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REPORT ON EVALUATION OF PROJECTS FOR THE CONVERSION OF CFC-BASED METERED DOSE INHALERS TO CFC-FREE TECHNOLOGIES

I. INTRODUCTION

1. The evaluation of projects for the conversion of CFC-based MDIs was approved by the Executive Committee as per decision 65/9. A desk study was carried out and presented at the 67th meeting which considered issues related to the formulation and implementation of projects dealing with the transition from CFC MDIs to CFC-free MDIs. It also analysed the institutional context of implementation and the variety of stakeholders that were involved. The desk study reviewed the components of transition strategies such as coordination mechanisms, examined the legal framework that had to be created for the new health products, technological aspects of the transition as well as the activities aimed at raising awareness among both medical practitioners and patients.

2. The desk study recommended further evaluative inquiry into the project implementation through field work, such as interviews with various stakeholders which would allow a better knowledge of the challenges in meeting project objectives. It requested clarifications concerning technical choices as well as more information about the sustainability of price control for CFC-free MDIs and the sustainability of the population's access to medication. Further 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 the attitude of the medical profession and patients concerning the new products.

3. This report synthesizes the findings of the individual country case studies carried out in Argentina, Bangladesh, China, Cuba, India and Pakistan by various consultants between September 2013 and March 2014[1].

4. More details and country-specific analysis are found in the country reports available on the Multilateral Fund website (for access by members of the Executive Committee).

II. EVALUATION OBJECTIVES

5. The evaluation assesses the effectiveness of the transition strategy in facilitating the achievement of project objectives, i.e. the replacement of CFC with CFC–free MDIs.

III. METHODOLOGY

6. A detailed questionnaire was prepared to collect information and was shared with the NOUs in each country. During field visits, the evaluation team interviewed the manufacturers, the NOU, the implementing agency, professional associations and other stakeholders. It visited manufacturing facilities and met members from the medical and pharmaceutical professions as well as official staff involved at various levels of project implementation.

IV. PROJECT BACKGROUND

7. All projects had the primary objective of phasing out the consumption of CFCs in MDIs manufactured in the countries. The projects also included awareness components to increase the knowledge of health professionals and the general public about the advantages of CFC-free MDIs. All the companies except one in Argentina opted for technologies using HFA-134a as the excipient (propellant). Laboratorio Pablo Cassará initially converted their salbutamol MDIs production to HFA, but is implementing its project to ultimately use isobutane as the excipient. In addition, two companies in India are also using HFA 227. The details of each of the projects is summarised in the Table 1 below.

Table 1. Sample of projects analyzed in the final report of the evaluation of MDIs

Country	Inventory No. and Date Approved	Agency	Short Project Title	Funding Approved	Expected Date of Completion
Argentina	ARG/ARS/56/INV/15 November 2008	World Bank	Replacement of CFCs with isobutane in the production of salbutamol MDIs at Laboratorio Pablo Cassará and replacement of CFCs to HFA in the production of salbutamol and budesonide by four locally-owned laboratories filling their own MDIs through third parties; and implementation of an MDI transition strategy	$2,806,874	Jan 2012 (revised Dec 2014)
Bangladesh	BGD/ARS/52/INV/26 July 2007	UNDP	Phase-out of CFC consumption in the manufacture of aerosol MDIs (Beximco, Square Pharmaceutical and Acme Pharmaceutical)	$2,776,778	July 2011
	BGD/ARS/52/INV/27 July 2007	UNEP	Transition strategy for phasing out use of CFCs in the manufacturing of MDIs	$70,000	July 2011 (completed Dec 2011)
China	CPR/ARS/56/INV/473 November 2008	UNIDO	Sector plan for phase-out of CFCs consumption in MDI sector	$13,500,000	Dec 2013 (revised Dec 2015)

[1] At the 71st meeting the Senior Monitoring and Evaluation Officer (SMEO) introduced an interim report that covered Argentina, Bangladesh, China and Cuba (UNEP/OzL.Pro/ExCom/71/15). She explained that for various reasons two countries included in the sample, Egypt and India, could not be visited. Decision 71/26 requested the SMEO to visit two additional countries and to submit a final report at the 72nd meeting. These two countries were India and Pakistan.

Country	Inventory No. and Date Approved	Agency	Short Project Title	Funding Approved	Expected Date of Completion
Cuba	CUB/ARS/41/INV/23 December 2003	UNDP	Phase-out of CFC consumption in the manufacture of aerosol MDIs	$5,960,000	Sept 2006 (completed Dec 2011)
Cuba	CUB/ARS/36/TAS/19 March 2002	UNDP	Development of MDI transition strategies	$24,002	April 2003 (completed March 2004)
India	IND/ARS/56/INV/423	UNDP	Plan for phase-out of CFCs in the manufacture of pharmaceutical MDIs (Zydus Cadila, Cipla, Midas Care, and Sun Pharma. GSK - opted out of project)	$8,082,267	November 2013 (All conversions completed by 2012, pending final verification)
	IND/ARS/56/INV/424	Italy		$2,000,000	
	IND/ARS/56/TAS/425	UNEP	National strategy for transition to CFC-free MDIs	$120,000	November 2013
Pakistan	PAK/ARS/56/INV/71	UNDP	Plan for phase-out of CFCs in the manufacture of pharmaceutical MDIs (GSK. Zafa opted out of project)	$449,996	November 2011 (GSK awaiting commercial production approval)
	PAK/ARS/56/INV/72	UNEP	National strategy for transition to CFC-free MDIs	$70,000	November 2011 (completed)

V. INSTITUTIONAL AND REGULATORY ISSUES

Organizational practices, including coordination and cooperation among various stakeholders

8. Three kinds of institutions can be distinguished as part of the institutional setting for the implementation of MDI projects. These are the enabling agencies which establish the policy and legal framework; the service providers which facilitate access to medicine and services; and the companies/manufacturers which produce the MDIs.

9. Enabling agencies are the institutions, organizations and agencies that play a “facilitating” role in establishing the laws, rules, policies and regulations that enable the allocation of resources, the functioning of the related structures and the achievement of the project objectives. Ministries, various coordination committees, NOUs and implementing agencies play a key role in articulating priorities and channelling them into policies and transition strategies.

10. The service providers include health institutions (hospitals, clinics), as well as less organized and informal service providers, such as alternative or traditional medicines. Sometimes, particularly for poorer and remote areas, access to formal service providers may be very limited and many of the health services may be provided through informal networks.

11. Because of the projects’ characteristics, ministries with different specialization were involved, such as the Ministry of Environment, Ministry of Industry and Ministry of Health. Therefore, the importance of coordination and communication among these institutions played an important role in project implementation.

12. To cope with the variety of institutions, some governments undertook modifications of the previous organizational flow or simply created new institutional mechanisms and structures to perform

the coordination. In Argentina, for example, the national responsibility with the Montreal Protocol lies with the Ozone Protection Office (OPROZ) integrated by the Ministry of Environment, the Ministry of Industry and the Ministry of Foreign Affairs. The coordinating responsibility for the MDI conversion project was discharged by PRESAO[2] (*Proyecto para la eliminación de las SAOs*) part of OPROZ, in charge of technical project implementation, reporting to the Ministry of Industry.

13. In Cuba, the design and implementation of the national MDI transition strategy required the creation of a coordinating body constituted by the Ministry of Science, Technology and Environment (CITMA), the Ministry of Health (MINSAP) and the chemical and pharmaceutical industry as part of the Ministry of Basic Industries (MINBAS). More specifically, the Centre for Health Promotion and Education (CNPES), National Coordinating Centre for Clinical Trials (CENCEC), National Centre for Control of Medications, Medical Equipment and Devices (CECMED) and the National Group for Asthma, all from MINSAP, were closely involved. Concerning the chemo-pharmaceutical industry, it was formed initially by several separate state organizations but has undergone an important reorganization since 2003 due to the implementation of a new economic model in the country. The former laboratory Julio Trigo Lopez (now AEROFARMA), the chemo-pharmaceutical industry QUIMEFA (now CUBAFARMA) and other research centres have integrated into BIOCUBAFARMA as a separate state-owned enterprise. The roles of each of these stakeholders are described in more detail under the specific activities in the country report.

14. In China, a more comprehensive process took place as a coordination mechanism was created since the approval of the country programme for ODS phase-out. A new structure, the National Leading Group (NLG) for Ozone Layer Protection had the task of providing strategic guidance and inter-sector coordination in ODS phase-out activities, including MDIs. The Ministry of Environmental Protection (MEP) played the lead role in the NLG, which included the Ministry of Foreign Affairs, Ministry of Finance, Ministry of Science and Technology, National Development and Reform Commission, Ministry of Public Security, Ministry of Information Industry, China Food and Drug Administration (CFDA) and selected government departments responsible for specific industrial sectors. This comprehensive structure allowed MDI-related activities such as methodology identification and exchange of information on alternatives to CFCs as early as 1995, long before the implementation of the transition strategy. Following the 2008 Executive Committee approval of the MDI sector plan, the Government established in 2009 a Special Working Group (SWG), which consisted of CFDA, the Foreign Economic Cooperation Office of Ministry of Environmental Protection of China (FECO/MEP) and individual experts. The China Centre for Pharmaceutical International Exchange (CCPIE) was selected as a domestic implementing agency (DIA).

15. While Argentina and Bangladesh have not reported any coordination problems, other countries faced some challenges. In Cuba, because of numerous stakeholders and their lack of interconnection, the coordination was complex and a supporting measure was needed to have more coordinating meetings and a more systematic approach to these meetings. In China, the completion of the MDI sector plan had to be extended to the end of 2015, representing approximately a 34-month delay from the original schedule. One of the reasons for this was that the implementation plan needed to be agreed upon by UNIDO, CFDA, and MEP/FECO and the coordination required more time than expected.

16. In addition, the implementing agency concerned had a role in both technical assistance and the allocation of resources, as well as in assisting in the phase-out process. For example, in Bangladesh, India and Pakistan, UNDP introduced a fast-track execution mechanism, which allowed compensating the enterprises for meeting the agreed milestones. In Cuba, UNDP played an important role as it had to take an active part in the day-to-day management of the project because of the need to coordinate extensively with international partners, and because of the uniqueness of the technical solution, which made the execution of the contract very challenging.

[2] Ozone depleting substances reduction project.

Evolution of the regulatory framework

17. In Argentina, Bangladesh, Cuba, India and Pakistan, there were no changes required to the existing regulations for registration and permission to produce CFC-free MDIs since the molecules were the same. However, the new formulations and packaging had to be approved by and licence obtained from the local Drug Authorities in order to start commercial production. In China, while the regulatory framework does not need to be amended, strict procedures must be followed when formulation of a drug, including the excipient, is changed, therefore, efforts to implement a "fast track system" to reduce the waiting time for CFC-free MDIs were not very successful.

VI. ACCESS TO MEDICINE AND HEALTH SERVICES

18. Access to medicine and health services depends on macroeconomic contexts and purchasing power of the population that shapes the demand-side needs and other diversities of the supply processes. The supply-side includes the manufacture and distribution of medicine. Knowledge about the benefits of the MDIs is another factor influencing demand.

19. In some of the countries under review, the problem that hampered access to medicine was the low purchasing power of the population. It was noticed that the proportion of patients using MDIs was higher in urban than in rural areas (Bangladesh, India, Pakistan) and in coastal areas than in inland areas (China) as the former are more developed than the latter. This problem, however, seems to be absent in Cuba where medicine is heavily subsidized by the Government and in Argentina where regulations and various social programmes facilitate access for the less favoured population.

20. Knowledge about MDI benefits is scarce in some countries where the population prefer traditional methods. In Bangladesh for example 10 per cent of asthma and chronic obstructive pulmonary disease (COPD) patients use MDIs, a proportion lower than in other countries. Most of the population in Bangladesh resides in rural areas where more affordable but less preferable treatments are used, such as oral medication and injectable treatment. Based on old habits of treatment, some doctors and patients in China still choose less effective oral medicines or injections instead of MDIs as well as traditional medicines to relieve or cure asthma. According to a 2012 investigation carried out as part of an awareness campaign, only about 10 per cent of the patients are using MDIs, but the numbers are growing in line with the rapid development of the country.

21. In addition, the demand for MDIs was also related to the novelty of the medicine. For example, MDIs as a therapeutic treatment for the asthma and COPD is relatively new in Bangladesh. The first CFC MDI product was only developed and launched in the market in 1997. Despite the fact that the average rate of growth in the use of MDIs is estimated at 20 per cent per year, the market has not matured yet and MDIs have not covered the potential portion of the patients as expected.

22. Supply depends on the locally produced and imported MDIs and by how these influence the price of the product. In China and Pakistan, MDIs are provided to patients by local and foreign manufacturers. In China, local production has been rising steadily from 12 million cans in 2004 to about 28 million cans in 2011. Foreign companies, however, apply a rather aggressive marketing strategy by putting pressure on the competitiveness of local MDI manufacturers and prefer to distribute their products to coastal areas where a more affluent population lives, than to inland and poorer areas.

23. In some countries, the legislation protects local production as well as the purchasing power of the patients. The Bangladeshi Law prevents importation of products from foreign companies when these are produced by local companies. The imported products are CFC-free MDIs and dry powder inhalers (DPIs), which are much more expensive than locally produced MDIs. The Government policy in China put a top limit on the locally produced MDI price that cannot exceed 25 RMB, while there is no price ceiling imposed on imported products. All these factors prevent the infiltration of imported products into

mainland towns and vast rural markets with high demand. The imported HFA-MDI and DPI products can only be purchased in larger cities where the emerging middle class frequently prefers to buy imported products despite their higher price.

24. In addition, in Bangladesh, India and Pakistan, the companies are required to get approval of the selling price for medication from the Drug Controller at the time of registration, particularly for salbutamol formulations. Increasing prices are difficult for the companies as they have to provide justification as well as be competitive with other local manufacturers. The average difference in price between CFC-based MDIs and HFA-based MDIs ranges from 30 per cent for salbutamol (the fastest moving MDI) to less than 10 per cent for other molecules.

25. In Argentina there was an increase in the price of MDIs since 2008 of approximately 15 to 20 per cent, mainly due to inflation. The manufacturers explained that since there is a regulation on medication prices by the Government, the increase in production costs cannot be transferred entirely to the patients. As a result of numerous medication donation programmes (both public and private), a sizeable part of the less affluent population receives the medication for free.

26. The strong improvement in availability and wider use of MDIs in general, rests in the accelerated build-up of local production capacity of CFC-free MDIs. It also depends on doctors and health practitioners in rural areas being aware of MDIs and their health benefits, feeling confident in prescribing this new medicine which is different from the traditional approaches to treatment, and advising the patients on its proper use.

27. Access to MDIs is also determined by the organization of the health service systems, which varies from one country to another. In Cuba and China state health services prevail. In China, the provision of health service to the population is organized through a network of hospitals and health centres that function on three different levels: county, township and village. Private sector providers cover a small fraction of the market mainly in big cities. Residents of urban areas are not provided with free healthcare, and must either pay for treatment or purchase health insurance. In rural areas, most health care is available in rather rudimentary clinics or by family doctors. These services are covered by the Government.

28. In Argentina the health care system has three sectors: public, social security and private, covering roughly 40.5 per cent, 50.5 per cent and 9 per cent of the population respectively. Since 2002, the Government implemented the National Medications Policy to facilitate the access to medicine. In addition various governmental programmes and NGOs ensure the provision of medication free of charge to the most disadvantaged patients.

29. All the evidence suggests that the accessibility of patients to MDIs has not changed significantly because of the conversion to CFC-free technologies, and its sustainability largely depends on the government health care policies and special programmes for health care assistance, and the level of awareness of doctors and patients about MDIs benefits.

VII. IMPACT OF AWARENESS CAMPAIGNS

30. Awareness campaigns about the benefits of the CFC-free MDIs, usually took place through meetings and workshops with the medical profession and the dissemination of informative material for both public and specialists. In some countries (Argentina, Bangladesh, India, Pakistan) funds for these activities were insufficient.

31. In Argentina, the Government and the MDI manufacturers conducted separate awareness campaigns. The Government campaign was of limited scope due to reduced funding, but it teamed with UNEP network meetings and with the Medical Technical Option Committee (MTOC) meetings, where

the national industry was invited to participate. The industry trained their sales forces, and through them, distributed brochures to the pharmacies and conveyed the information about the medication to the doctors.

32. In Bangladesh the campaign benefitted from high level political involvement. A meeting, organised by UNEP entitled "A New Lease of Life for Asthma Patients" was attended by the President of Bangladesh and various Ministers. The meeting acted as a catalyst for the pharmaceutical companies (mainly Beximco) to partner with the Bangladesh Lung Foundation to conduct more than 25 seminars addressed to doctors and medical students to create awareness. In addition, company representatives visited the doctors on a regular basis to brief them on the advantages of HFA-based MDIs from both an environmental and therapeutic point of view. Also, newspaper advertisements addressing the general population were used to raise awareness and technical articles were published in scientific magazines.

33. The China State Institute of Pharmaceutical Industry (CSIPI) conducted a series of surveys among asthma and COPD medical staff in hospitals, medical school students, pharmaceutical researchers, pharmaceutical manufacturers, patients and general public. The surveys revealed that the general public and patients were aware of the harmful impact of CFCs on the ozone layer but believed that CFCs in MDIs was unhealthy and only a few knew how to use MDIs. Approximately 85 per cent of the public surveyed believed that oral administration and injection are the most effective ways to treat asthma and COPD. The results of the surveys helped to outline the awareness campaign strategy.

34. The use of a variety of media outlets such as website, videos, newspapers, professional magazines among others, facilitated greatly in reaching out to the targeted population and professionals throughout several provinces in the country. At the end of the project, polls were conducted among target groups which showed very positive results.

35. In addition, continuing educational programmes have been initiated by the CSIPI especially for young pharmacists, including on the use of MDIs. Apart from awareness campaigns conducted under the MDI sector plan, a number of similar activities have been undertaken by the Chinese Medical Doctor Association (CMDA) and the Chinese Pharmaceutical Association (CPA). Better coordination with the Ministry of Health and professional associations at the SWG level is required to strengthen the patient-doctor cooperation.

36. In Cuba, the design and implementation of the training and awareness campaign was carried out under a very rigorous methodological approach that seems to be engrained in the organizational culture and supported by a vast infrastructure of institutions, personnel and know-how. Several workshops and training programmes were held and brochures, leaflets, posters and videos were prepared and distributed. A survey that targeted patients with asthma and COPD confirmed that 94.2 per cent knew the composition of the medication, 86.9 per cent affirmed to know the importance of CFC-free MDIs for the protection of the ozone layer, and 94.6 per cent knew the steps for proper use of MDIs.

37. In India, a national awareness workshop and a regional awareness workshop were conducted targeting key stakeholders as well as a national consultative workshop on policy and regulations on CFC MDI phase-out transition strategy implementation and adoption of CFC-free alternatives. Outreach work was taken up by industry as a spin-off of the three workshops/seminars organized under the MDI project. Also, approved funding was not sufficient as per the original plans in the project document. Unfortunately feed-back on the impact of these activities is missing.

38. In Pakistan, two international awareness and information exchange workshops on the transition strategy for CFC-MDIs were held. The awareness programs were held in advance of the locally manufactured products coming into the market (they are still awaiting approval). Some doctors felt that the awareness programmes benefited the introduction of imported HFA MDIs.

VIII. TRAINING AND SKILL DEVELOPMENT

39. MDI transition strategy has helped enhance professional capacity building in each of the countries in various respects. From the manufacturers end, the companies have gained capacity of formulation and method of analysis. Healthcare service providers continue to be made aware of the benefits of the transition into HFA inhalers.

40. In most of the countries, as the beneficiary companies had the know-how, or procured the know-how to develop their formulations, the only technical training necessary was dealing with the operation of the new equipment provided by the equipment manufacturer. This training provided the added benefit of building national capacity for future developments.

41. China planned to have six training workshops for participating enterprises consisting of training on new requirements and validation of new production processes, on the financial and management aspects of conversion projects and on rationalization of related policies. It was found that the technical and management gaps between companies were too big and four of the workshops were cancelled. Problems related to these issues were solved on case-by-case basis. A workshop was held on the registration process of new products and contracts with eligible enterprises. Training and skill development activities have been carried out by manufacturing companies according to their own plans and transition schedule.

42. In Pakistan, International Primary Care Respiratory Group (IPCRG) provided funding for the local chapter of the Primary Care Group to train general practitioners in the use of inhalers and the conversion to HFA. In addition, Glaxo Smith Klein (GSK) is funding the Aga Khan University in training the nursing assistants of doctors in the proper use of MDIs. This training is conducted by nurses from the university and each session is for about 2 to 2 1/2 hours with demonstrations, videos and hands on training.

IX. MARKETING/PRODUCT ACCEPTANCE

43. Manufacturers in Argentina, Bangladesh and Cuba advised that there were no reported adverse reactions to the medicine (although no statistical figures were provided) except for eventual complaints about a change in taste. This positive outcome is attributed to the Government's information and awareness campaign which is designed to take into account the psychological effect of the change on the patients. Users of CFC-based MDIs who have complained that the new product is less effective are being advised about the 'cold-Freon' effect from CFC MDIs that results from the impact of the aerosol plume on the back of the throat. The new HFA MDI produce much softer and warmer plumes when compared with the CFC MDIs and cause larger deposition in the peripheral airways, which is good. Another common complaint was the obstruction of the actuator due to the deposit of the HFA. The problem is solved by just washing the actuator with water which is explained in the indications for use on the canister. This did not happen with CFCs.

44. In China only one company has introduced HFA based MDIs but no market feedback has been reported thus far.

45. In India, all the generics that were available as CFC-based inhalers are now converted to HFA-based inhalers within a reasonable price, although the price of HFA-based MDIs are slightly higher than the equivalent CFC-based ones. It should be noted that the Indian Drug Price Control Organisation (DPCO) sets the prices for many products following discussions with manufacturers. Salbutamol, beclomethasone, and beclomethasone salbutamol combination MDIs come under the purview of the DPCO. For other products, companies can set their price. One company advised that while their salbutamol CFC-based MDIs cost Rs. 74 (US $1.20), the equivalent HFAs based MDIs cost Rs.84 (US $1.30).

46. In Pakistan, locally manufactured MDIs are still awaiting approval for commercial manufacture. Imported HFA-based MDIs are well established in the market.

X. FUNDING ISSUES

47. Some countries felt that the funding allocated for awareness campaigns has not been enough, resulting in the Government depending on the pharmaceutical companies to market their products. In Bangladesh, for example, the Lung Foundation (NGO) would prefer to train the doctors independently and do not appear to be favouring any particular company product.

XI. ESSENTIAL USE EXEMPTIONS

48. Argentina obtained approval for CFC essential use exemptions only in 2010 and 2011 for 178 and 107.2 ODP tonnes respectively at the 21st and 22nd meetings of the Parties although the original project foresaw the request of essential use exemption until 2014.

49. Bangladesh was given essential use exemption of 156.7 ODP tonnes in 2010, and 57.0 ODP tonnes in 2011 for CFC-11 and CFC-12 for MDI use. However, Bangladesh did not import any CFCs for MDI applications in 2012.

50. China received essential use exemption of 972.2 ODP tonnes in 2010, 741.15 ODP tonnes in 2011, 532.04 ODP tonnes in 2012 and 388.82 ODP tonnes in 2013 and planning to use exemption until 2015. The evaluators have noted that according to the national transitional strategy, the complete CFC phase-out in MDI sector might be delayed until the end of 2017, i.e. four years later than originally scheduled in the MDI sector plan and the date of completion established in project proposal. The 2011 independent verification of the production sector in China identified the availability of significant unutilized stock of MDI-grade CFCs. The producing company managed to sell only about 35 per cent of the nominated production. On-the-spot inspections carried out by DIA at MDI manufacturers revealed that purchases of quota production levels were less than those allowed under the exceptions for essential use. It is important to establish coordination between independent verification carried out by the World Bank according to decision 66/54[3] and inspection activities that have been undertaken by the local implementing agency. These efforts would further facilitate the implementation of decision XXII/4 whereby the Parties encouraged Article 5 Parties with essential-use exemptions to consider sourcing required pharmaceutical-grade chlorofluorocarbons initially from stockpiles where they are available and accessible.

51. Cuba did not apply for any essential use exemptions although it needed to import CFC-free MDIs when national CFC based MDI production ceased and national CFC-free MDI production could not meet national demand.

52. India was given essential use exemption of 343.6 ODP tonnes in 2010 for CFC-11 and CFC-12 for MDI use.

53. Pakistan was given essential use exemption of 34.9 ODP tonnes for 2010, 39.6 ODP tonnes for 2011 and 24.1 ODP tonnes for 2012 CFC-11 and CFC-12 for MDI use.

[3] Decision 66/54 includes, *inter alia*, modification of China's CFC production sector phase-out plan to permit exemptions for the production of CFCs for essential uses approved for other Parties for 2012.

XII. TECHNOLOGY AND TECHNICAL ISSUES

Access to technology, technology transfer or product development

54. The change of technology presented a number of technical, organizational, and political challenges. The resolution of technology and technical problems is one of the most difficult to address according to manufacturing enterprises.

55. The most challenged country was probably Cuba, which, in addition to being the first country to implement this type of project, it also had to deal with the trade restrictions imposed by the United States of America. After a first rejection, the country started anew in finding a provider. In 2005, a laboratory, Impopharma Inc. from Ontario, Canada, teamed with the equipment manufacturer Pamasol Willi Mader AG from Switzerland to provide the necessary technology and equipment for the two MDI products currently manufactured in Cuba: salbutamol and fluticasone. Nevertheless, both the identification process and the provision of two products took time. In addition the Canadian laboratory did not have the required experience with the infrastructure, the technology or the equipment, therefore, the transition from a laboratory stage to an industrial stage of production was challenging although successfully achieved.

56. In Argentina, the two companies, Laboratorio Pablo Cassará (LPC) and Denver Pharma (DF) developed the isobutane-based technology internally and therefore own the intellectual property rights to their own formulations. The molecules produced at LPC are: salbutamol, budesonide, ipratropium, salbutamol/beclomethasone, fluticasone/salmeterol, salbutamol/ipratropium and budesonide/salmeterol. The molecules produced at DF are budesonide, beclomethasone, salbutamol, salmeterol/fluticasone and salmeterol/beclomethasone. The selection of the molecules responded to the needs of the market and the corresponding market shares and niches of each of the enterprises. The selection of the MDI as the delivery method followed a careful analysis of all available alternatives. LPC undertook two conversions at once, namely the conversion of the existing production lines to HFA-based MDIs and the design and installation of a new production line for isobutane-based MDIs. The latter followed internationally recognized standards for manufacturing plant project development.

57. The formulation development at LPC for both HFA and isobutane followed the usual steps, namely: development of the formulation; development of the different elements of the packaging: valve, canister and actuator, in parallel; pilot batch tests; accelerated stability tests; start of registration process; and long term stability tests.

58. For LPC the biggest challenges occurred in the formulation process, the stability tests and the site acceptance test. The stability tests for some of the HFA formulation, when done off-legal requirements (more than required by local regulations) presented more interaction with the internal coating of the canisters, thus requiring a special coating of the internal surfaces of the canister by plasma induction in gas. For the isobutane formulation there was no such problem. On the other hand, eventually the formulations with HFA turned out to be more fluid and required less demanding equipment cleaning which increases productivity.

59. One special step in the process was the development of scaled equipment for the pilot batch tests since the substance to be handled was no longer a liquid but a gas. The company made an agreement with the Italian company Coster with local representation for the development of the valves. For one of the products, budesonide, the valve could not be developed locally and had to be procured internationally.

60. The formulation process with HFA is “one step” both at LPC and DF and they both use ethanol in their salbutamol MDIs with a maximum percentage of 14 per cent, the rationale behind this being that ethanol use is an advantage for tropical and wet climates with relative humidity above 65 per cent since in the absence of ethanol the salbutamol molecule could lose some of its properties taking into account its hydrophilic condition. Both companies report that it was necessary to develop the entire MDI device with

the valve being the most challenging part. LPC reports the use of both solutions and suspensions depending of the molecule while all of DF formulations are suspensions.

61. The canisters used for the HFA MDIs were the same as those used for CFC MDIs that is, made in aluminium. There was an important decision related to the canisters internal coating with polycarbonates. Both companies decided not to use the internal coating previously used despite the fact that this technique is still used by other laboratories in the world.

62. Together with the transition, DF developed a new spacer device with low electrostatic charge for MDIs use for infants and children while it reports that with the use of HFA instead of CFC the actuator tends to be more easily obstructed. Both the doctors and the patients were instructed on this point.

63. Notwithstanding that both enterprises consider the process for development of a new formulation a challenging one, there were no serious delays that could not be compensated for, and both companies carried out the conversions to HFA successfully and on schedule. LPC's conversion of the salbutamol line to isobutane is equally on schedule. As of February 2014, the registration process for the isobutane-based salbutamol MDI has been initiated and completion of the project is expected for end of 2014 as initially planned.

64. In summary it can be said that the local adaptation of the new technologies, both HFA and HC-based, posed technical challenges of varying complexity whose impact could be reduced through careful planning and technical preparation. The need for internationally approved safety measures and standards only added another layer of complexity to the project that needed to be accounted and planned for, and in turn ensure the safety of operations in handling flammable stocks acceptance test (SAT).

65. In Bangladesh, a technical issue was the volume of suspension left in the mixing vessel, which fell below the stirrer. The companies worked closely with the equipment manufacturer and were able to reduce the volume which could not be used. An MDI manufacturer (Square) was unable to launch some of its products because the demand was too small and had to find a smaller conical mixing vessel for smaller batches. All companies have developed state of the art manufacturing and testing facilities and have installed high speed equipment which has increased their capacities substantially (counterpart funding was provided by the enterprises).

66. In China, the pharmaceutical companies that decided to develop their own formulations faced challenges in the transition from CFC-based to HFA as they had to redesign the MDI formulation and readjust the production process. The development of its own formulation required sufficient research and development capability, laboratory and testing equipment. Other technical challenges in China were related to MDI components. The use of HFC-134a excipient requires new valve and coated canisters. The new physical properties of the formulation entail changes in the valve design to ensure the proper flow and dosing. Since HFC-134a is chemically less stable than CFCs, valve components (e.g. airproof rubber and its additives) should be compatible with the new propellant. In certain instances, a new actuator needs to be designed in order to ensure a proper distribution of active ingredient particles and adjust the flow speed. The four companies visited purchase canisters and valves from international suppliers. According to companies visited in China, the resolution of technology and technical problems is the most difficult to address for manufacturing enterprises and it may take up to four years to be solved.

67. In India, all product development was done in-house, with support to some companies from the packaging suppliers. There were some stability issues with alcohol. At one company, initial alcohol content of 4 – 5 ml caused stability issues. Reducing the alcohol content to one per cent caused large changes in concentration due to variations in the two-stage filling machine. With equipment supplier's support they moved to a single-stage filling machine and overcame their problems.

68. Cipla was having stability problems with HFA-134a for their ipratropium, ipratropium/salbutamol combination and triotropium molecules. They moved to HFA-227 and were able to obtain stable products. Cipla advised that the actuator choices were time consuming. Valves were also a major hurdle. Dry products need one type of valve, while alcohol-based products need another type of valve. Their export products use Spanish valves. Any change of valve supplier or orifice change in actuator has to go through the full approval process. The company is using plain cans for some products, anodised cans for other products and epoxy coated cans for still other products (which will soon be replaced by plasma coated cans).

69. At Midas Care there were stability issues with tiotropium, ipratropium, tiotropium/formoterol combination and formoterol/beclomethasone when developed with HFA-134a. Stability issues continued when formulated with HFA-227. Ultimately, a blend of HFA-134a and HFA-227 (approximately 50 per cent each) was found to provide a stable product.

70. All companies except Midas Care have both dry formulations and wet (alcohol-based) formulations. Cipla changed their entire production lines at all the facilities; Midas Care retrofitted one two-stage production line to handle high pressure HFA-134a, and procured one single stage line and one line with both one stage and two stage filling capability. Zydus Cadilla's filling line could handle both CFCs and HFA products. Sun Pharma retrofitted their filling line with a filling head for single stage filling.

71. In Pakistan, GSK the only beneficiary of the project obtained its technology from its parent company from their Everaux, France location. All research and development was done in France and all the equipment was recommended by them. Installation of all equipment was done by Pamasol, the equipment supplier. The company developed an alcohol-free formulation for salbutamol and is awaiting approval to begin commercial production.

72. While Macter in Pakistan was not a beneficiary of the project as they started production after the cut-off date, they proceeded on their own to convert their CFC-based MDI production to HFA-based MDIs. Initially, there were some issues due to the lack of pilot equipment but since they started this process early in 2009, they had enough time to sort out the alternatives. Issues related to testing were addressed with the assistance of Karachi University and the purchase of the equipment was later resolved. They also received assistance from Pharma Delivery Solutions (project consultant) and Bespak, the packaging components supplier. Issues of stability were resolved with advice from their consultant, and did not cause any significant delays. The company is using alcohol in their formulation, but have been able to reduce the quantity of alcohol as well as one chemical which left a bitter after taste. The original equipment was a six-head Pamasol two-stage filling and sealing machine, which was retrofitted in-house and have been fully tested using two-stage filling. The enterprise is currently studying how to retrofit to single-stage filling.

Incremental capital investments and incremental operating costs

73. Funds approved did not cover all the costs of transition from CFC to CFC-free MDIs and varied depending on the baseline production. All the companies had to put in counterpart contributions. The amounts remain confidential in most cases and can be attributed to the larger volume of production lines and costs for setting up and equipping the laboratories and research and development centres.

74. Incremental operating costs (IOC) were not available from the manufacturers in Argentina, Bangladesh, Cuba, India and Pakistan.

75. As mentioned earlier, one company in India advised that while their salbutamol CFC-based MDIs cost Rs. 74 (US$ 1.20), the equivalent HFA-based MDIs cost Rs.84 (US $1.30). The data from China show that the cost for one CFC-based MDI ranges from 4.18 to 6.01 RMB (US $0.67 to US $0.97) in four

enterprises. The cost for one HFA-based MDI ranges from 5.96 to 8.70 RMB (US $0.96 to US $1.40). The calculated IOC in the China MDI sector plan was 0.59 RMB (US $0.09) per can that represents about 23 per cent of averaged IOC based on current prices for MDIs components. The main variation is in the canister price followed by the price of CFC and HFA.

XIII. CAUSES FOR DELAYS

76. Delays occurred for various reasons. In the case of Bangladesh, although the project was approved in July 2007, the agreement between UNDP and the Government was approved in September 2008, and the agreements between the Government and the manufacturers were signed in October 2009. By 2011 the manufacturers had their HFA-based plants producing commercially.

77. In China, the registration of CFC-free MDIs remains a big challenge for manufacturers resulting in substantial delays. The structure of the MDI manufacturing industry is such that in 2007 four companies (out of 16) covered 91 per cent of the total annual production. The lack of capital in small companies and high price of patent rights and royalties is the impediment factor in technology transfer. This is the cause of many delays in starting early production of CFC-free MDIs. The total phase-out of CFCs in MDI production in China will not take place earlier than 2017.

78. Establishing the date of the ban on CFC consumption in China still remains an issue. The uncertainty in establishing the date of the complete CFC phase-out sends a confusing signal to MDI manufacturers. This uncertainty needs to be addressed as soon as possible. According to the implementing agency (UNIDO) this is a complex issue as the status of transition is difficult for the companies involved and is not easy to decide for an absolute ban of CFC consumption. A workable regulation would have to take into account the great variety of products as well as local needs of manufacturers and patients. The CFC ban could be supportive at the end of the transition process, in particular to guarantee the sustainability of the conversions. In addition, the prices for locally manufactured MDIs are regulated by the Government thus reducing the profit margin and availability of capital for manufacturing companies. Local MDI manufacturers are also facing competition from multinationals. These circumstances limit the investment potential thus making the conversion to CFC-free MDIs more difficult. Furthermore, the large number of applications and limited capacity of CFDA registration departments creates a backlog. In 2011, CFDA established “a fast track system” trying to reduce the waiting time for applications for CFC-free MDIs. However, the registration of CFC-free MDI remains a big challenge for manufacturers in China leading to big delays in transition to CFC-free MDIs.

79. In Cuba delays were related to the identification of a technology supplier that would not be affected by the commercial exclusion as a consequence of the United States of America embargo on the country; and the customary complications in creating a new pharmaceutical formulation and locally implementing a foreign complex technology, no other important causes for delay were identified.

80. In India, a Memorandum of Agreement (MoA) was signed by all the companies in October 2009. All four companies converted to HFA-based production by end of 2011 early 2012. Some of the companies had already introduced HFA-based MDIs before signing the MoA.

81. In Pakistan, there were delays by GSK in initially signing the MoA. Subsequently, it was realised that their foreign shareholding had increased from 78 per cent at time of project approval to 82.59 per cent in 2013. The funding had to be reduced and a new MoA was finally signed. While they are ready to start commercial production they are awaiting approval from the regulatory authorities.

XIV. CONCLUSIONS AND LESSONS LEARNED

82. All countries visited fulfilled the project objectives or are on the way to doing so. They achieved or will achieve the replacement of CFC MDIs with CFC-free MDIs by the end of 2014 while China will be in 2017. In addition, the transition was made without detriment to the patients with asthma or COPD.

83. Nevertheless project implementation had to face challenges:

(a) Because of the complexity of projects and of the large number of stakeholders involved such as the Ministry of Environment, Ministry of Industry and Ministry of Health, related departments, drug regulatory bodies, professional organizations, implementing agencies and private companies, the importance of coordination and communication among the involved institution played an important role in project implementation. To deal with this new situation organizational configurations had to be amended in several countries and new coordination bodies were created;

(b) Access to medicine and health services depends on both demand side needs and complexity of supplies, and is influenced by several factors such as the purchasing power of the population; the awareness of both patient and medical providers of the benefits of the new medication; the organization of the medical system and the manufacture and distribution of medicine. The evaluation highlights that there are major differences in the purchasing power between rural and urban areas as well as between coastal and inland areas; international companies prefer to focus on more affluent areas; in some places patients still prefer traditional medicine. To solve these problems it is necessary to develop a strong local production, develop the distribution system and increase the awareness activities to reach a larger number of stakeholders and patients;

(c) The accessibility of the patients to the MDI medications, and its sustainability have not changed after the conversion of MDIs to CFC-free technology mostly because of Governments' policies concerning public health care; price regulations for medications; and in some countries, free health care for an important segment of the population and numerous social programmes that guarantee free access to medications for the beneficiaries;

(d) The effect of awareness campaigns was positive in raising the level of knowledge on the benefits of MDIs. The campaigns highly benefitted from the involvement of high political levels, as in Bangladesh, and from the participation of private companies, professional medical and pharmaceutical associations;

(e) In China, the establishment of formal communication channels among various stakeholders (MEP/FECO, CFDA and Ministry of Health (MOH), CMDA and CPA) would be beneficial for the implementation of the MDI sector plan. The incorporation of representatives of MOH, CMDA, and CPA into the special working group would benefit the promotion of locally-produced CFC-free MDIs at the hospital level, by strengthening the patient-doctor-industry cooperation, and would facilitate the continuation and minimize the costs of awareness campaigns;

(f) In Cuba, the design and implementation of the training and awareness campaign within the MDI transition strategy was carried out under a very rigorous methodological approach supported by a vast infrastructure of institutions, personnel and know-how. This methodology alone would ensure a higher cost-effectiveness for similar programmes and should be shared with other Article 5 countries. Implementing agencies could play a more proactive role in spreading the experience gained in organizing these MDI-related

awareness campaigns in other Article 5 countries;

(g) Technology transfer met challenges of a technical, organizational and political nature and often led to delays in project implementation. Technical training took place in all projects and was essential for the success of the project and provided the added benefit of building national capacity for project results sustainability as well as for future developments;

(h) It would be useful to establish a coordination between independent verifications carried out by the World Bank according to decision 66/54 and spot inspection activities, such cooperation would facilitate the implementation of decision XXII/4 that encourages Article 5 Parties with essential-use exemptions to consider sourcing required pharmaceutical-grade CFCs initially from stockpiles where they are available and accessible;

(i) A great number of stakeholders and their lack of interconnection made project coordination even more challenging and necessitating more coordinating meetings. It is therefore needed for a more systematic approach to these meetings as a supporting measure; and

(j) The existence of the relevant national institutions greatly facilitated the implementation of the training and information campaign within the MDI transition strategy, by providing the appropriate infrastructure, the know-how and much of the resources for a successful implementation.

XV. RECOMMENDATION

84. The Executive Committee may wish to note the report on evaluation of projects for the conversion of CFC-based metered dose inhalers to CFC-free technologies contained in document UNEP/OzL.Pro/ExCom/72/9.
