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DESK STUDY FOR EVALUATION OF METERED-DOSE INHALERS (MDI) PROJECTS

EXECUTIVE SUMMARY

1. The desk study for evaluation of metered-dose inhalers (MDIs) is part of the 2012 monitoring and evaluation programme which was approved by the Executive Committee at its 65th meeting, as per decision 65/9. As MDI projects approach completion, assessing success and challenges in their implementation is both opportune and useful.

2. The desk study considered issues related to the formulation and implementation of projects dealing with the transition from CFC MDIs to CFC-free MDIs. The phasing out of the ozone-depleting substances (ODS) in the form of CFC propellants in the production of MDIs means to replace them with equivalent MDIs containing propellant with non-ODS.

3. This process however is different from the phasing out of CFCs in other sectors and presents a series of challenges. It addresses not only economic issues but also problems related to the health of the population. For example, any delay between the phase-out of CFC MDIs and the starting of the production of CFC-free MDIs can seriously limit people's access to medication. An important issue is how to avoid a possible gap in the people's access to medicine. In some countries the persistence of CFC MDIs after the deadline for phasing out in 2010 raised the risk of non-compliance. In addition, CFC-free MDIs had to be accepted by both the medical professionals and patients.

4. Despite these complications, the majority of projects were implemented successfully. There is evidence that since 2006 there has been a substantial increase in HFC MDIs made in Article 5 countries. Many domestic producers now have the capability to supply HFC MDIs both for domestic use and for export.

5. The sample of countries considered by the desk study includes Article 5 countries that manufacture MDIs and which encountered the above mentioned challenges. The desk study considered the institutional context of implementation and the variety of stakeholders that were involved. It reviewed components of transition strategies such as coordination mechanisms and found out that multinational companies may have had an important but indirect role in the acceptance of new CFC-free MDIs.

6. The desk study examined the legal framework that had to be created for the new health products as well as the activities aimed at raising awareness among the medical practitioners as well as the patients. It also considered issues related to essential-use nominations and concluded that the number of countries requesting it has decreased significantly.

7. Among the constrains and hurdles to project implementation, the desk study lists some related to the need for replacement of the technology provider; political and physical issues; and delays related to institutional context. A number of technical issues have been identified. These relate to funding of some specific items; selective equipment destruction; flammable MDIs and ethanol-related aspects. A second stage of the evaluation including field visit to five or six countries is suggested, to allow a more in-depth perception of the implementation issues as well as of the acceptance of the CFC-free MDIs among various stakeholders.

I. SCOPE AND PURPOSE OF THE EVALUATION

8. The desk study of the evaluation of the MDI projects is the first phase of an evaluation approved by the Executive Committee at its 65th meeting (decision 65/9). The desk study examines issues related to project implementation and points out issues to be further analysed during future field visits.

9. More specifically, the desk study focused on institutional, legal and regulatory, capacity and technical issues that facilitated or limited project functioning; causes of delays; the type and impact of technical assistance provided; issues concerning the launch of CFC-free alternatives and withdrawal of associated chlorofluorocarbon products; role of national and multinational companies in achieving phase-out; and issues related to information and awareness making activities among various stakeholders, including the medical sector.

Methodology sampling and sources of information

10. A consultant undertook the study of existing documents. Furthermore the draft report has been shared with members of implementing and bilateral agencies involved in project implementation as well as with members of the Multilateral Fund Secretariat for comments.

11. The consultant reviewed projects in 9 out of the 15 countries. The countries were selected according to the size of the project, complexity of implementation, status of implementation, size of budget and regional distribution. All countries manufacture MDIs. They correspond to paragraph 2 (c) of the guidelines for the preparation of transitional strategies and development of investment projects for phasing out CFCs in the MDI sub-sector that specify "where the production could be from nationally-owned companies, … This is where most of the financial support will be focussed and could cover both the development and dissemination of transition action plans, as well as access to non-CFC alternate products"[1].

II. BACKGROUND

12. In 2000, at their 12th meeting the Parties to the Montreal Protocol decided to address the issue of transition to CFC-free MDIs. The Parties therefore, requested the Executive Committee to provide financial and technical support to Article 5 countries to develop an effective transition strategy to achieve economically and technically feasible substitutes (decision XII/2).

13. The phasing out of the ODS in the form of CFC propellants in the production of MDIs requires replacing them with equivalent MDIs containing propellant with non-ODS. The impact of such an approach is twofold. By replacing CFC MDIs with hydrofluorocarbon (HFC) MDIs the emissions of ODS would be eliminated. In addition, this would also bring up benefits for climate change, in agreement with the obligations under the Kyoto Protocol to address climate impacts of alternative technologies as HFC MDIs have about 10 times less climate impact than CFC MDIs. In addition, in the process of reformulation for this transition, there is the opportunity to improve today's pulmonary delivery technology and to create new systems to treat a wide array of infirmities and afflictions[2].

14. Historically CFCs have been preferred in the manufacture of pressurized medical inhalers for the treatment of asthma and chronic obstructive pulmonary disease (COPD) products due to the low cost and low irritation as the propellant in the finished products. However a series of alternative MDIs based on non-ODS is now available on the market. Table 1 presented in Annex I lists and briefly describes these existing alternatives.

15. In considering these alternatives, the Parties further stated that strategies should be acceptable from the standpoint of environment and health and should include effective criteria and measures for determining when CFC MDIs can be replaced with CFC-free alternatives (decision XII/2).

[1] UNEP/OzL.Pro/ExCom/37/58

[2] http://www2.dupont.com/Medical_Device_Material/en_US/assets/downloads/metered_dose.pdf

16. The process however was different from the phasing out of CFCs in other sectors and presented a series of challenges. It addressed not only economic issues but problems related to the health of the population. An important issue was how to avoid a possible gap in the people's access to medicine. In addition, CFC-free MDIs had to be accepted by both the medical profession and patients.

17. Other issues related to transfer of technology and intellectual property had to be solved. In many countries, during the preparation of national phase-out plans (NPPs) the consumption of CFCs for MDIs was not reported and therefore phase-out activities relating to MDIs were not included in the NPPs. The projects were therefore implemented at a later stage, often when CFCs were close to or already phased out by countries. For many countries, therefore phasing out CFCs in MDIs could become a compliance-related issue in completing total phase-out of CFC production and consumption.

18. At their 17th meeting, the Parties to the Montreal Protocol discussed the difficulties faced by some Article 5 countries with respect to the phase-out of CFCs used in the manufacture of MDIs. In decision XVII/14 they expressed their concern that Parties operating under paragraph 1 which manufacture CFC-based MDIs might find it difficult to phase out these substances without incurring economic losses to their countries. They also pointed out the possibility of serious risk that for some Parties operating under paragraph 1, consumption of CFCs for MDIs may exceed the amounts allowed under the Montreal Protocol. In the same decision the Parties requested the Executive Committee of the Multilateral Fund to "consider options that might assist potential situation of non-compliance". They also insisted on the need for appropriate regional workshops to create awareness and educate stakeholders, including doctors and patients on alternative MDIs.

19. These complications notwithstanding, the majority of projects were implemented successfully. According to a 2010 Medical Technical Options Committee (MTOC) report[3] since 2006 there has been a substantial increase in HFC MDIs made in Article 5 countries. Many domestic producers now have the capability to supply HFC MDIs both for domestic use and for export. In 2009 CFC MDIs formed only 30% of all MDI sales, compared to over 60% in 2005. In addition to that the conversion of majority of CFC consuming sectors in Article 5 countries under the Montreal Protocol has been completed in 2010.

20. The Multilateral Fund funded projects in Article 5 countries mainly focused on technology transfer and institutional strengthening to convert CFC MDI manufacture to CFC-free alternatives. Funding approved by the Executive Committee of the Multilateral Fund for MDI projects amounts to US $52.2 million.

Governments' agreements and other undertakings

21. All Article 5 Parties where CFC MDIs are currently manufactured have committed not to request any additional funding for any controlled uses of CFCs. This was made either through specific agreement with the Executive Committee or through decisions by the Executive Committee. Exceptions were Argentina, China, Egypt and Indonesia, which had excluded specific amounts of CFCs used for the manufacturing of MDIs from the national phase-out plans. Therefore, with the exception of these four countries, the fund cannot provide further assistance of the phase-out of CFC MDIs[4].

III. EXECUTIVE COMMITTEE STRATEGY AND GUIDELINES

22. At their 13th meeting the Parties requested the Executive Committee to prepare guidelines for the presentation of MDI projects to help Article 5 countries in the preparation of strategies and investment

[3] http://protocolodemontreal.org.br/eficiente/repositorio/publicacoes/567.pdf
[4] UNEP/OzL.Pro/ExCom/49/39

projects that would facilitate the phasing out of CFC MDIs and the transition to CFC-free production of MDIs, and enable them to meet their obligations under the Montreal Protocol (decision XIII/9).

Content of guidelines

23. Inspired by the experience of Cuba, the first Article 5 country to formulate an MDI transition project, the guidelines point out the necessary elements to be included in every project proposal prepared by Article 5 countries in seeking financial support for phasing out CFC MDIs. According to the guidelines there are three large categories of countries: (a) low consumers of MDIs, with an annual usage of less than one million MDIs (equating to less than 25 tonnes of ODS per annum), and who are totally supplied by imports and will need minimal assistance. Experience in CFC-free alternatives can be introduced promptly within the regulatory framework of the country, and the corresponding numbers of CFC MDIs being phased out. Secondly (b) large consumers of MDIs, with an annual use of more than one million metered-dose inhalers, and who are totally supplied by imports. They will need more assistance in developing an understanding of the currently available range of products in their country, drafting an action plan for transition and communicating this to doctors and asthma/COPD patients. Lastly (c) MDI producer countries"[5].

24. The guidelines state that each country should provide basic information on the volume and characteristics of CFC MDIs used, list the companies manufacturing or marketing the product, describe the existing legislation regarding the testing and approval of new drugs. Major MDI user countries should also describe the anticipated availability of non-CFC MDIs and the feasibility of replacing MDIs by other alternatives (i.e., dry powder inhalers (DPIs)) through the most likely source of the alternative products (e.g. local development; licencing of technology; establishment of joint ventures); the proposed time frame for the introduction of non-CFC MDIs and the proposed duration of the transitional period where both CFC and non-CFC MDIs will be available in the market concurrently; furthermore they should inform on the planned awareness programmes addressed to health care professionals and patients as well as on monitoring requirements during the transitional period and what remedial action will be taken if the initial target reductions in CFC volumes are not met. Countries that produce MDIs should in addition inform on existing CFC MDI production facilities. The document includes specific guidelines for investment projects, requiring a description of the baseline as well as retrofit and new production line information.

IV. MAIN FINDINGS

Quality of project proposals and their adequacy to guidelines

25. The analysis of the project proposals of the nine countries in the sample shows that they have followed the guideline requirements. All provide information about the national phase-out plan and about the pharmaceutical MDI manufacturing sector, a justification for the selection of the alternative technology, financial information as well as a description of the transition strategy for the elimination of CFC MDIs. In most of the documents transition strategies include descriptions of role and responsibilities of institutions, description of the key stakeholders. Some of the countries (Bangladesh, China, Cuba and the Islamic Republic of Iran) provide a history of MDI production and consumption in the country. All documents include a description of institutional arrangements, policy and regulatory framework relating to ODS as well as the required modifications. Some countries (Bangladesh, Egypt, India, the Islamic Republic of Iran and Pakistan) mention or describe the awareness and capacity building and the related activities. One document (Argentina) includes an environmental assessment of the benefits of replacing CFC MDIs. In all documents the main principle underlying the transition strategy is that patient's health should be the first priority.

[5] UNEP/OzL.Pro/ExCom/37/58

Institutional setting

26. Institutional settings vary from countries with one state owned company that covers the MDI needs of the population (Cuba), to countries with several locally owned companies and to countries with a mixture of locally and internationally owned companies. In all countries, however, various institutions share responsibilities in implementing the projects. Usually the coordinator and supervisor of the project implementation is the Ministry where the National Ozone Unit is located, most of the time the Ministry of Environment. In this case, however, because of the medical implications of the projects, the Ministry of Health is either coordinating the project implementation (the Islamic Republic of Iran) or collaborates with the lead Ministry (India) and is also in charge of all matters pertaining to health services. In addition drug regulating institutions supervised the modification brought to regulations.

27. Specific to the projects is the collaboration between the government and manufacturing companies. For example, in Argentina the Government is responsible for any campaign at the national level to educate both doctors and patients on the benefits and changes that can be expected from using HFA-based MDIs. The laboratories are responsible for reaching their network of doctors and to train them on the benefits of their particular drug. The same collaboration is found in Bangladesh between the Government and manufacturing companies, the drug regulatory agency, the lung association and the medical community. In addition, other stakeholders appear as actors in the process of project implementation and/or acceptance of the new product. In most of countries the medical profession, national lung associations and other professional organizations are mentioned as having a role in the process.

28. Non-governmental organizations (NGOs) are mentioned as an active actor once only, in India. To strengthen and sustain momentum UNEP contracted Development Facilitators (DF) a national level not-for–profit organization in Delhi to implement the UNEP component related to awareness and education.

Coordination mechanisms

29. Specific coordination mechanisms have been set to deal with the Montreal Protocol's requirements, the complexity of project implementation and the variety of actors in some countries. India's Ministry of Environment and Forests has created an Empowered Steering Committee, an apex body mandated for the formulation and review of policy actions for the Montreal Protocol related projects implementations.

30. In China a project implementation and monitoring unit was established to assist in the preparation of 32 technical dossiers for the active ingredients produced currently at the 16 manufacturing plans. It has an array of functions such as validating the 16 manufacturing plants; validating workshops; facilities; equipment installation; training staff at the manufacturing plant in addition to the technical training that will be provided by the equipment provider; monitoring, including the development of monitoring, management and verification system; dealing with stockpiles.

31. In Egypt the Egyptian Environmental Affairs Agency (EEAA through the Ozone Unit) worked together with the Ministry of Health and Population, with the Central Administration of Pharmaceutical Affairs and with local enterprises.

32. Some mechanisms have a regional role. In the Islamic Republic of Iran the establishment of a Science and Technology Committee at local and regional levels by UNEP/ROAP led to the cooperation of all involved countries of the region towards a smooth transfer of technology in general, and especially the process of replacement of CFC MDIs with HFA MDIs.

South-south cooperation

33. Under south-south cooperation initiatives the Government of India provided support to the Government of the Islamic Republic of Iran on CFC MDI phase-out related technical information exchange associated with phase-out project implementation with assistance from Cipla Ltd., India. In addition, in 2011 UNEP organized a bilateral exchange between China and India, to discuss how India was able to successfully phase out the production of CFC MDIs. The conclusion was that Chins has a strong potential for policy replication particular by fast-tracking the regulatory approval processes for CFC-free MDIs. This could contribute to the accelerated transition to CFC-free technologies in China under its National Strategy[6].

Role of multinational companies

34. Multinational companies non eligible for funding by the Multilateral Fund had an indirect, but important role in the acceptance of CFC-free MDIs on the national market. They phased out and replaced the CFC MDIs with CFC-free MDIs and contributed to the spread of awareness on these new products. As mentioned in the a policy paper[7],multinational pharmaceutical companies (will) switch their CFC products by introducing HFA-MDIs, quickly evaluating their acceptance in the marketplace and then ceasing the supply of the corresponding CFC product. This transition will be driven by the desire of pharmaceutical companies to introduce products globally once they have been developed. Furthermore, as pharmaceutical-grade CFCs become less available, multinational companies will rapidly introduce already-developed non-CFC alternatives.

35. A lesson learned from previous experiences in non-Article 5 countries is that the most effective management of the transition to non-CFC MDIs has been through the co-operation of industry and government in working towards a common goal of having target dates for the cessation of sale of certain CFC MDI products[8].

Transition strategies

Regulatory issues

36. In most of countries there was need to amend the existing regulatory framework to make place for the transition to CFC-free products. In India the primary law concerning pharmaceutical MDIs is the Drugs and Cosmetics Act, 1940 amended in 2005 that rules the licensing concerning import, manufacturing, registration and sale. Furthermore, the national health policy of 2002 establishes standard for drugs. There was need to regulate the CFC-based MDI manufacturing beyond 2009; the new formulations or products with CFC-based MDIs; import of new CFC-based MDIs. In Egypt, the Islamic Republic of Iran and Mexico the regulatory process required nearly two years to get approval for registration from initial submission. In the Islamic Republic of Iran the institutions in charge implemented a streamlining programme aimed at reducing the approval period. It is worth noting that, after considering the situation in several countries (Bangladesh, China) the 2011 TEAP progress report recommended Parties to consider domestic regulations to ban the launch or sale of new products in Article 5 countries, even if already approved but not launched.[9]

[6] http://www.unep.org/SOUTH-SOUTH-COOPERATION/case/casedetails.aspx?csno=48)
[7] UNEP/OzL.Pro/ExCom/49/39
[8] UNEP/OzL.Pro/ExCom/37/58
[9] http://www.unep.org/ozone/teap/Reports/TEAP_Reports/

Access to technology

37. In its 2010 report MTOC concluded that formulation patents will not constitute a major barrier to the introduction of CFC-free MDIs. According to this report the most urgent need CFC MDIs for successful transition to CFC-free products in Article 5 Parties will be access to skilled technical consultants with the expertise to develop and implement HFA-MDI production and analysis. The report stresses that one option for countries that do not have the HFA products widely available could be to arrange a license system with a pharmaceutical company that has developed those products. The report stresses that "These countries might be able to achieve access sooner and less expensively through the provision of a royalty payment rather than through *ab-initio* product development". On the other hand if no patent coverage exists or if patents are not enforceable, the country could get access to technology granted in exchange for a greater market presence for example by establishing a joint venture in that country. This would provide a sufficient incentive to the pharmaceutical company with developed products.

38. In some countries the issue of intellectual property was moot. In India for example intellectual property issues are not foreseen, as India does not have to comply with WIPO requirements until 2016 which is beyond the timeframe of the project. Also by that time the patent for the drug molecules involved in this project will have expired.

Awareness, information and education

39. All countries have implemented awareness, education and information activities through various approaches. As mentioned before in India UNEP employed development facilitators a national NGO which organized five awareness workshops (one national and four sub national) on transition from CFCs to non-CFC-free MDIs to garner support for strengthening patient-doctor-industry–cooperation. These workshops brought together various stakeholders especially MDI manufacturing industries, importer of inhalation products, general practitioners. It is worth noting that enhanced communication across different sectors of government and between government and industry was a major factor in India's successful transition. During the south-south cooperation meeting between India and China the issue of comprehensive programme of awareness and education was also discussed.

40. Awareness workshops were organized in the Islamic Republic of Iran and Pakistan. In Bangladesh it was the Lung foundation in collaboration with Beximco that organized information activities. In Argentina the Government organized a dissemination strategy including radio, television and newspaper information; letters to pharmacists; promotional materials to doctors; in addition to awareness workshops. In addition to the awareness programme the Islamic Republic of Iran developed a human resources strategy under which it trained technicians.

Access to medicine

41. Access to medicine is related to awareness of new medical products, but also to the price of MDIs. Because the health of the population was the first priority in implementing transition strategies concerns were expressed about the possible increase in price of CFC-free MDIs as compared to previous product.

42. Since price is such an important factor in accessing the therapy, CFC alternatives should match or cost less than CFC products. In general, prices of DPIs and brand-name MDIs of the same drug are similar if compared on a cost per dose basis. However, in some countries there is a significant difference in price between DPIs and generic MDIs for the same drug. Since government authorities will favor lower priced medicines, countries will need to address the means to have their constituents accept the non-CFC alternatives. In some cases this could mean a demand to return to lower priced oral medicines for the

treatment of asthma and COPD[10]. Similar concerns were raised by the Secretariat in the comments on progress reports.

43. Several examples follow access facilitation through price control. The MDI usage in India is predominantly in urban areas and medical drugs and devices are provided at subsidized costs or no costs to patients. It resulted in increased interest and the number of patients, which in turn led to a significant increase of MDI production. In Pakistan prices of medicine are controlled by the Government. In the case of locally manufactured MDIs the price is the lowest in the region and there are questions concerning the sustainability of this low cost policy. Between 5-10% of the population has asthma and the population that could have access to MDI treatment is very small. There is little awareness on phase-out of CFC MDIs and adoption of alternatives. In Bangladesh the population access is facilitated because the Government buys MDIs and offers them free of charge. While access is not an issue, problems of sustainability could be raised (Multilateral Fund progress report comments and answers on project implementation in Bangladesh).

Causes of delays in project implementation

44. Delays in project implementation occurred because of a variety of cases. In Cuba, because of trade constraints between the United States and Cuba a new technology provider had to be found. As requested by the Government of Cuba, UNDP identified a technology provider specializing in research and development that could develop upon request the two MDI products currently manufactured in Cuba: salbutamol and fluticasone. Nevertheless both identification process and the provision of two products took time. It is worthy to note that Cuba was the first country to implement this type of project and at a time when no guidelines were available. The case of Cuba yielded valuable lessons learned that served in both the formulation of guidelines and to improve the implementation of other similar projects in other countries.

45. In Pakistan agreement with enterprises could not be completed during the year 2009. In addition, security concerns as well as intense flooding have further affected implementation progress. The Secretariat's comments pointed out that as of August 2010 only 57% of funds had been disbursed under this project.

46. For almost one year project implementation was delayed in Egypt due to construction works associated to preparation of new clean rooms. Furthermore the political situation in the country let to further delay and test period could not be shortened as initially planned because of personnel changes in the Ministry.

47. In Bangladesh conversion of the CFC MDIs was delayed due to several technical and policy issues related to the difficulty of re-formulation of the products and the high cost of transfer of technology from non-Article 5 to Article 5 countries as well as intellectual property rights concerns.

Other issues

Essential-use exemption for CFCs

48. The essential-use exemption was addressed by the Meeting of the Parties. Decision XX/3, paragraph 1 (e) of the Meeting of the Parties requires that "Parties operating under paragraph 1 of Article 5 submitting essential-use nominations for chlorofluorocarbons for metered-dose inhalers for the treatment of asthma and chronic obstructive pulmonary disease to present to the Ozone Secretariat an initial national or regional transition strategy by 31 January 2010 for circulation to all Parties".

[10] 2010 Report of the Medical Technical Options Committee (MTOC)

49. The Montreal Protocol control schedule requires a complete phase-out of CFCs by 2010. The manufacture of these drugs however has been essential for ensuring effective therapeutic treatment to asthma and COPD patients and a gap in the availability of medicine is not acceptable. Decisions 49/33, 50/19, and 50/20 of the Executive Committee recognized this risk in countries manufacturing MDIs, and urged for the preparation of conversion projects in this sector, to address this issue as soon as possible. Table 3 in Annex I shows the situation of essential-use authorizations of CFC MDIs in countries in the sample. While several countries were requesting essential-use authorization for 2010 and 2011, in 2012 only Bangladesh, China and Pakistan have requested. Pakistan may not apply for essential-use nominations in 2013.

50. The case of China is particular since its CFC production sector phase-out plan had been modified to permit exemptions for the production of CFCs for essential uses approved for other Parties. This issue was further discussed during the meeting of the Sub-group on the production sector at the 66th meeting of the Executive Committee. A recommendation was made to modify the production sector Agreement for China to allow the production for export of pharmaceutical-grade CFCs in 2012, with an annual review, for purposes of meeting the 2012 essential-use exemption for MDIs authorized by the Parties in decision XXIII/2 for the other countries, provided the exporting country had reporting and verification systems in place to collect and report specific information[11].

Elimination of residual stocks

51. The use of CFC stockpiles or recycled CFCs for manufacturing MDIs has major constraints and requires strict conditions often difficult to achieve. A study concluded that because of the very complex nature of the contaminants and their number present in recycled CFCs, it is impractical to develop commercial facilities to purify used CFCs to pharmaceutical standards.[12]

52. An example of effective elimination is the Islamic Republic of Iran. To ensure the effective decommission of CFC manufacturing equipment and elimination of any residual stock of CFCs – following up the successful implementation of the active part of the strategy and the removal of all CFC MDIs from the Iranian market, the Iranian Environmental Agency ensured that there are no residual stocks of CFCs at the national manufacturer and that all CFC manufacturing equipment made redundant by the transition to HFC propellant has been destroyed. The destruction was witnessed by the NOU representative.

V. TECHNICAL ISSUES

Funding requests for questionable items

53. In those reports where equipment lists are provided (with prices of each item) it is seen that Pamasol equipment is proposed to replace equivalent ODS-based equipment that would be quite serviceable for an HFA filling line. Examples are crimpers and pumps. These items are unaffected by a change from CFC to HFC propellants. In fact, for regular aerosol lines the same crimpers and pumps are successfully used with a dozen or more propellants and blends. As a notation, there are Chinese MDI equipment suppliers who are said to produce high quality MDI production line equipment. The Chinese MDI fillers are very probably utilizing this equipment in their transition to use of HFA.

54. Proposals for funding have sometimes included such peripheral increments as very costly Battelle Cascade Impactor and Malvern Multisizer laboratory equipment, revised structures, air purification and

[11] UNEP/OzL.Pro/ExCom/66/53
[12] UNEP/OzL.Pro/ExCom/49/39

humidity control systems and propellant “tonne cylinder” (or “pig”) storage platforms. When such items are listed for some countries but not others this dichotomy should be investigated.

55. Costly HEPA air filters, able to retain particulate matter with aerodynamic diameters as small as 0.2 micron (200 nm.) have been requested by fillers in some countries and placed in funding proposals. In the consultant’s opinion, filtration down to 1.0 micron is quite adequate. Particles of this size cannot plug or partly plug MDI valves, even if filamentous, or otherwise interfere with production quality.

56. Actually particles detected in MDI production ISO 8 Clean Rooms (ISO 15378:2006/ISO 9001) are found to come mainly from human sources --- for instance, from people improperly wearing hair and beard nets, instead of the preferred plastic or lint-free coverings and facial filter-masks. Dirty shoes are another source, solved by using special slippers surrounded by 0.25 mm. thick PE coverings. Electrical grounding of personnel at entry ways is beneficial as well.

57. Another funding proposal listed the purchase and installation of a large dehumidifier, to reduce the humidity to 40%. This would actually be a dangerous detriment to any line using iso-butane in MDI formulas. At below about 68% RH static charges can build up on non-conductive or electrically isolated surfaces causing sparks. Sparks of over 0.2 kJ. (energy) can ignite iso-butane vapors, if present at 1.86 v.% or more in air --- 20 C. basis.

58. Listings of Pamasol production equipment often include a costly 15 liter pressure-resistant compounding tank for the mixing of anhydrous ethanol, excipient and drug substance. This is regarded as an over-specification, since a small open-top tank, with lid and explosion-proof or pneumatic 0.10 H.P. “lightning” type mixer will suffice.

59. In equipment lists there are (atmospheric) crimpers for some lines and vacuum crimpers for others. It is generally considered useful to remove most of the tramp air from MDI cans prior to sealing and gassing them. While purchasing the atmospheric or non-vacuum crimper one saves equipment money, this approach necessitates the addition of an air-purging gas to the can. Although HFC-134a is almost always used, nitrogen and argon gases are other options. Depending on the purging device a stream of gaseous HFC-134a is directed into every can, so that the heavy vapor can displace most of the air. Over an eight hour shift the cost of the HFC-134a will range from about US $150 to US $450, and for a year this direct loss will be rather impressive.

Selective equipment destruction

60. The documents under review sometimes mention the destruction of CFC MDI filling equipment. Before “wielding the sledge-hammer” an investigation should be made to see if there are any other internal uses for it, or if it can be sold. This is especially true for stainless steel pumps which, in several listings, are scheduled for destruction at the rate of about 4 per revised production line. If destruction is inevitable, it should be carried out with a minimum of delay. Verification by third parties, by photographs, or by signed record sheets should be required.

Flammable MDIs

61. In one case the transition to replace CFC propellants with pharmaceutical-grade iso-butane, is one of great potential significance. It is doubtful if the International Pharmaceutical Aerosol Consortium (IPAC) has developed specifications for pharmaceutical-grade iso-butane, which can be specially distilled to a purity of 99.9%, but still contains propane, n.butane, iso-pentane, neo-pentane, various unsaturates, organo-sulfur compounds, hydrogen sulfide, water and traces of other compounds. The primary barrier to its use in MDIs is the firm position of the U.S. Food and Drug Administration that MDIs must be non-flammable. With about 80 to 98% of pharmaceutical-grade iso-butane in an MDI there is no way to make the spray non-flammable. Proponents point to the typical metered dosage of about 50 micrograms

(0.05 mg.), claiming that this is too small to create a hazard. Actually, 50 milligrams of iso-butane is sufficient to bring about 1.05 liters of ambient air to the lower explosive limit (LEL), if evenly distributed.

62. Most MDI filling facilities have never dealt with iso-butane. They are unaware of how dangerously flammable it is. While the Pamasol production equipment is pneumatic, it would have to be checked for the presence of any electrical motors, switches, control systems and so forth. With the liquid being brought into an interior room, high intensity, rapid turn-over ventilation, explosion-proof equipment, non-sparking substrates and a multitude of other safety measures would normally be implemented. It would not be possible to reasonably purify the air of particles under such conditions.

63. Other aspects of ISO-butane are that it can cause a slightly stinging, slightly oily taste on the tongue – markedly different from the taste of HFC-134a, for instance, and that it has the same fluidity as HFC-134a but only about 46% of its density. This may permit suspended drug substances to precipitate more rapidly, even though the particles only have a mean aerodynamic diameter of about 2.3 microns. If any significant settling occurs during consumer use, the first doses will contain more of the drug substance than the average and the last doses will then provide less therapeutic activity; i.e. less clearing of the bronchioles. (This aspect has probably been studied in the validation process and found to be insignificant.)

64. Political and economic expediencies must also be considered. The price of pharmaceutical-grade iso-butane is unknown, but the regular grade is less than about 5 to 10% of the price of pharmaceutical-grade HFC-134a. This means a dramatic price reduction for the factory cost of pharmaceutical-grade iso-butane based MDIs. Such formulas may also escape the very costly Patent royalties demanded by various multinationals in regard to HFA formulations. However, international Patents may already have been developed in regard to the unprecedented use of pharmaceutical-grade iso-butane in MDIs.

65. If the pharmaceutical-grade iso-butane based MDIs do well in the marketplace their economic advantage will be noted worldwide. Fillers in other countries will want to convert their HFA formulas to the much lower cost option. Some governments, who purchase MDIs and then sell them to consumers, will probably support the transition. A two-tier MDI business strategy would then develop, since the pre-requisite of non-flammability is a firmly requirement in North America, the United Kingdom of Great Britain and Northern Ireland, Japan and some other countries is not likely to be abandoned in the foreseeable future. Firms may have to invest in both some new equipment and in the reconfiguration of their production facilities, doing the gassing of pharmaceutical-grade iso-butane in “gas houses” with major ventilation and many other anti-explosion attributes.

Ethanol aspects

66. Some MDIs require the inclusion of anhydrous ethanol as a solvent for both the excipient and drug substance. Generally about 10 to 20% by weight of the finished formula can be ethanol, depending upon the drug choice and its amount. The ethanol mixture may be compounded in the production room, although preparing it nearby and piping it in is considered preferable. In any event, there are opportunities for spills, leaks “open air filling” and so forth to be considered, especially since anhydrous ethanol is very flammable (the Tagliabue Closed Cup Flash Point is about 13 C.) To minimize the fire hazard, the area around the liquid (ethanol) filler should be made explosion-proof (Group D) and spark resistant. Suitable fire extinguishers should be mounting in sensitive area, with workers instructed in their safe and efficient use. Additionally, anhydrous ethanol needs to be verified as truly anhydrous (as by the FFM) and stored only in sealed tanks or containers. Otherwise it can capture air humidity and become diluted with up to 7 weight-% of water at 50% RH. The use of this mixture will ruin at least several MDI formulations. This information should be imparted to prospective HFA MDI fillers.

VI. ISSUES RECOMMENDED FOR FURTHER EVALUATION

67. Field visits as well as a case study approach will allow a more in-depth perception of the issues related to the implementation of these projects. Face to face interviews with various stakeholders would allow a better knowledge of challenges in implementing projects.

68. Technical choices raised by this report may be clarified. More information can be obtained about the sustainability of price control for CFC-free MDIs and therefore on the sustainability of population access to medication. While government subsidizes the price of MDIs this may not ensure access of all concerned patients.

69. Furthermore, questions could be asked on educational programmes for health care professionals, government health authorities and patients about the transition to CFC-free treatments as well as about the attitude of the medical profession and patients concerning the new products.

70. As asthma rates seem to increase worldwide so will the production of CFC-free MDIs. How this will be addressed by the respective governments needs to be considered.

Countries to be visited

- India;
- Cuba;
- Argentina;
- China;
- Egypt; and
- Bangladesh.

Recommandation

71. The Executive Committee may wish to take note of the information provided in the desk study for evaluation of metered-dosed inhalers projects as presented in document UNEP/OzL.Pro/ExCom/67/9, including the proposed evaluation issues for the second phase of the evaluation.

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Annex I

Table 1

ALTERNATIVE TO CFC MDIs

Type of method	Description
HFC MDIs	Inhaler that uses a propellant.
Dry powder inhalers	Inhaler devices that deliver powdered medication without the need for a propellant.
Nebulisers	Devices that are filled with drug dissolved or suspended in aqueous solution, which is converted to inhalable droplets using compressed air.
Soft mist inhalers	Small portable devices that produce aerosols of respirable diameter from aqueous formulations have been under development for a number of years.

Table 2

ARTICLE 5 PARTIES WITH SIGNIFICANT MDI MANUFACTURING

No.	Country	2007 allowable CFC consumption	CFC consumption for MDIs		Ratio CFC for MDI/CFC allowed	
			Total	Nationally-owned	Total ratio	Eligible ratio
	(a)	(b)	(c)	(d)	(e) = (c)/(b)	(f) = (d)/(b)
1.	Argentina	704.59	187.69	130.85	26.64%	18.57%
2.	Bangladesh	87.24	61.81	51.40	70.85%	58.92%
3.	China	8,672.81	431.50	369.00	4.98%	4.25%
4.	Cuba	93.77	109.00	109.00	116.24%	116.24%
5.	Egypt	250.20	154.00	154.00	61.55%	61.55%
6.	India	1,002.16	375.00	300.00	37.42%	29.94%
7.	Iran (Islamic Republic of)	685.75	98.00	98.00	14.29%	14.29%
8.	Mexico	693.73	47.00	0.94	6.77%	0.14%
9.	Pakistan	251.91	85.77	19.57	34.05%	7.77%
	Total		**1,874.12**	**1,282.99**		

(a) Article Parties with CFC MDI manufacturing plants.
(b) CFC consumption allowable in 200, equivalent to 15 per cent of the CFC baseline consumption as reported under Article 7 of the Montreal Protocol.
(c) Total amount of CFC used for the manufacturing of MDIs by national and multinational companies. For several countries, this information has been extracted from the 2002 ATOC Report.
(d) Amount of CFC used for the manufacturing of MDIs by nationally-owned companies (i.e., excluding consumption by multinational companies).

Table 3

ESSENTIAL-USE AUTHORIZATIONS OF CHLOROFLUOROCARBONS FOR METERED-DOSE INHALERS (METRIC TONNES)

No.	Country	2010	2011	2012
1.	Argentina	178	107.2	-
2.	Bangladesh	156.7	57.0	40.35
3.	China	972.2	741.15	532.04
4.	Cuba	-	-	-
5.	Egypt	227.4	-	-
6.	India	343.6	-	-
7.	Iran (Islamic Republic of)	105	-	-
8.	Mexico	-	-	-
9.	Pakistan	34.9	39.6	24.1

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