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Matters relating to issues covered in the 2009 progress report of the Technology and Economic Assessment Panel: report of the Secretariat of the Multilateral Fund for the Implementation of the Montreal Protocol on the status of agreements to convert metered-dose inhaler manufacturing facilities in Parties operating under paragraph 1 of Article 5 (decision XX/4)

Report of the Executive Committee of the Multilateral Fund on the status of agreements to convert metered-dose inhaler manufacturing facilities in Parties operating under paragraph 1 of Article 5 and implementation of approved projects (decision XX/4)

Note by the Secretariat

The Secretariat has the honour to circulate, in the annex to the present note, the report of the Executive Committee of the Multilateral Fund on the status of agreements to convert metered-dose inhaler manufacturing facilities in Parties operating under paragraph 1 of Article 5 and implementation of approved projects (decision XX/4) for the consideration of the Open-ended Working Group. The report is being circulated as received and has not been formally edited by the Secretariat

* UNEP/OzL.Pro.WG.1/29/1.

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Annex

Report of the Executive Committee of the Multilateral Fund on the status of agreements to convert metered-dose inhaler manufacturing facilities in Parties operating under paragraph 1 of Article 5 and implementation of approved projects (decision XX/4)

Background

1. At its 20th Meeting , the Parties to the Montreal Protocol specifically requested the Fund Secretariat to report to the Open-ended Working Group (OEWG) at its 29th Meeting (July 2009) on the status of agreements to convert MDI manufacturing facilities, and on the implementation of approved projects in Article 5 countries. The Parties also requested TEAP to present a report on the potential timing for final campaign production, taking into account, *inter alia*, essential use nominations (EUN) from Article 5 and non-Article 5 Parties, options for long-term storage, distribution, and management of produced quantities of pharmaceutical-grade CFCs before they are needed by Parties, and options for minimizing the potential for too much or too little CFC production as part of a final campaign (decision XX/4).

2. The Fund Secretariat prepared this paper in response to paragraph 2 of decision XX/4, and submitted it for consideration by the Executive Committee at its 57th Meeting (April 2009). In preparing the paper, the Fund Secretariat requested relevant implementing agencies to provide a progress report on the status of implementation of MDI projects, including yearly amounts of CFCs used in MDIs until conversion to a non-CFC alternative is achieved. A draft version of the paper was sent to relevant implementing agencies for their review. Comments received by Executive Committee Members and the implementing agencies have been incorporated into the final version.

3. Accordingly, the paper is being submitted to the 29th Meeting of the Open-ended Working Group.

CFC-MDI phase-out projects under current implementation

4. The Executive Committee has approved funding for the conversion of CFC-MDI manufacturing plants to non-CFC alternatives in 12 Article 5 countries. Implementation of these projects will result in the phase-out of over 1,800 ODP tonnes of CFCs. Table 1 below lists all CFC-MDI phase-out projects under current implementation. Additional information on the MDI sector in these countries can be found in Annex I to the present paper.

Table 1. Phase-out projects for the conversion of CFC-MDIs to alternative technologies approved by the Executive Committee

Country	Project	Agency	CFC (ODP tonnes)			Dates	
			CFC-11	CFC-12	CFC-114	Approval	Completion
Argentina	Phase-out of CFC consumption in the manufacture of aerosol MDIs	World Bank	35.5	82.9		Nov-08	Jan-12
Bangladesh	Phase-out of CFC consumption in the manufacture of aerosol MDIs (Beximco, Square Pharmaceutical and Acme Pharmaceutical)	UNDP	21.8	54.5		Jul-07	Jul-11
China	Sector plan for phase-out of CFC consumption in MDI sector	UNIDO	48.4	274.1		Nov-08	Dec-13
Colombia	Phase-out of CFC in the manufacturing of MDIs	UNDP		7.4		Nov-08	Nov-11
Cuba	Phase-out of CFC consumption in the manufacture of aerosol metered dose inhalers (MDIs)	UNDP	37.6	71.5		Dec-03	Apr-2009
Egypt	Phase-out of CFC consumption in the manufacture of aerosol metered	UNIDO	4.1	153.0	2.4	Nov-06	Dec-09

Country	Project	Agency	CFC (ODP tonnes)			Dates	
			CFC-11	CFC-12	CFC-114	Approval	Completion
	dose inhalers (MDIs)						
India	Plan for phase-out of CFCs in the manufacture of pharmaceutical MDIs	Italy/ UNDP	215.7	488.6		Nov-08	Nov-13
Indonesia	Technical assistance to implement national transition strategy to CFC-free MDI	World Bank		16.3		Nov-08	Dec-10
Islamic Rep. of Iran	Phase-out of CFC consumption in the manufacture of aerosol MDIs	UNIDO	28.9	67.5		Jul-07	Sep-10
Mexico	Phase-out of CFC consumption in the manufacture of aerosol MDIs	UNIDO	25.7	65.2	6.1	Nov-07	Jan-10
Pakistan	Plan for phase-out of CFCs in the manufacture of pharmaceutical MDIs	UNDP	25.0	58.8		Nov-08	Nov-11
Uruguay	Phase-out of CFC consumption in the manufacture of aerosol metered dose inhalers (MDIs)	UNDP	3.0	7.0		Jul-04	Dec-2009
Total			445.7	1,346.8	8.5		

5. CFC-MDIs[1] are also manufactured in the following three Article 5 countries. The Executive Committee decided that those projects were not eligible for funding from the Multilateral Fund:

(a) Algeria: Production of 0.5 million salbutamol MDIs per year with a CFC consumption of 11 ODP tonnes of CFCs;

(b) Syrian Arab Republic: Production of 1.9 million salbutamol, beclomethasone, salmeterol, fluticasone, salmeterol MDIs per year with a CFC consumption of 41.3 ODP tonnes; and

(c) Venezuela: Production of 2.0 million salbutamol, fenoterol/ipratropium, beclomethasone and budesonide MDIs per year with a CFC consumption of 43.4 ODP tonnes.

Estimated amounts of CFC for MDI production post 2009

6. The estimated amounts of CFCs that will be required by Article 5 countries for the production of CFC-MDIs post 2009 is presented in Table 2 below. This data has been provided by relevant Article 5 countries through the agencies assisting in the conversion of manufacturing lines to non-CFC alternatives.

Table 2. Estimated amount of CFCs for production of MDIs post 2009 (ODP tonnes)*

Country	2010	2011	2012
Algeria	11.0	8.0	0.0
Argentina	178.0	n/a	n/a
Bangladesh	156.7	0.0	0.0
China	977.2	n/a	n/a
Colombia	0.0	n/a	n/a
Cuba	0.0	0.0	0.0
Egypt	227.4	36.6	0.0
India	360.0	n/a	n/a
Indonesia	0.0	0.0	0.0
Islamic Republic of Iran	105.0	0.0	0.0
Mexico	0.0	0.0	0.0
Pakistan	130.0	n/a	n/a
Syrian Arab Republic	41.0	25.0	0.0

1 CFC-MDIs that will be converted to HFA-MDIs.

Country	2010	2011	2012
Uruguay	0.0	0.0	0.0
Venezuela	0.0	0.0	0.0
Total	**2,186.3**		

* Mixture of CFC-11 and CFC-12 typically in a ratio 30:70.
(n/a) Not available.

7. From the data presented in Table 2 above and further discussions with relevant implementing agencies, it is noted that:

(a) Based on information provided by relevant Governments through the implementing agencies, the total estimated amount of CFCs required for the production of MDIs in Article 5 countries in 2010 is about 2,190 ODP tonnes. Several countries have not indicated the levels of EUN post 2010;

(b) The Governments of Cuba, Indonesia, Mexico, Uruguay and Venezuela will not request essential uses of CFCs for manufacturing of MDIs[2];

(c) The Government of Colombia will not request essential uses of CFCs for manufacturing of MDIs for 2010. The decision to submit EUN for 2011 and 2012 will depend on the status of the implementation of the approved investment project;

(d) Documentation for requests for EUN have been prepared and submitted for consideration by the Medical Technical Options Committee (MTOC) by the following Governments:

(i) Bangladesh for the amount of 156.7 ODP tonnes for 2010;

(ii) China for the amount of 977.2 ODP tonnes for 2010. Information provided in the project for the phase-out of CFCs in the manufacturing of MDIs indicates that an additional 1,798.3 ODP tonnes of CFCs might be required for the production of MDIs between 2011 and 2013. The Government of China has confirmed that the CFC production facility currently producing CFCs for the MDI sector is expected to produce CFC beyond 2009 to meet the needs of the MDI sector in China and other Article 5 countries;

(iii) Egypt for the amount of 227.4 ODP tonnes and 36.6 ODP tonnes for 2010 and 2011, respectively;

(iv) The Government of India had submitted its request for EUN directly to MTOC. Information provided in the project for the conversion of the MDI manufacturing plants in India indicates that between 240 and 340 ODP tonnes of CFCs might be required for the production of MDIs in 2011 and 2012 (more precise figures will be known only by mid-2009);

(v) Islamic Republic of Iran for the amount of 105 ODP tonnes for 2010;

(vi) The Government of Pakistan had submitted its request for EUN request directly to MTOC.

(e) At the time of the preparation of this paper, the Government of Argentina was preparing the EUN request for the amount of 178 ODP tonnes for 2010. Information provided in the project for the conversion of the MDI manufacturing plants in Argentina indicates that an

2 Mexico and Venezuela will satisfy their 2010 CFC demand for the manufacturing of MDIs 2010 from stocks available in the countries. The projects for the conversion of the CFC-MDI manufacturing plants in Cuba and Uruguay will be completed in 2009.

additional 1,088 ODP tonnes of CFCs might be required for the production of MDIs between 2011 and 2015. However, the Government will review these figures on a yearly basis in light of the progress achieved in converting the CFC-MDI manufacturing line;

(f) The Governments of Algeria and Syrian Arab Republic will request EUN for a total of 85 ODP tonnes of CFCs in 2010 and 2011.

Annex I

SUMMARY REPORT ON CFC-MDI PHASE-OUT PROJECTS UNDER CURRENT IMPLEMENTATION IN ARTICLE 5 COUNTRIES[3]

1. Projects for the conversion of CFC-MDIs to alternative non-CFC propellants have been approved for the following 12 Article 5 countries: Argentina, Bangladesh, China, Colombia, Cuba, Egypt, India, Indonesia, Islamic Republic of Iran, Mexico, Pakistan, and Uruguay. A summary of these projects, based on the information contained in the documents that were prepared for consideration by the Executive Committee, is presented below.

ARGENTINA[4]

2. CFC-MDIs are manufactured in Argentina by the following enterprises: Laboratorio Pablo Cassará (100 per cent local ownership), which consumes approximately 80 per cent of the pharma-grade CFCs imported into the country for the manufacturing of MDIs; 3M, a multinational enterprise that fills MDIs for a group of 15 laboratories, five of which are nationally owned; and Denver Farma, a local laboratory (100 per cent local ownership) that used to fill its MDIs through 3M but established its own CFC-MDI production line in 2007. The level of CFC consumption used for the manufacturing of MDIs in Argentina is shown in the table below.

Description	ODP tonnes		
	2005	2006	2007
Consumption for domestic use	135.7	123.6	136.4
Export to Article 5 countries	51.3	49.5	59.5
Total consumption	187.0	173.1	195.9
Consumption eligible for funding			
Pablo Cassará	83.5	85.0	106.4
Denver Farma(*)	2.0	2.0	3.1
Phoenix(*)	10.9	10.9	4.4
Dallas(*)	0.1	0.1	0.1
Raffo(*)	2.7	3.1	3.6
Roux(*)	0.7	0.6	0.8
Sub-total eligible enterprises	99.9	101.7	118.4
Consumption by multinational			
3M(**)	51.2	49.5	59.5
IVAX(***)	35.9	21.9	18.0
Sub-total multinationals	87.1	71.4	77.5

(*) CFC-MDIs filled through 3M. Denver Farma established its own CFC-MDI production line in 2007.
(**) Excluding CFC consumption used for filling CFC-MDIs for locally-owned enterprises.
(***) Stopped production of CFC-MDIs during 2007.

3. As of 2007, CFC-MDIs with the following seven different active ingredients were registered and sold in Argentina: salbutamol, budesonide, fenoterol, ipratropium, fluticasone, fluticasone/salmeterol, ipratropium/fenoterol, ipratropium/salbutamol and salmeterol/beclomethasone.

4. The objectives of the project are: replace the use of CFCs at Laboratorio Pablo Cassará for the production of salbutamol CFC-MDIs to isobutane; to replace the use of CFCs at Laboratorio Denver Farma for the production of salbutamol and budesonide CFC-MDIs to HFA technology; to provide technical

3 Status of implementation of MDI projects as of March 2009.

4 UNEP/OzL.Pro/ExCom/56/22.

support for development of HFA-MDI formulations for four locally-owned laboratories filling their own MDIs through third parties; and to support the MDI transition strategy (information dissemination, awareness programmes and clinical symposiums and workshops).

5. Agreements between the MDI manufacturing plants and the World Bank for commencing implementation of the project will be signed by mid-April 2009. CFC consumption will be completely phased out by 2014 in Laboratorios Pablo Cassará and by 2012 in all other MDI manufacturing plants.

BANGLADESH[5]

6. The first CFC-MDI in Bangladesh was developed and launched in 1997, with production reaching 507,000 units. The demand for MDIs in Bangladesh is satisfied primarily by the following three locally-owned manufacturing enterprises:

(a) Beximco Pharmaceutical: The company began manufacturing CFC-MDIs in 1997, with the production of 270,000 salbutamol and salmeterol MDIs. Currently, the company has a production capacity of 2.4 million MDIs per year with over ten different active ingredients. Since 2002, Beximco has manufactured salbutamol CFC-MDIs for GlaxoSmithKline (680,000 MDIs produced in 2006); and since 2006 for Eskayef (30,000 MDIs). In 2006, Beximco invested in the development of HFA salbutamol and beclomethasone MDIs through collaboration with Bespak, United Kingdom;

(b) Square Pharmaceutical: The company began manufacturing CFC-MDIs in 1997 with the production of 240,000 salbutamol, beclomethasone and salmeterol MDIs, and currently produces MDIs with over nine different active ingredients. The MDI formulation technology has been based on in-house research work. In 2002, Square began producing dry powder inhalers (DPIs) that were developed by the enterprise. Currently, the company manufactures single dose (capsule) DPIs of salbutamol, and salmeterol plus fluticasone;

(c) Acme Pharmaceutical: The company began manufacturing CFC-MDIs in 2004 with the production of 100,000 salbutamol, beclomethasone and salmeterol MDIs. In 2006, a total 250,000 MDIs were produced with four different active ingredients. Also in 2006, Acme produced 210,000 DPIs with four different active ingredients (salbutamol, salmeterol, salmeterol plus fluticasone and beclomethasone).

7. Production levels of CFC-MDIs in Bangladesh over the 2004-2006 period by active ingredient are shown in the table below:

Active ingredient	**Beximco**			**Square Pharmaceutical**			**Acme**		
	2004	**2005**	**2006**	**2004**	**2005**	**2006**	**2004**	**2005**	**2006**
Salbutamol	1,225,437	1,167,517	1,300,000	276,000	325,000	388,500	57,082	92,197	181,188
Salbutamol+ipratropium		30,724	25,000		52,500	105,000			
Levosalbutamol			20,000			15,000			
Beclomethasone	101,128	104,462	95,000	125,000	160,000	199,500	22,463	13,411	20,842
Salmeterol	47,590	36,869	40,000	31,500	52,500	21,000	21,233	7,864	15,417
Salmeterol+fluticasone	41,641	47,930	85,000	10,000	32,000	32,000		15,575	22,568
Ciclesonide			28,000	24,000		33,000			
Budesonide	17,846			42,000	43,000	31,500			
Ipratropium		6,145			33,000	10,500			
Triotropium			3,000						
Total MDIs	**1,433,642**	**1,393,647**	**1,596,000**	**508,500**	**698,000**	**836,000**	**100,778**	**129,047**	**240,015**
CFC (ODP tonnes)*	**49.5**	**44.2**	**52.9**	**10.3**	**14.3**	**17.3**	**2.5**	**3.3**	**6.1**

* In 2006, 13.6 and 0.6 ODP tonnes of CFCs were used by Beximco for the production of MDIs for GlaxoSmithKline and Eskayef respectively.

5 UNEP/OzL.Pro/ExCom/52/26.

8. Only some 127,900 HFA seretide MDIs and 26,427 seretide multi-dose dry powder inhalers (DPIs) are imported into the country.

9. MDIs containing salbutamol, beclomethasone, salbutamol plus ipratropium, and salmeterol plus fluticasone represent over 90 per cent of total current CFC-MDI production in Bangladesh. Therefore, the Government of Bangladesh, together with the three manufacturing companies, the Drug Regulatory Agency, the Lung Association and the medical community, decided to convert these MDIs to HFA technology. The Government of Bangladesh is proposing to implement a transition strategy with adequate awareness activities for enhancing MDI use and regulations aligned to the phase-out timing by the industry.

10. The project proposes that a third party company will provide technical assistance for the development of the formulation for each specific drug molecule and strength, and transfer the technology to each one of the three MDI manufacturing enterprises. These enterprises will then use their own staff to adapt to the new technology with the supervision of the service provider's technical expert. In the case of the salbutamol plus ipratropium, there is currently no suitable HFA-MDI approved. It is expected that the development of formulations for these MDIs will take approximately one year. During this time there will be a need for consultation with suitably experienced experts to advise the technical staff at the companies on the technical aspects of this project.

11. Due to non-availability of non-CFC formulations for ipratropium bromide, triotropium and salmeterol combination, these MDIs have not been considered for product development. The future need for these products was discussed with the Government of Bangladesh and the Lung Foundation. As a result, it has been decided to allow stockpiling of 45.4 ODP tonnes of CFCs for the continued production of MDIs for a three-year period starting in 2010. It is expected that the conversion process would be undertaken by the industry in Bangladesh as soon as feasible conversion options are available for these formulations.

12. The project document between the beneficiary enterprises and UNDP was signed in February 2009. The status of implementation of the project at the enterprise level is as follows:

(a) Beximco Pharmaceutical has substantially completed the conversion of its MDI manufacturing lines and is currently manufacturing HFA-based salbutamol and beclomethasone MDIs. These two products are available on the market and are produced in parallel with CFC-MDIs. For the other active ingredients, the installation and commissioning of filling lines is expected to be completed by December 2009. The HFA-MDIs are currently being formulated and it is expected to be on the local market during 2010;

(b) Square Pharmaceutical is currently developing HFA formulations for salbutamol and beclomethasone MDIs; stability tests and product registration is expected to be completed by July 2010 and products offered in the local market in the second half of 2010 or early 2011. Technical specifications for formulations of the other four active ingredients are being finalized and will be sent out for competitive bidding during the second quarter of 2009. It is expected that these four MDIs will be launched on the local market during the first half of 2011. The equipment for the new filling lines is currently being procured.

(c) Acme Pharmaceutical is currently finalizing specifications for equipment required for the manufacturing of HFA-MDIs and for formulations of HFA-MDIs with three different ingredients. It is expected that HFA-salbutamol and HFA-beclomethasone MDIs will be launched on the local market by the end of 2010 and the HFA-salmeterol/fluticasone by mid-2011.

CHINA[6]

13. There are 38 MDI manufacturing plants in China, with 104 production licenses. Sixteen manufacturing plants with 36 licenses have reported production in 2007[7] while 18 plants have not reported production for that year. The remaining five plants are owned by multinational corporations (one of which ceased production in 2005).

14. The MDI sector in China can be summarized as follows:

(a) CFC consumption for the production of MDIs increased from 152.1 ODP tonnes in 2004 to 340.5 ODP tonnes in 2007;

(b) Seven MDI manufacturing plants are also producing pharmaceutical aerosols in China[8];

(c) Three transnational corporations[9] have been producing MDIs over the last three years, as shown in the table below:

Company name	**Active ingredient**	**CFC 2005 (kg)**	**CFC 2006 (kg)**	**CFC 2007 (kg)**
AstraZeneca Pharmaceutical	Budesonide	3,494.0	4,538.0	
AstraZeneca Pharmaceutical	Terbutaline	7,460.0	8,665.0	
Beijing Shengdelaibao Pharmaceutical	Salbutamol	745.9		730.0
Beijing Shengdelaibao Pharmaceutical	Beclometasone	180.3		
Weifang Zhongshi Pharmacy	Beclometasone	-	-	57.0
Weifang Zhongshi Pharmacy	Salbutamol	1,350.0	900.0	597.0
Weifang Zhongshi Pharmacy	Salbutamol (suspension)	-	-	70.7
Total		**13,230.2**	**14,103.0**	**1,454.7**

(d) There are only 13 different active ingredients in MDIs that are currently produced in China, as shown in the table below. The total production of MDIs with beclomethasone, terbutaline, cromoglicate, salbutamol (both in solution and in suspension), and isoprenaline represents more than 97 per cent of total production in 2007:

6 UNEP/OzL.Pro/ExCom/56/24.

7 The 16 enterprises hold an additional 22 licenses without production.

8 The seven plants are: Beijing Haiderun Pharmaceutical; Guangzhou Dongkang Pharmaceutical; Guiyang Dechangxiang Pharmaceutical; Heilongjiang Tanglong Pharmaceutical; Penglai Nuokang Pharmaceutical; Shanghai Pharmaceutical Group; and Wuxi Shanhe Group.

9 An additional multinational corporation, GlaxoSmithKlein, stopped producing CFC-based beclomethasone MDI from 2005.

Active ingredient	CFC consumption (kg)			% CFC*
	2005	2006	2007	
Salmeterol xinafoate		10.0	10.0	0.00%
Dimethicone	22.2	70.0	100.0	0.03%
Zhichuanling	30.0	130.8	320.0	0.09%
Iprartropium bromide	-	27.0	325.0	0.10%
Ketotifun fumarate	-	1,271.0	1,271.0	0.37%
Ribavirin	1,851.0	7,395.0	3,443.0	1.01%
Budesonide	6,273.5	8,037.0	4,069.0	1.20%
Sodium cromoglicate	6,902.0	7,541.5	13,591.0	3.99%
Terbutaline sulphate	7,460.0	8,665.0	16,612.7	4.88%
Isoprenaline hydrochloride	40,647.2	47,324.0	43,452.0	12.76%
Beclometasone dipropionate	16,796.6	23,048.0	59,954.0	17.61%
Salbutamol (solution)	69,905.3	91,650.0	85,378.0	25.07%
Salbutamol (suspension)	93,793.1	85,396.2	111,968.7	32.88%
Total	**243,680.9**	**280,565.5**	**340,494.4**	**100.0%**

(*) Percentage of the total CFC consumption in 2007.

15. At the time of the preparation of the project proposal, it was expected that CFC consumption will increase annually from 341 ODP tonnes in 2007 to a maximum level of 748.3 ODP tonnes in 2011 and then will decrease annually, achieving complete phase-out by 2014. The total cumulative CFC consumption between 2008 and 2014 amounts to 3,332.3 ODP tonnes[10]. According to the CFC production closure agreement between the Government of China and the Executive Committee, a total of 1,100 ODP tonnes of CFCs could be produced in 2008 and 2009[11]. Considering that reformulation to HFA-technology for beclomethasone and salbutamol MDIs is well known, it could be expected that conversion of at least these two MDIs, representing more than 75 per cent of total CFC consumption in China, could have been done at an earlier stage. If this is the case, the amount of CFCs that might be needed from 2010 could be substantially reduced. However, further reduction of the need for CFCs after 2010 phase-out cannot be proposed at this stage, although it will be pursued during the implementation process.

16. Since the approval of the project, meetings between the Ministry of Environment Protection and the State Food and Drug Administration and UNIDO have been organized to discuss project implementation modalities. The terms of reference for the contract for implementation of the project are under preparation and expected to be signed by July 2009. China has one production line in operation specifically designated for pharmaceutical-grade CFCs. It is expected that this line will be operational until the final MDI project is completed.

COLOMBIA[12]

17. Laboratorios Chalver is the sole locally-owned enterprise producing CFC-MDIs. The MDI production line was established in 2001 with the first batch manufactured by the end of 2002. The enterprise has developed CFC-MDIs with seven different active ingredients, as shown in the table below:

10 According to information provided by UNIDO, the 2008 CFC consumption for manufacturing MDIs instead of 415 ODP tonnes that were estimated at the time of the preparation of the project.

11 Under the agreement between the Government of China and the Executive Committee for the CFCs/CTC/halon accelerated phase-out plan, China could export 100 ODP tonnes of CFCs in 2008 and 50 ODP tonnes in 2009.

12 UNEP/OzL.Pro/ExCom/56/25.

Active ingredient	MDI (units) CFC consumption (ODP tonnes)									
	2003		2004		2005		2006		2007	
	MDI	CFC	MDI	CFC	MDI	CFC	MDI	CFC	MDI	CFC
Beclomethasone	63,000	1.1	69,000	1.2	3,000	0.1	9,000	0.2	45,366	0.8
Ipratropium	0	-	42,000	0.7	78,000	1.3	12,000	0.2	118,819	2.0
Salbutamol	144,000	2.4	300,000	5.0	0	-	72,000	1.2	239,501	4.0
Salbutamol/beclomethasone	6,000	0.1	3,000	0.1	36,000	0.6	15,000	0.3	32,750	0.5
Salbutamol/ipratropium	0	-	0	-	10,000	0.2	5,000	0.1	8,913	0.1
Budesonide	0	-	0	-	0	-	0	-	0	-
Fluticasone	0	-	0	-	0	-	0	-	0	-
Total	213,000	3.6	414,000	6.8	127,000	2.1	113,000	1.9	445,349	7.4

18. The National Institute of Food and Drug Surveillance is responsible for the registration of new drugs. In May 2004, the Drug Review Commission allowed the use of CFC-MDIs until 2010. In 2008, the Ministry of Health issued a ban on the registration of new CFC-MDIs and the renewal of existing registered CFC-MDIs, and established December 2009 as the deadline for the conversion of CFC-MDIs except for those active ingredients where conversion is not feasible.

19. The project is to assist Laboratorios Chalver to convert the CFC-MDI manufacturing line to HFA technology by 2012, including the development of HFA-MDIs for beclomethasone, ipratropium, salbutamol and salbutamol/beclomethasone.

20. The project document between Laboratorios Chalver and UNDP for commencing implementation of the project is currently being prepared. It is expected that the installation of equipment for the manufacturing of HFA-MDIs will be completed by the end of 2009. Laboratorios Chalver has begun re-formulating CFC-MDIs to HFA using its own laboratory (technical assistance will be provided through the approved project to ensure the reformulation of MDIs in a technically sound manner). It is expected that stability tests and registration of HFA-MDIs will be completed by early 2010.

CUBA[13]

21. Laboratorio Farmacéutico Julio Trigo López consumes both CFC-11 and CFC-12 in the manufacture of salbutamol and beclomethasone CFC-MDI. The company has decided to stay with the MDI as the drug delivery system. For salbutamol, it is proposing to base the formulation on HFC-134a alone, and for beclomethasone, it is proposing dissolution in ethyl alcohol and the use of HFC-134a propellant. Implementation of the selected technologies requires technology transfer from established enterprises.

22. The Government of Cuba is proposing to phase out the use of CFCs in MDIs through implementation of the national transition strategy and the conversion of the CFC-MDI manufacturer to HFC-134a MDIs. Once the project is completed, the Government of Cuba will prohibit the use of CFCs in all aerosol products, including MDIs.

23. Currently, the HFA manufacturing line has been successfully installed. Major engineering work (financed by the Government of Cuba) had to be completed to adapt the plant to the required conditions for MDI production with HFA. The first industrial batch for one of the HFA-MDIs was manufactured with the new equipment. Technical discussions with the equipment provider are ongoing to fine-tune some elements of the manufacturing line. It is expected to complete the work during April 2009.

24. Formulations of HFA-based salbutamol and fluticasone were developed with assistance from an external company specialized in developing pharmaceutical products. Both formulations have been developed and stability tests have been completed. Industrial production of HFA-salbutamol (representing 80 per cent of the MDI production in the country) has been completed using the new equipment; the results of the analytical tests are expected soon. Industrial production of HFA-fluticasone is expected to be completed by May 2009, when the conversion to non-CFC MDIs could be considered to be completed.

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EGYPT[14]

25. Production of MDIs in Egypt began in 1984. There are two established domestic manufacturers of CFC-based MDIs in Egypt: the Arab Drug Company (ADCO) and the Egyptian International Pharmaceutical Industries Co., (EIPICO). Additionally, a number of multinational corporations offer several medications for asthma and CODP, including CFC-based salbutamol MDIs, salbutamol and fluticasone both as HFC-134a-based MDIs and as dry powder inhalers (DPI), and budesonide DPIs.

26. In 1991, ADCO began manufacturing two CFC-based MDIs under license from Chiesi Farmaceutici. Currently, these MDIs continue to be manufactured under the same brand name, although there is no longer a commercial license or limitation in place. ADCO has also introduced its own branded MDIs for: salbutamol; salbutamol with beclomethasone (produced from individual actives); beclomethasone; and, since 2002 salmeterol. Between 1991 and 1999, MDI production increased from about 294,000 MDIs to 2.1 million MDIs. In 1999, the company started to export MDIs to other Article 5 countries (some 590,000 MDIs). Since then, MDI production has increased continuously, reaching 6.6 million MDIs in 2005. The total current CFC consumption used for the production of MDIs is 145.9 ODP tonnes.

27. EIPICO began the production of CFC-based MDIs in 1984 as a licensee of 3M Riker (who is still the license holder for Aerolin salbutamol in Egypt). Between 1995 and 2005, the production of salbutamol CFC-MDIs increased from 600,000 to 1.05 million units. The total current CFC consumption used for the production of MDIs is 17.2 ODP tonnes.

28. The 2003-2005 levels of CFC consumption and MDI production in these two manufacturing plants is presented in the table below.

Year	ODP tonnes				MDI units
	CFC-11	CFC-12	CFC-114	Total CFC	
ADCO					
2003	37.4	100.6		138.0	4,831,367
2004	43.2	107.7		150.9	6,028,894
2005	42.5	106.1		148.6	6,600,000
EIPICO					
2003	2.0	10.8	1.9	14.7	800,000
2004	2.5	13.6	2.4	18.4	1,000,000
2005	2.5	13.6	2.4	18.4	1,000,000
Total					
2003	39.4	111.4	1.9	152.7	5,631,367.0
2004	45.7	121.3	2.4	169.3	7,028,894.0
2005	45.0	119.7	2.4	167.0	7,600,000.0

29. The two companies have decided to convert their CFC-based MDIs to HFC-134a technology, which will require technology transfer from an established enterprise. The Government of Egypt has prepared a national strategy for the phase-out of CFC-based MDIs, aimed at meeting a timetable and criteria that has been agreed by all stakeholders. The strategy is based on patients' health as the first priority, ensuring that access to appropriate treatment is not interrupted, and on the development and implementation of an education programme with participation from major stakeholders.

30. The contract for the provision of the manufacturing equipment required by the two enterprises has been placed. Major difficulties were encountered in identifying technology providers for the formulation and development of HFA-MDIs. The international tender process was completed in November 2008. However, since no offers were received after two years, manufacturers of MDI valves were invited to bid for technology provision. Accordingly, a company has been selected. The manufacturing equipment required for both enterprises is currently being manufactured and is expected to be installed by September 2009.

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Development of the HFA-salbutamol MDI (6-month pilot batch stability tests) will commence during the first half of 2009. Commercial batch production (three batches) of HFA-based MDIs will start once the equipment is installed. Final approval and registration of the HFA-salbutamol MDIs is expected by the end of 2010, and during the first quarter of 2011 for the other HFA-MDIs. The equipment and manufacturing capabilities for CFC-MDIs will be operational until mid-2011, when the four HFA-MDIs are to be registered.

INDIA[15]

31. There are currently five MDI manufacturers in India. Three of these manufacturers produce both CFC- and HFA-MDIs. The total production levels of MDIs in India in the 2003-2007 period are shown in the table below:

Manufacturer	Total production (million MDIs)				
	2003	2004	2005	2006	2007
CFC-MDIs					
Cadila Healthcare Ltd.	0.15	0.30	0.42	0.69	0.71
Cipla Ltd.	26.27	33.04	28.18	35.44	27.39
GlaxoSmithKline Pharmaceuticals Ltd.	1.15	0.94	1.21	0.79	0.94
Midas-Care Pharmaceuticals Ltd.	0.97	1.02	1.65	1.85	1.76
Sun Pharmaceutical Industries Ltd.	0.29	0.39	0.31	0.39	0.39
Subtotal CFC-MDIs	**28.83**	**35.69**	**31.77**	**39.16**	**31.19**
HFA-MDIs					
Cipla Ltd.	0.47	1.21	4.03	11.01	24.06
Midas-Care Pharmaceuticals Ltd.	0.00	0.024	0.035	0.15	0.26
Sun Pharmaceutical Industries Ltd.	0.00	0.00	0.00	0.029	0.00
Subtotal HFA-MDIs	**0.47**	**1.23**	**4.06**	**11.19**	**24.32**
Total	**29.30**	**36.92**	**35.84**	**50.35**	**55.51**

32. The level of CFC consumption for the manufacturing of MDIs increased from 578.9 ODP tonnes in 2003 to 763.6 ODP tonnes in 2006. In 2007, CFC consumption decreased to 608.1 ODP tonnes, as shown in the table below:

Manufacturer	CFC consumption (ODP tonnes)				
	2003	2004	2005	2006	2007
Cadila	2.9	5.9	7.5	11.6	8.5
CIPLA	526.6	687.6	670.9	698.2	537.7
GSK	24.6	20.1	25.9	16.9	20.1
Midas-Care	18.8	21.3	29.8	29.0	34.0
Sun Pharma	6.0	7.9	6.3	7.9	7.8
Total	**578.9**	**742.8**	**740.4**	**763.6**	**608.1**

33. The forecast of CFC and HFA demand for MDIs in India in 2008-2013 is shown in the table below:

Propellant	CFC and HFA consumption (metric tonnes)*					
	2008	2009	2010	2011	2012	2013
CFC	604	484	338	203	71	0
HFA	566	760	983	1,205	1,405	1,556
Total	1,170	1,244	1,322	1,408	1,476	1,556

(*) Based on growth rates over the last five years, with the presumption of technical and financial assistance for the transition from CFC to HFA technologies, in the absence of which an additional three years will be needed for the complete phase-out of CFCs.

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34. In 2003, CFC-MDIs with thirteen different active ingredients were manufactured in India, as shown in the table below. Several of the CFC-MDIs have been formulated in multiple strengths.

Ingredient	CFC-MDIs manufactured by enterprise						
	Cadila	Cipla	GSK	Midas-Care	SunPharma	Total MDI	%MDIs
Salbutamol	30,010	16,905,000	1,044,505	611,800	56,600	18,647,915	64.6%
Beclomethasone		4,663,000	107,475	117,900		4,888,375	16.9%
Beclomethasone/salbutamol		1,925,000		27,400		1,952,400	6.8%
Salmeterol/fluticasone		778,000		10,000	163,771	951,771	3.3%
Ipratropium	20,070	786,000		43,000		849,070	2.9%
Budesonide	10,010	300,000		15,200	51,738	376,948	1.3%
Ipratropium/salbutamol	20,070	293,000		61,200		374,270	1.3%
Budesonide/formoterol	69,293	191,000		75,900	27,379	363,572	1.3%
Salmeterol		154,000				154,000	0.5%
Fluticasone		134,000				134,000	0.5%
Cromoglycate		66,000				66,000	0.2%
Tiotropium		45,000				45,000	0.2%
Formoterol	1,910	31,000		11,700		44,610	0.2%
Total MDIs	**151,363**	**26,271,000**	**1,151,980**	**974,100**	**299,488**	**28,847,931**	**100.0%**

35. With regard to the data presented in the above table and information presented in the MDI project, it is noted that:

(a) In 2003, almost 82 per cent of all CFC-MDIs contained salbutamol (64.6 per cent) or beclomethasone (16.9 per cent). An additional 10 per cent contained a combination of beclomethasone/salbutamol or salmeterol/fluticasone;

(b) One enterprise, Cipla, manufactures more than 91 per cent of all CFC-MDIs manufactured in India;

(c) GSK, the second largest manufacturer of CFC-MDIs, with 4 per cent of total production, is partially owned by a non-Article 5 company (50.67 per cent) foreign ownership.

36. It is estimated that the conversion to HFA technology will be completed by December 2013, i.e., four years after the mandatory date for the complete phase-out of CFCs. There are no CFC stockpiles available with MDI manufacturers to cover needs during the transition period. Stakeholders have been fully briefed by the Government on the essential use nomination process. Accordingly, the Government of India, with the assistance of the implementing agencies and MDI manufacturers, would be in a position to request essential uses by January 2009.

37. The project document between the MDI manufacturing plants and UNDP is expected to be signed in April 2009. The status of implementation of the project at the enterprise level is as follows:

(a) Cadila Healthcare is expecting to achieve the conversion to HFA-MDIs in 24 to 26 months. Product development would be carried out in-house. Specifications for the equipment needed for the manufacturing line are expected to be finalized by mid-2009, and installation and commissioning of the equipment is proposed for the first quarter of 2011. It is expected that the HFA-MDIs will be launched on the domestic market during 2012;

(b) Cipla has already developed in-house HFA-MDIs for 15 different products. Since the enterprise exports part of its production to Article 5 and non-Article-5 countries, it is necessary to develop all HFA-MDIs in compliance with the demands of numerous regulatory bodies. It is expected that the complete conversion to HFA-MDIs will take between 25 and 27 months. It is proposed that equipment specifications will be finalized by mid-2009; installation and commissioning will occur during the first quarter of 2011; and launching of all HFA-MDIs on the domestic market will occur during 2012.

(c) GSK has already developed HFA-salbutamol and HFA-beclomethasone MDIs through its parent corporation. Filling equipment suitable for the HFA-based formulations needs to be installed and institutional approval for indigenously manufactured HFA-MDIs will need to be obtained. The new equipment is expected to be in place by the last quarter of 2011 and the launching of indigenously manufactured HFA-MDIs on the local market is expected during 2012;

(d) Midas-Care Pharmaceuticals has carried out extensive preparatory activities for converting to HFC-based technology. The enterprise expects that it would take 22 to 25 months to completely convert to HFA-based MDIs. Product development would be carried out in-house. The equipment specifications are expected to be finalized by mid-2009, with installation and commissioning by early 2011. It is expected that the new HFA-based products will be launched on the domestic market during 2012;

(e) Sun Pharma expects that it would take between 24 and 26 months for complete conversion to HFA-based formulations. Product development would be carried out in-house. The equipment specifications are expected to be finalized by mid-2009, with installation and commissioning by early 2011. It is expected that the new HFA-MDIs will be launched on the domestic market during 2012.

INDONESIA[16]

38. CFCs were used for the manufacturing of MDIs and other aerosol pharmaceutical products by several national (Otsuka, Daya Varia and Konimex) and multi-national (Astra Zeneca, Boehringer Ingelheim and GlaxoSmithKline) enterprises. In 2005, Konimex ceased production of MDIs in 2005 due to scarcity of pharmaceutical-grade CFCs on the local market, and high costs associated with the conversion to non-CFC propellant.

39. Of the four multinational enterprises currently providing MDIs in Indonesia, one company, PT. Boehringer Ingelheim Indonesia, is locally manufacturing CFC MDIs. The 2006-2009 production levels of CFC MDIs by active ingredient are shown in the table below. Boehringer has decided to completely stop manufacturing CFC MDIs by the end of 2009. There is a sufficient stock of pharmaceutical-grade CFCs for the manufacturing of MDIs in 2009 and 2010. Therefore, the Government of Indonesia will not request any essential uses of CFCs for the manufacturing of MDIs.

Active ingredient	**CFC MDIs (units)**			
	2006	**2007**	**2008**	**2009**
Metaproterenol	81,661	170,709	108,500	94,500
Ipratropium	21,366	21,687	37,500	-
Ipratropium/fenoterol	10,758	10,731	22,500	11,250
Fenoterol (two different strengths)	208,044	214,391	491,250	112,500
Ipratropium/albuterol	49,511	47,377	91,000	73,500
Budesodine (four different strengths)	23,716	127,630	198,000	150,800
Total	395,056	592,525	948,750	442,550
CFC consumption (ODP tonnes)	**8.9**	**11.5**	**14.9**	**9.3**

ISLAMIC REPUBLIC OF IRAN[17]

40. About 2 million MDIs and 85,000 dry powder inhalers (DPIs) are imported into the country annually by multinational enterprises. Approximately 10 per cent of the imported MDIs are HFA-based. Sina Darou Laboratories Co., is the only locally-owned manufacturer of MDIs in the Islamic Republic of Iran. Current production includes salbutamol, beclomethasone, salmeterol and cromolyn MDIs. Technology

16 UNEP/OzL.Pro/ExCom/56/35.

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for the production of salbutamol was provided by Norton-Waterford Limited (Ireland). The three other CFC-MDIs were developed and formulated by the company. The production levels of these MDIs are shown in the table below:

Active ingredient	2003		2004		2005		2006	
	MDI units	CFC tonnes	MDI units	CFC tonnes	MDI units	CFC tonnes	MDI units	CFC tonnes
Salbutamol	3,175,660	66.34	3,600,762	75.40	2,664,758	55.82	4,299,304	89.91
Beclomethasone	2,844	0.06	2,920	0.06	267,033	5.59		
Cromolyn					5,353	0.11	95,450	2.00
Salmeterol			1,706	0.04	99,131	2.08	214,966	4.50
Total	3,178,504	66.40	3,605,388	75.50	3,036,275	63.60	4,609,720	96.40

41. The company has decided to convert three of their CFC-based MDIs (salbutamol, beclomethasone and salmeterol) to HFC-134a technology. This will require technology transfer from an established enterprise. CFC-MDIs with cromoglycate will not be converted to an HFA-MDI under this project.

42. Since the approval of the MDI conversion project, contracts for the development of HFA-MDI formulations and for the new manufacturing equipment have been awarded. It is expected that the equipment will be installed by the end of September 2009, with the approval of HFA-salbutamol MDIs by the end of 2010, and remaining MDIs during the first quarter of 2011. CFC equipment and manufacturing capabilities at Sino Darou will be maintained until HFA-MDIs are approved by the relevant authorities.

MEXICO[18]

43. CFC-MDIs have been produced in Mexico by Laboratorios Salus since 1999, containing the following three active ingredients: salbutamol, beclomethasone and cromoglycate. Production of salbutamol and beclomethasone MDIs represents 99 per cent of the enterprise's total MDI production. About 70 per cent of MDIs produced by this company are for the Mexican Social Health system and other government medical health services. The remaining 30 per cent production is for the local market. The production levels of these MDIs are shown in the table below:

Active ingredient	2004		2005		2006	
	MDIs	CFC (tonnes)	MDIs	CFC (tonnes)	MDIs	CFC (tonnes)
Salbutamol	1,746,347	40.35	2,136,750	37.34	2,902,704	58.60
Beclomethasone	655,005	15.13	542,527	9.48	575,246	11.61
Cromoglycate	73,909	1.71	38,736	0.68	34,664	0.70
Total	2,475,261	57.19	2,718,013	47.50	3,512,614	70.91

44. Ipatropium CFC-MDIs are also produced in Mexico by one transnational corporation. In 2006, about 26 tonnes of CFCs were used by this company. In June of 2004, this company introduced tiotropium dry powder inhaler to provide significant and sustained improvements in lung function for patients with chronic obstructive pulmonary disease. Non-CFC-MDIs are also being imported into Mexico by three multinational companies with the following active ingredients: cromoglycate, budesonide, beclomethasone, fluticasone, salbutamol, combined salbutamol/beclomethasone and salmeterol. In 2006, over 2.4 million non-CFC MDIs were imported by these companies.

45. The bidding for the selection of a technology provider for the development of HFA-MDIs with three different active ingredients was completed in November 2008. However, since no offers were received after one year, manufacturers of MDI valves were invited to bid for technology provision. Accordingly, a company has been selected. The new filling machines are expected to be installed by September 2009. Commercial batch production (three batches) of HFA-salbutamol MDI will commence after the installation of the new equipment is completed. In the event that the conversion of the HFA-salbutamol MDI is successful, the development and formulation for the two other MDIs could be completed by the end of 2010.

18 UNEP/OzL.Pro/ExCom/53/44.

Registration of the three HFA-MDIs is expected during the first half of 2011. The Government of Mexico is proposing to stockpile already available pharmaceutical-grade CFCs, to be used by the enterprise during the conversion process. The manufacturing equipment required for the production of CFC-MDIs will be operational until mid-2011 when all four HFA-MDIs are to be registered.

PAKISTAN[19]

46. The manufacturing of CFC-MDIs in Pakistan was started in 1981 by GlaxoSmithKline (GSK) Pakistan Limited, with a current annual production of 4 million MDIs. Since then, the following two additional MDI manufacturing enterprises have been established:

(a) Zafa Pharmaceutical Laboratories, that established and registered its products in 1998 (current production of 0.2 million MDIs/year); and

(b) Macter International, that purchased a used CFC-MDI production line in 2004, and where development and testing for two MDI products began in 2007 and the first three products were launched in 2008 (with current production of 10 million MDIs/year). Accordingly, the enterprise was not eligible to receive assistance from the Multilateral Fund.

47. Currently, all MDIs manufactured in Pakistan are CFC-based, and there is no local capacity or capability to produce non-CFC-MDIs. In 2007, total CFCs used for the manufacturing of 4.21 million MDIs was 99.6 ODP tonnes. The active ingredients in MDIs are salbutamol (manufactured by the three enterprises), salbutamol/beclomethasone (manufactured by Macter and Zafa), and beclomethasone, salmetrol/fluticasone, ipratropium, salmeterol and triamcinolone acetonite (manufactured only by Macter).

48. The project proposes to assist the manufacturing enterprises to convert to HFA technologies with supporting public education and awareness activities. There is no capacity in the country to allow for stockpiling of CFCs. Therefore, the Government will utilize the essential use nominations procedure for requesting CFCs post 2009.

49. The signature of the project document between the MDI manufacturing plants and UNDP is expected to be signed in April 2009. The status of implementation of the project at the enterprise level is as follows:

(a) GSK is developing specifications for the formulation of the HFA-salbutamol MDI and the associated manufacturing equipment, through an external consultant. It is expected that the equipment will be in place by the last quarter of 2010 and HFA-salbutamol MDIs will be launched on the local market during the first quarter of 2011;

(b) Zafa Pharmaceutical Laboratories, with assistance from UNDP, is developing specifications for the formulation of the HFA-salbutamol MDI and filling equipment, for bidding during the second quarter of 2009. The approval of the new HFA formulation and the installation of commissioning of manufacturing equipment is proposed for the end of 2010, with launching of HFA-salbutamol MDIs on the domestic market by mid-2011; and

(c) Macter International is utilizing the services of a local university to develop the HFA formulation. The enterprise is also in negotiations with equipment suppliers for new filling lines. Although there is no firm date yet for launching the new HFA-MDIs, it is expected that they will be on the domestic market during 2011.

19 UNEP/OzL.Pro/ExCom/56/42.

URUGUAY[20]

50. Since 1980, Laboratorios Haymann S.A., (100 per cent locally owned), produces CFC-based MDIs both for the domestic market and for a limited amount of export. By 1994, the installed capacity was 1.5 million MDIs/year (similar to the current capacity), with a CFC consumption of about 10 ODP tonnes for the manufacturing of the following MDIs:

Drug	Total units
Salbutamol	209,300
Salmeterol	2,700
Cromoglycate	3,400
Fluticasone	1,800
Beclomethasone	17,600
Salbutamol/beclomethasone	177,300
Fenoterol	16,800
Ipratropium	5,900
Budesonide	1,100
Salmeterol+fluticasone	150
Total	**436,050**

51. Laboratorios Haymann, S.A., is proposing to reformulate the following drugs with HFA propellant: salbutamol (170,000 units), salmeterol/fluticasone (140,000 units), fenoterol (20,000 units), ipratropium (40,000 units), and fluticasone (50,000 units). Presently, there are no patents in Uruguay for HFA MDI formulations. The replacement formulations for HFA MDIs would be developed locally by the staff of Laboratorios Haymann. Therefore, a technology transfer or a license agreement would not be required for implementing the investment project.

52. It is expected that all HFA-MDI formulations will be registered by the end of 2009, and therefore, essential uses of CFCs might not be requested post 2009. However, this situation is being closely monitored in case of incidents that could occur during the reformulation of MDIs.

53. The new HFA-manufacturing line was successfully installed in 2007, and was used to produce the stability batches for the four new HFA-based formulations. Currently, CFC-MDIs are being produced because the HFA-MDIs have not yet been launched on the market. It is expected that all HFA-MDIs will be registered by the end of 2009. At that time, manufacturing of CFC-MDIs will cease and all equipment needed exclusively for the production of CFC-MDIs will be destroyed.

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20 UNEP/OzL.Pro/ExCom/43/44.