase in the consumption of metered-dose inhalers consists largely of Russian-manufactured products, use of which increased in real terms from 2002 to 2003 by 205 per cent (while that of imported drugs increased by 120 per cent). This trend can be attributed to the limited purchasing power of the patients, which has as its consequence a continued deterioration in their health because of their inability to obtain any new and effective long-term treatments. Accordingly, sales of Russian-manufactured metered-dose inhalers are expected to continue growing over the next two or three years.

Figures compiled by the Russian Federal Pulmonology Centre 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.

3. Use of ozone-depleting substances in the manufacture of metered-dose inhalers over the period 1999–2004

ODS	**1999**	**2000**	**2001**	**2002**	**2003**
CFC-11	85.0	90.0	96.0	82.0	72.0
CFC-12	284.0	350.0	420.0	343.0	258.0
Total	**369.0**	**440.0**	**516.0**	**425.0**	**330.0**

4. Development of ozone-friendly metered-dose inhalers in the Russian Federation

At Russian firms manufacturing metered-dose inhalers, work is under way in accordance with duly ratified plans to phase out the use of ozone-depleting substances in the production of metered-dose inhalers by 2008. Currently, efforts are being undertaken in these firms to promote an ozone-friendly composition for the asthma drug salbutamol, used for emergency treatment of bronchial asthma. The ozone-depleting halons CFC-11 and CFC-12 are to be replaced with new propellants (HFC-134a and HFC-227a), which do not harm the ozone layer and whose production is permitted. The following work has been carried out:

- New compositions have been developed for new products;
- Draft pharmaceutical standards have been worked out for a firm producing an HFC-134a-based 200-dose salbutamol inhalation spray, giving 0.000120 g per dose;
- Specimens of HFC-134a and HFC-227a-based salbutamol sulphate treatments have been prepared and analysed throughout their shelf-life (two years);
- Agreements have been concluded on the supply of a new salbutamol formulation, the chemical formula of which will make it suitable for the production of new treatments;
- Technologies have been developed for the production of treatments and laboratory specimens of such treatments prepared;
- Quality control methods have been developed for the new treatments;

- Draft regulatory and technical documents have been drawn up for the conduct of expert studies and the registration of the medicinal products;
- Preclinical tests are being conducted by the Pyatigorsk Pharmaceutical Academy and the stability of the treatments in question is being analysed.

N.A. Semashko Moscow Pharmaceuticals and Altaivitaminy have developed the following ozone-friendly medical sprays and some production has begun (for which registration licenses have been granted):

- Ingalipt, a preparation which uses nitrogen as its propellant;
- Kameton spray, which uses a mechanical method to spray its active ingredient, dissolved in propylenglycol;
- [first line illegible] […] HFC-227a;
- Hiposolum, which uses the halons HFC-134a and HFC-227a as its propellant.

Work is also under way at the firms to introduce new long-term asthma treatments which do not use ozone-depleting propellants, such as beclomethasone, which is already being promoted on the market as follows:

- Agreements have been concluded on the supply of the substance beclomethasone;
- Intake monitoring and quality analysis methods have been developed for the substance;
- Technology for its preparation has been developed and laboratory specimens prepared;
- Quality control methods have been developed for the product;
- Preclinical trials have been conducted;
- A package of regulatory and technical documents is being prepared, for the conduct of expert studies and registration of the medicinal product.

5. Availability in the Russian Federation of imported ozone-friendly metered-dose inhalers and other alternatives

Currently, ozone-friendly metered-dose inhalers using the halon CFC-134a and absolute (anhydrous) ethanol, and also the halon HFC-227a are manufactured by such firms as Norton (United Kingdom) and Chiesi (France); and also by ASTA Medica, Aventis, Boehringer Ingelheim, Otsuka, Fujisawa, Cipla, Aldo Union, Chiesi and others. At the same time, only a few of the ozone-friendly metered-dose inhalers manufactured by these firms have been registered in the Russian Federation: salbutamol, an asthma drug, and beclomethasone, an anti-inflammatory, anti-allergenic, anti-oedema and anti-asthma treatment – by the firm Norton (United Kingdom), beclomethasone by the firms Chiesi (France), intal, an anti-allergenic treatment, by the firm Aventis, which is manufactured in the United Kingdom by the firm Rhone-Poulenc Rorer and others.

A fairly wide range of imported asthma treatments is available on the Russian pharmaceutical market, where they have about a 33 percent share. The State register of medicinal drugs lists 268 trade names for bronchial asthma treatments and 34 international unpatented treatments. Statistics on the import of medication to the Russian Federation in 2003 indicate that some 80 patented inhalers for bronchial asthma treatment and 11 unpatented international treatments (sprays, aerosols, inhalation suspensions, turbo-inhalers, nebulizers etc.) are imported.

The costs of imported drugs range from 80 to 531 roubles (2.7 to 18 US dollars) per item. The average price of Russian-manufactured salbutamol fluctuates between 24 and 31 roubles (0.8 and 1.1 US dollars).

Accordingly, notwithstanding the reasonably wide range of imported asthma drugs available on the Russian pharmaceutical market, the share of their actual use is relatively low because of their high cost and the low purchasing power of the population.

N.A. Semashko Moscow Pharmaceuticals and Altaivitaminy obtain CFC-11 and CFC-12 from the Fiton 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.

Currently, Russian metered-dose-inhaler manufacturers are reviewing the possibility of undertaking the manufacture of HFC-227a, suitable for use as a propellant, on a trial basis at the State Applied Chemistry Centre and the B.P. Konstantinov chemical plant in Kirovo-Chepetsk. Attention is also being given to the possibility of obtaining HFC-134a and HFC-227a from the company Solvay in Germany, which supplies these halons to other countries of Europe and to the United States of America. These substances have not been properly registered in the Russian Federation, however. A master file for the halon HFC-134a will be developed by Solvay in 2006 and for the halon HFC-227a no sooner than 2010.

6. Current rules for the registration of metered-dose inhalers in the Russian Federation

The State registration of medicinal treatments (including metered-dose inhalers) in the Russian Federation is regulated by the Federal Medications Act, No. 86-FZ, and also by various subsidiary enactments and sectoral regulations and guidelines.

The functions of registering metered-dose inhalers are performed by the Federal Health and Social Development Oversight Service (hereinunder – "the Federal Service"), under whose authority expert appraisals of medicinal products are carried out by the Federal State Scientific Centre for the Conduct of Expert Appraisals of Medicinal Products, the Pharmacopoeia Committee and the Pharmacological Committee.

Any enterprise wishing to manufacture a medicinal product completes an application attaching the registration file, comprising the following set of documents compiled in the prescribed manner:

1. Draft regulatory and technical documentation (the pharmaceutical standards of the enterprise);

2. Draft instructions for use of the medicinal product;

3. Mock-up of the commercial product;

4. Suggested wholesale price;

5. Documentation (reports) on preclinical trials of the medicinal product;

6. Production prototypes and samples of the medicinal product for the conduct of pharmaceutical and toxicological assessments (for quality, effectiveness and safety);

7. Samples of the medicinal product for the conduct of clinical tests (if such tests are indicated in the expert appraisal);

8. Other materials requested by expert organizations in the process of considering the application.

Under the rules and procedures for the registration of metered-dose inhalers in force in the Russian Federation the following measures must be taken:

1. Submission to the Scientific Centre for the Conduct of Expert Appraisals of Medicinal Products of the set of documents, including the product file (results of preclinical and clinical trials, scientific and technical documentation, technological regulations, etc.) and the manufacturer file (license to manufacture, etc.);

2. Expert appraisal of documents by the Scientific Centre for the Conduct of Expert Appraisals of Medicinal Products;

3. Expert appraisal of the product samples submitted;

4. Conduct (where necessary) of clinical analyses in medical clinics recommended by the Pharmacological Committee;

5. Issuance of a registration licence for the product (upon obtaining the go-ahead from the Pharmacopeia Committee and the Pharmacological Committee);

6. Expert appraisal of the product itself and of the active substance by the Scientific Centre for the Conduct of Expert Appraisals of Medicinal Products;

7. Obtention of a permit for the import of the product (where it is to be imported into the Russian Federation).

Once the expert appraisal has been completed, the Federal Service prepares the registration licence, and the medicinal product is included in the State register. Ratified copies of the scientific and technical documentation and of the instructions for use are attached to the registration licence.

As a parallel exercise, the company develops technical documentation (technical regulations, instructions, route maps, etc.) and conducts a study of the health standards relating to the substances being used (where such information is still lacking).

7. Planned measures to reduce emissions of ozone-depleting substances in the process of manufacturing metered-dose inhalers over the period 2005–2007

Over the period 2005–2007, Russian metered-dose-inhaler manufacturers plan to carry out the following measures to reduce emissions of ozone-depleting substances:

1. Reducing losses incurred in pumping, cleaning and drying CFC-11 and CFC-12 (by bringing these into line with Russian Federation standards);

2. Replacing worn and obsolete equipment used to transport and pump ozone-depleting substances in workshop containers;

3. Sealing the joints of reactors used to prepare production solutions;

4. Replacing equipment used for the manufacture of metered-dose inhalers with new equipment (filling lines, seal inspection units, etc);

5. Working with the suppliers of cylinders and aerosol valves to ensure their improved quality and reliability;

6. Tackling the problem of recovering halons from reject aerosol products with a view to their reuse.

Companies are giving attention to the possibility of purchasing new [text illegible] for the period 2006–2008, which may make possible the production of treatments using propellants (halons and nitrogen) and those which do not use them (mechanical pumps).

Planned reduction of ozone-depleting substances in emissions occurring in the manufacture of metered-dose inhalers over the period 2005–2007

	2003	**2004**	**2005**	**2006**	**2007**
ODS consumption, tonnes	330.0	378.0	336.0	286.0	243.0
Losses, emissions,	72.6	68.0	54.0	40.0	32.0

tonnes (%)	(22%)	(18%)	(16.0%)	(14%)	(14.0%)
Use in MDI production, tonnes	257.4	310.0	282.0	246.0	211.0

8. Non-governmental organizations active in the Russian Federation whose activities are concerned with the phase-out of the use of ozone-depleting substances in the manufacture of metered-dose inhalers

The private enterprise Altaivitaminy and the Federal State enterprise N.A. Semashko Moscow Pharmaceuticals form part of the Moscow Bioprom association, whose members include virtually all Russian pharmaceutical manufacturers and all manufacturers of medical aerosol products. The Bioprom association has on several occasions reviewed issues relating to the phase-out of the use of ozone-depleting substances in the manufacture of metered-dose inhalers and other aerosol products. Proposals on this matter have been addressed to the Government of the Russian Federation and the Russian Ministry of Health.

9. Procedures and rules in force in the Russian Federation which must be observed when placing medicinal products on the markets

The process of placing any medicinal product on the Russian markets is regulated by the Federal Licensing (diverse products) Act, No. 128-FZ, and the regulations on the licensing of the manufacture of medicinal products, ratified by decision No. 500 of the Government of the Russian Federation of 4 July 2002.

Companies manufacturing metered-dose inhalers must complete the following steps before releasing any new product or product whose composition has been altered:

1. Formulating methods and conducting incoming quality tests of the substance;

2. Refining the product composition and the technology for the manufacture of the new product in laboratory and production conditions;

3. Developing and introducing quality control methods for the product;

4. Conducting studies of the stability of the product;

5. Conducting preclinical studies of the product;

6. Compiling draft production regulations;

7. Preparing the set of technical regulatory documents for the product and submitting it to the Scientific Centre for the Conduct of Expert Appraisals of Medicinal Products for the conduct of an expert appraisal and the registration of the medicinal product (new products using CFC-11 and CFC-12 as propellants are not accepted for expert appraisal);

8. Arranging for the conduct of expert studies of specimens of the new product and, where necessary, clinical studies in medical clinics recommended by the pharmacological committee.

Once the registration licence has been received, the company:

1. Proceeds to the production of the first batches (series) of the metered-dose inhaler products;

2. With the authorization of the Federal Service, transmits samples of the first three [? – *original illegible*] batches (series) of the products and samples of the active substances in the prescribed manner for preliminary monitoring by the Scientific Centre for the Conduct of Expert Appraisals of Medicinal Products;

3. Obtains the written finding of the Federal Service, removing the products from the preliminary monitoring procedure and transferring it is to a periodic random sampling process (in accordance with the statute in force);

4. Submits an application to the Federal Service for a permit authorizing the release of the medicinal product and confirming the preliminary quality, effectiveness and safety control procedures;

5. Submits an application to the Federal Service for an amendment to the existing license for the manufacture, storage and use of the medicinal product;

6. Submits samples of the production batches for State certification, with a view to the preparation of a certificate for each batch (series);

7. Releases the medicinal product on to the market, accompanied by an analysis sheet and a State certificate of the prescribed type.

10. Planned measures to raise awareness among patients, physicians, pharmacists and others of new ozone-friendly metered-dose inhalers and of the procedures for their use

Companies manufacturing metered-dose inhalers include in their organization marketing departments which deal with the promotion of medicinal products on the market. The following steps are to be taken by these departments over the period 2006–2008 to raise awareness among specialists and patients of new Russian-manufactured ozone-friendly metered-dose inhalers:

1. Participation in annual trade exhibitions ("Pharmacy Fair", "People and Medicines" and others);

2. Participation in scientific conferences and seminars in the Russian Federation and abroad;

3. Work by representatives of N.A. Semashko Moscow Pharmaceuticals and Altaivitaminy in different regions of the country with physicians, pharmacists, pharmaceutical wholesalers and others;

4. Publication of information on the new products in specialized periodicals (*Pharmaceutical Gazette* and others), journals (*Remedium* and others) and manuals (*Vidal*, *RLS* and others);

5. Dissemination of information brochures to wholesale buyers, including through the Pharmaceutical and Information Centre of the Moscow Department of Health;

6. Conduct of publicity campaigns in the media;

7. Placing diagrams in instructions for the use of the new product alongside the written text, to ensure that patients use the products correctly;

8. Posting information on the internet sites of the companies and, where possible, on the site of the Federal Service.