Strategy to eliminate CFCs in metered dose inhalers (MDIs) in Poland

1. Introduction

Development of national strategies for elimination of CFCs contained in metered dose inhalers (MDIs) has been recommended in decisions made during the meetings of the Parties to the Montreal Protocol on the substances that deplete ozone layer.

This strategy for Poland has been prepared pursuant to report commissioned by Ministry of the Environment and drawn up by the Ozone Layer Protection Unit, who is active within the Industrial Chemistry Research Institute in Warsaw and being the result of consultations carried out with physicians, patients and manufacturers of MDIs.

2. The use of MDIs in Poland

It is estimated that total quantity of MDIs packaging used in Poland amounts currently to about 6 million items annually. The medicaments which are mostly applied in Poland are: Berotec, Salbutamol, Budesonid and Berodual. In the recent years, the use of Atrovent, Serevent, Ventolin, Beclocort and Horacort has been also grown.

MDIs preparations currently available in Poland, likewise in the world-wide scale, can be structured into the following groups (therapeutic categories) relating to their application method:

Category A - Short-acting beta-agonist bronchodilators
Category B - Inhaled steroids
Category C - Non-steroidal anti-inflammatories
Category D - Anticholinergic bronchodilators
Category E - Long-acting beta-agonist bronchodilators
Category F - Combination of the products (containing two or more different active substances)

3. Manufacture, imports and exports of MDIs containing CFCs in Poland

Domestic production of MDIs containing CFCs covers the needs of about 65% of patients in Poland, and of a large patient group in other countries, mostly in Central and Eastern Europe.

In Poland, MDIs are manufactured by GlaxoSmithKline, in Poznañ (Salbutamol, Astmopent, Beclocort, Budesonid and Cropoz), and also in an insignificant quantity (of Horacort) by Pharmaceutical Institute, in Warsaw.

It is estimated, that about 3.5 million MDI packaging containing CFCs were imported in Poland in 2000. The dominant group among the medicaments in form of MDIs includes: Berotec, Berodual, Atrovent and Serevent.

Given the fact, that there are MDI manufacturers in Poland, the imports can be considered as that supplementing this production. Nevertheless, this Strategy relates to elimination of all of CFC-containing MDIs, hence also those imported to Poland.

No detailed data is available on MDI exports from Poland. It is only known, that GlaxoSmithKline supplies their preparations mostly to the markets in Central and East

Europe. The case of exports of MDIs containing CFCs will be separately considered in this Draft Strategy due to the fact, that when introducing, under this Strategy, any possible restrictions concerning production of CFC-containing MDIs, the needs of patients in the countries should be considered, where they have been exported to, and where CFC-free MDI substitutes could not have been available.

4. CFC-free MDIs currently manufactured in Poland

GlaxoSmithKline have already implemented MDIs based on HFC-134a as propellant ~~agent~~. They are Ventolin with *salbutamol* as active substance, and another medicament named Flixotide with *fluticasoni propionas* as active substance.

At present, GlaxoSmithKline carry out the implementation study on subsequent CFC-free substitutes to be applied in their other products based on their own technologies. Studies on the substitutes are also carried out by the Pharmaceutical Institute, but given the scarce resources appropriated to this end, no soon completion can be expected. In manufacturing their MDIs, the Institute apply a mix of CFC-11 and CFC-12, and by the end of 2002 they are going to conclude the work on elimination of CFC-12. According to the Institute, it is unlikely, that CFC-11 could be eliminated in the near future.

In relation of other medical aerosols, it should be stressed, that also some other medical aerosols containing CFCs produced by GlaxoSmithKline, being not MDIs, have still valid registration. Those are: Decubitol (for external application), Lignocainum 10% (for external application). These preparations will have to be eliminated from the market. That relates also to CFC-containing Beclomed Nasal manufactured by Finnish company Orion Corp (for nasal application), that has still valid registration.

5. Availability in Poland of CFC-free MDIs and other medicament dosing systems for treatment of asthma and COPD

Apart from MDIs manufactured in Poland and presented in item 4 above, yet 5 CFC-free MDIs have still valid registration, those are manufactured in other countries. They are:

- Airomir containing also Salbutamol (manufactured by 3M - USA);
- Berotec N100 containing *fenoteroli hydrobromidum*, hence its falls also into therapeutic category A (manufactured by Boehringer Ingelhein - Germany);
- Flixotide (3 dose types) containing *fluticasoni propionas*, so belonging to therapeutic category B (manufactured by GlaxoWelcomeGroup - United Kingdom).

At present, 2 MDIs falling into therapeutic category B, 3 MDIs - therapeutic category F, and 1 MDI - therapeutic category D, are under their registration process.

At the same time, there are many medicament types available on the market which serve for treatment of asthma and COPD with similar therapeutic effects, and which have been applied in other forms (turbohalers and „diskhalers" [powder inhalers], nebulisers, tablets, etc.). Currently, 22 medicaments in such forms have valid registration. It is estimated, that total 3 million packaging - mostly powder inhalers, were sold in Poland in 2000. So, a tendency is apparent to replace MDIs with powder inhalers. However, it is noteworthy to emphasise, that nebulisers and powder inhalers can be only applied by a certain group of patients who suffer from asthma and COPD. Restrictions for application of nebulisers and powder inhalers relate first of all to children and elderly patients. Also, there

can be the cases, when the patients suffer from poor tolerance of these methods for application of the medicaments. So, having in mind the good of the patients, this Draft assumes, that nebulisers and powder inhalers, as well as the medicaments for treatment of asthma and COPD applied in the other forms, cannot be admitted as direct substitutes for CFC-containing MDIs, despite they could have been ~~be~~ in many cases applied successfully.

6. The Current situation in Poland in relation to registered MDIs containing CFC or those planned to be registered, and their potential CFC-free substitutes

Currently 38 medicaments are registered in Poland in form of MDIs containing CFCs. Registration of the most of them (25) is valid until 2004, for six other MDIs registration is valid until 2005, for five others until 2006, whereas for three the registration will expire already in 2003. Valid registration have also two nasal aerosol preparations (until 2003 and 2004), and two other preparations for external use (both until 2004).

According to information provided by Ministry of Health, no aerosol preparation containing CFCs is currently planned to be registered.

Six CFC-free MDIs have valid registration, and six such other MDIs are planned to be registered. It could be then envisaged, that the elimination process of CFC-containing MDIs will begin immediately once relevant legal provisions are implemented.

Elimination of CFC-containing MDIs should be much easier because valid registration have also 21 powder inhalers containing the same active substances. Nevertheless, according to our assumptions in the Strategy for elimination of CFC-containing MDIs, those have been consulted with physicians, patients and manufacturers, the powder inhalers cannot be considered as safe substitutes for MDIs.

For sure, also MDI containing aerosol preparations destined for external use, or so called „nasal" ones, could be eliminated at once, since as much as several dozen such CFC-free preparations have already been granted valid registration certificates.

7. Reduction of CFCs emissions related to manufacturing MDIs in Poland

GlaxoSmithKline in Poznañ have commenced a series of steps to reduce CFCs from manufacturing process of MDIs, and to improve management of production waste containing CFCs. These are described below.

7.1. Reduction of CFCs emissions in course of manufacturing process

- reducing the pipeline connections, which diminishes the leakages,
- conducting the dosing process within three-shift labour system, which results in shortening the process and reduction of CFCs emission,
- reducing the pipeline diameter, which decreases diameters of the connections,
- installing permanent (rigid) pipelines where the aforementioned changes are feasible,
- dedicating the tanks and containers to sole material type, which reduces the number of washing processes, and hence the evaporation of CFCs,
- carrying out preventive inspections of pumps, which reduces both the number of their failures and CFC leaks,
- carrying out preventive inspections of the connections, which reduces the number of CFC leaks,
- installing leak-proof sealing, where possible, on the production tanks,

- applying different than CFCs solvents for certain elements in washing process.

7.2. Reduction in CFCs emissions when managing waste

- proper management of recycling the waste containing CFCs, which results in considerable reduction in CFC emissions into the atmosphere,
- attempting to export larger quantity of waste with the aim of recycling,
- attempting to purchase yet more leak-proof container for CFC waste.

8. Existing in Poland non-governmental organisations of physicians and patients, whose activity profile substantively relates to elimination of CFC-containing MDIs

8.1. Physicians' associations

At present, two associations of physicians are active in Poland, who relate directly to the issue of treatment of asthma and COPD. They are: Polish Allergological Society and Polish Phtisiological and Pneumonological Association. Their activity scope includes following the world-wide progress in asthma and COPD treatment, promoting new therapy types, exchanging practical experience, and co-ordinating the efforts to improve conditions for curing the patients. These Associations were initially consulted on this Strategy to eliminate CFC-containing MDIs, and they are envisaged to play very important role in this process.

Irrespective of the national associations of physicians, also the Working Group of the International Aerosol Society in Medicine is very active in Poland. The activities in the field of medical aerosols are co-ordinated on the level of the Ministry of Health, in form of the Allregological and Pneumonological Supervision (i.e. experts - advisors to the Minister of Health).

8.2. Patients' associations

The following 9 organisations of patients suffering from asthma and COPD are presently active in Poland:

- The Gdañsk Society to Assist Asthmatic Children,
- The „Breathing" Foundation
- Foundation to Assist Allergic and Asthmatic Children,
- The Centre to Assist Allergic Children, of the Child Assistance Society,
- Polish Association to Assist Asthmatic and Allergic Children,
- Polish Association to Assist Children Suffering from Respiration Diseases and Atop,
- Polish Society to Control Allergic Diseases,
- School for the Suffering from Allergy and Their Families,
- School for the Suffering from Asthma and the Society to Assist the Suffering from Asthma.

Representatives of these organisation have been informed on the assumptions for the Strategy to eliminate CFC-containing MDIs, and they have been invited to participate to meetings held in this field. Generally, these organisations do not have any objections

against the assumptions made for the Strategy, supposing that the price for new CFC-free preparations will be similar to that of MDIs containing CFCs, and that their application will not be more arduous to patients. The necessary condition is of course the total conformity of therapeutic effects between new and currently applied preparations. Patients' associations could play an important role in raising awareness of the patients about the reasons for implementation of CFC-free MDIs and monitoring the effect from their application.

9. The mandatory rules for placing on the market of medical products in Poland

Since 1 January 2002, the following Acts regulate the market for medical products:

- Act of 27 July 2001 *on the Agency for Registration of Healing, Medical and Biocidal Products* (O.J. No. 126, Item 1379),
- Act of 27 July 2001 *on Medical Products* (O.J. No. 126, Item 1380),
- Act of 6 September 2001 *on Pharmaceutical Law* (O.J. No. 126, Item 1381),
- Act of 6 September 2001 *on the Provisions Introducing the Act on Pharmaceutical Law, the Act on Medical Products, and the Act on the Agency for Registration of Healing, Medical and Biocidal Products* (O.J. No. 126, Item 1382).

9.1. Allowance for placing on the market

Such medical products shall be admitted to be placed on market, those obtained permit for the admittance to placing them on market to be granted by the President of the Agency for Registration of Healing, Medical and Biocidal Products. Prior to granting the permit, the President shall collect, inter alia, the opinion to be issued by the Commission for Medical Products. The opinion should be submitted in 30 days (Article 8). Overall proceedings on the admittance to placing the products on market should be resumed in 210 days after the date, when the application was submitted (Article 18), and the permit shall be granted for 5-year period (Articles 4 and 7).

The President of the Agency shall be empowered to decide on refusal to grant the permit, refusal to prolong the validity period of the permit, and to revoke the permit (Article 4), however he shall have the right to exercise these powers only in case, when the medical product in question does not comply with its healing function. At present, no right has been vested to exercise these powers in case of adverse environmental impact of the product in question.

Once admitted to be placed on market, the medical product shall be put on the *Register of Medical Products Admitted to Placing on Market in the Territory of the Republic of Poland*, that is managed by the President of the Agency. The medical product which obtained no prolongation of the permit for the admittance to placing medical products on market, shall be allowed to be manufactured for 6 month-period, beginning from the date when final decision was made, and to be retained on the market until its validity time-limit is expired, unless the decision on refusal of the prolongation has been attributed the rigour of its immediate enforcement (Article 29).

9.2. Manufacture of medical product

It is required to obtain the permit to manufacture medical product, that is to be granted by the Chief Pharmaceutical Inspector, who is also empowered to revoke or change the permit which has been granted (Article 38).

9.3. Transitional provisions

Additionally, under the *Act on the Provisions Introducing the Act on Pharmaceutical Law, the Act on Medical Products, and the Act on the Agency for Registration of Healing, Medical and Biocidal Products*, by 31 December 2002 (Article 19) the applications shall be allowed to be submitted for the admittance to placing on market yet in accordance with the „old" Act of 10 October 1991 *on Pharmaceutical Agents, Medical Materials, Pharmacies, Warehouses and Pharmaceutical Inspection*. Moreover, (Article 27), until administrative regulations to *Pharmaceutical Law* are issued, the provisions so far in force shall be mandatory in parallel, unless they do not contradict the *Law*, but no longer than by 1 January 2003.

At the same time, (Article 14) the certificates of registration / admittance to placing on market granted under the „old" provisions shall become the permits within meaning of the *Pharmaceutical Law*, and they shall became valid by the time-limits as set out for them, but no longer than by 31 December 2008, whereas a refusal to grant the permit can be made only in cases as laid down in *Pharmaceutical Law*.

10. Legal assumptions for elimination of CFC-containing MDIs in Poland

It is proposed to introduce the following amendments in the provisions specified in Item 9 above.

a) Refusal, because of ecological reasons, to grant the permit for the admittance to placing medical products on market

In order to allow to refuse, in relation to the protection of ozone layer, granting the permit for the admittance to placing medical products on market, it is proposed to add the following words in Article 30, paragraph 1, item 6 of the Act of 6 September 2001 *on Pharmaceutical Law*: „medical product contains substances that deplete ozone layer, such use is controlled by the international agreements which Poland is the signatory to. In such case, President of the Agency, having previously obtained opinion from Minister responsible for the environment, shall make the decision."

b) Amendment in another Act in relation to the aforementioned proposal

Pursuant to the aforementioned proposal, it is also proposed to introduce amendment in Article 14, paragraph 4 in the Act of 6 September *on the Provisions Introducing the Act on Pharmaceutical Law, the Act on Medical Products, and the Act on the Agency for Registration of Healing, Medical and Biocidal Products*. So, the last sentence in that paragraph would be replaced with the following words: „Refusal to grant decision on prolongation of the permit validity time-limit shall be made exclusively in cases as set out in *Pharmaceutical Law*, Article 30, paragraph 1, items 2-6, and paragraph 2 thereof.".

c) Introduction of the opportunity to cease sales or withdraw from the market of medical product in relation to the protection of ozone layer

In Article 108, paragraph 4 of the of the Act of 6 September 2001 *on*

Pharmaceutical Law, it is proposed to add new item 2a, as follows:
„to cease sales or to withdraw from the market or to apply in medical care establishments the medical product in case, when it has been ascertained, that a product in question contains any substance that deplete ozone layer, that use is controlled by the international agreements which Poland is the signatory to. If this is the case, the authorities of Pharmaceutical Inspection shall make decision upon application moved by Minister responsible for health, having previously obtained relevant opinion to be made by Minister responsible for the environment. Minister responsible for health in agreement with Minister responsible for the environment shall specify detailed principles for cessation of sales, or withdrawal from the market, or application in medical care establishments the medical products in relation to their adverse environmental effects from the substances contained therein."

11. Assumptions to eliminate CFC-containing aerosols which are not MDIs in character (aerosols for external use and nasal ones)

The first step to be taken prior to commencing any withdrawal of CFC-containing MDIs should be to implementation as soon as possible the ban to place on market any other medical aerosols which contain CFCs, and to adopt the principle to refuse to grant the permits to placing on market, or to prolong them in case of such type aerosols. The question is about the aerosols for external use and nasal ones, which are no more considered in the Montreal Protocol as those for „essential use" in case of CFCs, because their substitutes are commonly available. It is proposed, that immediately once the legal provisions referred to in item 10 above are introduced, the Minister of the Environment shall forward relevant motion to Minister of Health.

Already now, based upon agreements made on the meeting held by representatives of Ministry of Health, Ministry of the Environment, Ministry of Economy, the manufacturers, and the Commission for Registration of Pharmaceutical Products and Medical Materials, who is active at the Institute of Medicaments, the Ozone Layer Protection Unit addressed a letter to the Commission for Registration of Pharmaceutical Products and Medical Materials requesting to adopt a resolution, that after 1 February 2002, no further application will be received to register such aerosols.

12. The assumptions for withdrawal of CFC-containing MDIs

In case of CFC-containing MDIs, the following sequence of proceedings is proposed when eliminating CFCs:

a) CFC-containing MDIs which have valid registration shall retain it until its validity is expired. Any possible prolongation of the registration will be only possible, when other conditions will be met;

b) Immediately, once legal regulations referred to in item 10 above are in force, the principle should be laid down on refusal granting any permits for the admittance to placing on the market new MDIs containing CFCs and to prolonging any permits for already registered MDIs which contain CFCs;

c) If it is feasible, the proceedings should be speeded up on registration of CFC-free MDIs, and also CFC-free medicaments for treatment of asthma and COPD which are applied in other forms (DPI, nebulisers, atomisers, and other forms of medicaments);

d) Withdrawal from the market of particular MDI preparations containing CFCs will be implemented pursuant to the following principles for various types of therapeutic categories described in the item 2.

Category A

Withdrawal from market of all of CFC-containing MDI preparations falling into Category A can be executed not earlier than 24 months from the moment, when two substitutes being also MDIs of sufficient dose range are present on market, those contain CFC-free propellant gas and have valid registration, that have been produced by two different manufacturers and included Salbutamol as the basic active substance, as well as one substitute being also MDI which contains another active substance falling into therapeutic category A. During 24 months, when the aforementioned three CFC-free substitutes are available on market, the manufacturers of CFC-free MDIs would be obliged to conduct observations of their application effects pursuant to Article 24 of the *Pharmaceutical Law*. In case, when no negative effects from the application of CFC-free MDIs are ascertained during 24 month after placing them on market, Minister of the Environment shall forward relevant motion to the Minister of Health requesting a ban to be introduced to place on domestic market any MDI which falls into therapeutic category A and contains any CFC as propellant gas.

Category B

Withdrawal from market of all of CFC-containing MDI preparations falling into Category B can be executed not earlier than 24 months from the moment, when two substitutes being also MDIs of sufficient dose range are present on market, those contain CFC-free propellant gas and have valid registration, that have been produced by two different manufacturers and included Beclomethasone as the basic active substance, as well as two other substitutes being also MDIs which contain another active substance falling into therapeutic category B. During 24 months, when the aforementioned four CFC-free substitutes are available on market, the manufacturers of CFC-free MDIs would be obliged to conduct observations of their application effects pursuant to Article 24 of the *Pharmaceutical Law*. In case, when no negative effects from the application of CFC-free MDIs are ascertained during 24 month after placing them on market, Minister of the Environment shall forward relevant motion to the Minister of Health requesting a ban to be introduced to place on domestic market any MDI which falls into therapeutic category B and contains any CFC as propellant gas.

Categories C, D, E

Withdrawal from market of all of MDI preparations falling into each of therapeutic categories C, D or E, that contain a CFC as propellant gas, can be executed not earlier

than 24 months from the moment, when for given therapeutic category a substitute is present on market, that is also a MDI of sufficient dose range and has valid registration. During 24 months, when at least one CFC-free substitute in each of the aforementioned categories is present on market, the manufacturers of CFC-free MDIs would be obliged to conduct observations of their application effects pursuant to Article 24 of *Pharmaceutical Law*. In case, when no negative effects from application of CFC-free MDI are ascertained during 24 month after placing it on market, Minister of the Environment shall forward relevant to the Minister of Health requesting a ban to be introduced to place on domestic market any MDI falling into therapeutic categories C, D and E, and containing any CFC as propellant gas.

Category F

The combined products (which contain active substances falling into different categories within the same preparation) shall undergo withdrawal from market pursuant to the same principles as described above, when CFC-free substitutes are present on market for each active substance contained in such product.

e) The aforementioned principles would not relate to MDIs containing CFCs manufactured in Poland with the aim to be exported to the other countries, where their application has not yet been prohibited.

f) Once registered, the CFC-free MDI which conforms to the requirements for MDI substitute containing CFC, presented in point d), the surcharges should be fixed in such an amount, that its price would not be higher than 5%, than that of its CFC-containing equivalent. In case, when production cost of a MDI substitute is lower than that for its CFC-containing equivalent, the surcharges should remain on their current level, that will enable cutting the price of the substitute in relation to its CFC-containing equivalent.

It is difficult to decide at the moment on the time-schedule for withdrawal from market under the aforementioned principles of CFC-containing MDIs which are currently available on the Polish market. Nevertheless, based on the current knowledge concerning the world-wide situation in the field of CFC-free MDIs, it seems that at least two types of MDIs containing CFCs could be in such a way withdrawn for market in Poland by the end 2004, hence during the next 3 years. Those will be likely the MDIs which are based on Salbutamol and Beclomethasone as the basic active substances. Withdrawal from market would relate to all MDIs containing these active substances, irrespective of the manufacturer.

Majority of the other CFC-containing MDIs could have been probably replaced with CFC-free MDIs by the end 2006, so in a time limit close to expectations expressed by Technical and Economic Panel of the Montreal Protocol and the European Union.

Alternative solution would be to stop the surcharges for CFC-containing MDIs, or to introduce excise tax in case, when the change in legal provisions referred to in item 9 appears difficult, those are prerequisites for their withdrawal from market and cessation of granting or non-prolongation of the permits.

13. Other recommendations relating to withdrawal of CFC-containing MDIs

Domestic manufacturers of MDIs shall be also obliged to:

- take all economically reasonable activities to minimise CFC emissions from production processes;
- avoid to carry out any unjust, misleading for the users, promotion of both CFC-free and CFC-containing MDIs (this regards also the importers, distributors, wholesalers and sellers);
- utilise any impaired and outdated packaging, or that returned by the users of MDIs, in a manner aimed to minimise CFC emission (this regards also the importers, distributors, wholesalers and sellers);
- conduct annual revision of CFC demand, and to analyse envisaged market needs, and to keep the respective agencies controlling use of ODS informed in case, when it results from such analysis, that the needs are below the CFC quantity assigned in the framework of the „essential use".

14. Educational campaign addressed to patients, physicians and chemists

All of the manufacturers and importers of CFC-free MDIs, who are intended to place them on market in Poland, shall be obliged to conduct educational campaign informing on the necessity to withdraw CFC-containing MDIs from market, and to promote application of CFC-free MDIs among patient, physician and chemist circles. In the framework of this campaign, the brochures, leaflets, training sets and any other necessary materials should be developed.

Important role in this educational campaign should be played by physicians' and patients' associations, who should broadly inform physician and patient circles on the reasons for withdrawal of CFC-containing MDIs, and on any opportunities to replace them with CFC-free MDIs which have the same therapeutic effects.

Ministry of the Environment, in co-operation with the Ozone Layer Protection Unit and in consultation with physician circles, should also join such campaign by means of:

- dissemination of appropriately developed leaflets and posters;
- publication of relevant information in professional journals, radio and TV;
- arranging relevant meetings and conferences.