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REPORT OF THE
TECHNOLOGY AND ECONOMIC ASSESSMENT PANEL

OCTOBER 2009

RESPONSE BY TEAP AND ITS MTOC TO DECISION XX/4: CAMPAIGN PRODUCTION FOR SOME ARTICLE 5 PARTIES MANUFACTURING METERED-DOSE INHALERS WHICH USE CHLOROFLUOROCARBONS

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1.1 Executive Summary

The Parties considered the issue of a final campaign production of chlorofluorocarbons (CFCs) (for metered dose inhalers (MDIs) granted an essential use exemption) at their 20th Meeting and, under Decision XX/4, requested the Technology and Economic Assessment Panel (TEAP) to present a report to their 21st Meeting, concerning timing, storage, distribution, and management, minimizing the potential for over- or under-production, contractual arrangements, and minimizing the production of waste non-pharmaceutical-grade CFCs and options for its disposal, to be preceded by a preliminary report to the 29th Open-ended Working Group. This final report is presented in response to Decision XX/4.

A coordinated final campaign production for essential MDI uses was recommended previously by the TEAP and its Medical Technical Options Committee (MTOC) when it was understood that after 2009 only the CFC producer in Spain would be supplying the majority of CFCs needed for Article 5 Parties, and that China would supply itself. However, with changed circumstances (resulting from the recent EC ban on CFC production from 1st January 2010) and the current uncertainty of CFC supply, it is difficult to predict where essential use CFCs approved by Parties will be sourced for 2010 and beyond. Therefore, it is uncertain whether a coordinated final campaign production would still be relevant or recommended. TEAP and its MTOC will continue to follow the developments concerning production and supply of pharmaceutical-grade CFCs, but is unable to provide Parties with a detailed response to Decision XX/4 until Parties clarify the CFC production situation.

This report does outline options for the possible future supply of bulk pharmaceutical-grade CFCs to meet demand for MDI manufacture and estimated CFC requirements after 2009. If approved by Parties, about 2,300 tonnes of essential use pharmaceutical-grade CFCs for MDIs would need to be produced in 2010 or sourced from stockpiles that would otherwise be destroyed, with an estimated further demand of about 3,700 tonnes (that is, about 6,000 tonnes in total) until phase-out.

Options considered in this report include supplying pharmaceutical-grade CFCs from a single production facility source or multiple production facilities. Parties might wish to consider a fixed timetable for CFC production at a single facility or multiple facilities to avoid open-ended CFC production. Remaining stockpiles that would otherwise be destroyed are also a potential source of pharmaceutical-grade CFCs. If Parties do not resolve the current CFC production uncertainties, the default outcome could be that CFC MDI production ceases at the end of 2009 in many countries. With such uncertainty, Parties may wish to consider the source of production of CFCs for granted essential use exemptions for MDIs, and vigorously pursuing opportunities to source stockpiles that would otherwise be destroyed.

TEAP and its MTOC emphasise that given the uncertainties and risks associated with the long-term supply of suitable quality CFCs after 2009, the highest priority for continued supply of metered dose inhalers is to complete transition as quickly as possible and ensure the expeditious introduction of CFC-free alternatives.

1.2 Background to Decision XX/4

At their 17th Meeting, the Parties to the Montreal Protocol discussed the difficulties faced by some Article 5 Parties with respect to the phase-out of CFCs used in the manufacture of MDIs. In Decision XVII/14 the Parties expressed concern that Article 5 Parties that manufacture CFC MDIs might find it difficult to phase out these substances without incurring economic losses to their countries. There was the further risk that, for some Article 5 Parties, consumption levels in 2007 of CFCs for MDIs might exceed the amounts allowed for all CFC uses under the Protocol.

The Parties considered the issue again at their 18th Meeting and took Decision XVIII/16. Paragraph 12 of this Decision requested:

> "*TEAP to assess and report on progress at the 27OEWG and to report to the MOP19 on the need for, feasibility of, optimal timing of, and recommended quantities for a limited campaign production of chlorofluorocarbons exclusively for metered-dose inhalers in both Parties operating under paragraph 1 of Article 5 and Parties not operating under paragraph 1 of Article 5.*"

The TEAP and its MTOC included its response to Decision XVIII/16 in the April 2007 *Progress Report of the Technology and Economic Assessment Panel* to the 27th Open-ended Working Group Meeting. The Open-ended Working Group discussed the possibility of maintaining the current system of "just-in-time production". However, the Working Group did not achieve consensus, nor was consensus achieved at the 19th Meeting of the Parties.

In its 2008 Progress Report, in an updated response to Decision XVIII/16, MTOC reviewed new information available from the Multilateral Fund Secretariat, implementing agencies, countries, and industry sources and considered not only those Parties manufacturing CFC MDIs but also issues surrounding CFC MDI transition in importing Article 5 Parties.

The Parties considered the issue at their 20th Meeting and, in taking Decision XX/4, requested TEAP to present a report to their 21st Meeting, preceded by a preliminary report to the 29th Open-ended Working Group, concerning:

(a) The potential timing for final campaign production, taking into account, among other things, the information submitted in the nominations for 2010 and that some Parties operating under paragraph 1 of Article 5 may prepare essential use nominations for the first time for the Twenty-First Meeting of the Parties;

(b) Options for long-term storage, distribution, and management of produced quantities of pharmaceutical-grade chlorofluorocarbons before they are needed by Parties, including existing methods used by Parties not operating under paragraph 1 of Article 5;

(c) Options for minimizing the potential for too much or too little chlorofluorocarbons production as part of a final campaign;

(d) Contractual arrangements that may be necessary, considering the models currently used by Parties not operating under paragraph 1 of Article 5 that submit essential-use nominations consistent with decision IV/25;

(e) Options for reducing production of non-pharmaceutical-grade chlorofluorocarbons, together with options for final disposal of such chlorofluorocarbons.

1.3 Bulk CFC production and campaign production issues

Progress has been made towards phase-out of the use of CFC in MDIs in Article 5 Parties for certain key moieties, with a range of technically feasible alternatives now available. However, for some Article 5 Parties, the MLF-funded projects for conversion of locally owned CFC MDI manufacturing are underway, but not yet complete.

The continued use of CFC MDIs, after CFC-free alternatives have become available, has been justified over the last several years because CFC MDIs still provide affordable medication to many patients. This situation could now change as the cost of pharmaceutical-grade CFCs has become higher than that of pharmaceutical-grade hydrofluorocarbons (HFCs). Therefore the price differences between CFC and HFC MDIs are not currently a consequence of propellant cost, but rather other factors such as MDI component cost differences (canisters, valves etc), development costs, marketing, return on investment of capital costs and, in some cases, due to tariffs imposed to protect CFC MDIs that are manufactured locally against imported HFC MDIs. The price differential between CFC and HFC MDIs has become progressively smaller.

The mandated phase-out date under the Montreal Protocol for the global production of CFCs is a few months away. The Montreal Protocol's Decision IV/25 allows for the production of CFCs for essential uses, if approved by Parties, after the mandated phase-out date. The pace of implementation of projects to convert CFC MDI manufacturing in Article 5 Parties will determine the quantities of CFCs that will be required for CFC MDI manufacturing after 2009.

However, the lower the quantities of CFCs produced, the higher the price will be of CFCs; as a result, CFC producers/buyers may be reluctant to produce/buy the CFCs. After 2009, when out-of-specification CFCs made during the production of pharmaceutical-grade CFCs would need to be destroyed as waste, the manufacture of pharmaceutical-grade CFCs may become uneconomical with production runs less than several hundred tonnes.

Given the uncertainties and risks associated with the long-term supply of suitable quality CFCs after 2009, the highest priority for continued supply of inhalers is to complete transition as quickly as possible and ensure the expeditious introduction of CFC-free alternatives.

In its 2007 report, MTOC proposed a final campaign in 2009. However, in 2007 Parties did not adopt a decision on a final campaign, deferring consideration until a later date.

In its 2008 Progress Report, the MTOC considered a number of options for the production of pharmaceutical-grade CFCs after 2009 and recommended a preferred option of a final campaign production that, at the time, could have best facilitated the final phase-out of CFC MDIs in countries that were still manufacturing CFC MDIs. The options considered by MTOC in 2008 were as follows.

- Open-ended annual CFC production after 2009 (under essential use exemptions): This option was not recommended. It does not provide a clear target or timetable for ending CFC production, predictability for CFC producers, or incentive for those companies manufacturing CFC MDIs to switch to CFC-free alternatives. At a certain point, the economics of CFC production would not be favourable and would make impractical and too uncertain the continued production of relatively small amounts of pharmaceutical-grade CFCs. Overall destruction costs for out-of-specification CFCs would be relatively high with this option.

- A final campaign production of pharmaceutical-grade CFCs: This was the preferred option at the time of the 2008 Report. MTOC believed that, with appropriate planning and coordination, a final campaign could be feasible in 2011 to provide for CFC MDI manufacturing countries that do not have domestic CFC production. This option assumed that:

    - Project implementation was not delayed further;

    - The majority of Article 5 Parties obtained their pharmaceutical-grade CFCs from a plant located in Spain; and

    - China maintained domestic production of pharmaceutical-grade CFCs for its own use under an essential use exemption until a stage of its CFC MDI phase-out where it would undertake its own final campaign.

  Anticipating a final campaign production at an agreed date provided a clear target for ending CFC production, predictability for CFC producers, and an incentive for those companies currently manufacturing CFC MDIs to switch to CFC-free alternatives. In 2008, MTOC expected that in 2011 it would have been possible to run a final campaign of around 2,000 tonnes to cover MDI production requirements in several countries for multiple years.

1.3.1 New considerations in the supply of bulk pharmaceutical-grade CFCs

In early 2009, the European Community passed regulations to stop all production of pharmaceutical-grade CFCs (including for export) from the 1st January 2010. In the United States, Honeywell has a swing plant currently producing HCFC-22 that could be switched to CFC production. The United States has been considering these issues, and early indications are that significant regulatory changes would be required to allow export. An initial review indicates that FDA would likely need to pursue a 'notice-and-comment' rulemaking. While the outcome and timing for a rulemaking are difficult to predict, an estimate of timing is that the rulemaking process might require more than a year to complete. After that, US EPA could authorize production amounts. China and India both have production facilities capable of manufacturing pharmaceutical-grade CFCs that are subject to MLF production phase-out agreements.

With such uncertainty, Parties may wish to consider the source of production of CFCs for granted essential use exemptions for MDIs, and vigorously pursuing opportunities to source stockpiles that would otherwise be destroyed.

A number of producers of CFC MDIs in Article 5 Parties that were supplied from Europe will now have to find new sources of pharmaceutical-grade CFCs to supply any essential use CFCs approved by Parties for 2010 onwards. Many CFC MDI producers are currently without a confirmed supply of CFCs for any essential uses approved for 2010.

Assuming a supply becomes available, a change of CFC supplier will require that CFC MDI producers validate the suitability of a newly sourced propellant in each specific MDI product. Validation takes time to be completed, and in some cases would require the approval of the relevant health authorities. Total time to register a new source could be up to 6 months. This could disrupt the normal flow of the MDIs that are locally produced in Article 5 Parties, risking patient health. Validation efforts for CFCs for MDIs could also consume valuable technical resources in MDI manufacturing companies that would otherwise be devoted to the conversion to CFC-free technologies. These factors could further delay the transition from CFC MDIs.

There are a number of possible options considered below for the future supply of bulk pharmaceutical-grade CFCs to meet demand for MDI manufacture after 2009.

1.3.2 Single Source Supply

Under this option, there would be a single source to supply pharmaceutical-grade CFCs for any approved essential uses. The plant would need sufficient capacity to manufacture and store sufficient CFCs to satisfy the demands of all Article 5 Parties that are requesting essential use exemptions. The plant might need to remain operational until towards the end of transition from CFC MDIs to CFC-free alternatives, which could be as late as 2015[1]. With a single facility, global CFC manufacture would be rationalised to allow larger production runs than could be provided by using multiple production facilities. Compared with multiple CFC producers, a single producer could provide certain economies of scale and minimise costly waste by-product[2].

However, a sole manufacturing facility would hold a monopoly, which could create a potential risk to supply if the sole supplying plant was forced to shut, a lack of competition that could increase costs, and less storage capacity for inventory. Pharmaceutical-grade CFC supply by one supplier could encourage open-ended annual CFC production for Parties with essential use exemptions, until a time when demand has reduced to a level when a final campaign becomes necessary. Overall destruction costs for out-of-specification CFCs in this open-ended scenario could be relatively high.

As reported in 2008, open-ended annual CFC production does not provide a clear target for ending CFC production or incentive for CFC MDI manufacturers to switch to CFC-free alternatives. Parties might wish to consider a fixed timetable for CFC production at a single facility to avoid open-ended CFC production.

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[1] China has the largest consumption of CFCs for MDIs and has estimated that it could take until about 2015, possibly the latest of all Article 5 Parties, to complete its transition from CFC to HFC MDIs. However, it should also be noted that access to essential use CFCs should not be linked necessarily to the completion of all conversion projects of CFC MDIs to CFC-free alternatives, but rather to the satisfaction of the essential use criteria. It is worthwhile to remember that the concept of therapeutic equivalence (such as within the group of inhaled corticosteroids where one corticosteroid has similar therapeutic benefits to another) implies that not all moieties that were formulated as CFC MDIs need to be reformulated as HFC MDIs to complete the CFC phase-out process. The experience with phase-out in non-Article 5 Parties shows that in some cases reformulation may not be possible at all. So CFC production to satisfy essential uses may not be needed for the total duration of transition from CFC MDIs to CFC-free alternatives.

[2] Depending upon operational parameters, a bulk CFC production facility will produce a certain percentage of CFCs that do not meet the pharmaceutical-grade specifications required by MDI manufacturers. Although the expectations for purity may vary, the percentage of production not fit for pharmaceutical use is projected to be no lower than 25 per cent and may be as high as 50 per cent of CFC production. Before 31 December 2009, CFCs that do not meet pharmaceutical specifications can be used for basic domestic consumption. This will not be possible after 2009 when these non-pharmaceutical-grade CFCs would need to be destroyed. Further, the larger the quantity of a single production of CFCs, the lower the proportion of low quality, out-of-specification, CFCs will be produced. Conversely, the smaller the quantity is, the higher the proportion of low quality CFCs produced. For a single plant, a quantity of about 200 tonnes may be the limit below which CFC production becomes impractical, both for the efficiency and cost of CFC production.

1.3.3 Multiple Source Supply

Under this option, more than one CFC production facility would supply pharmaceutical-grade CFCs for any approved essential uses. This option would spread the risks of plant failure and avoid the problem of a monopoly and its attendant risks.

However, multiple sites for CFC production would create smaller production runs and possibly increase the cost of pharmaceutical-grade CFCs, through potentially less favourable economies of scale and more costly waste by-product[3]. A final campaign at each production facility would be needed under this scenario. Pharmaceutical-grade CFC supply by multiple CFC suppliers could still encourage open-ended annual CFC production for Parties with essential use exemptions, until a time when demand and production at each facility has reduced to a level when a final campaign becomes necessary. This would depend on the split of global production between facilities. Overall destruction costs for out-of-specification CFCs in this open-ended scenario could be relatively high.

As reported in 2008, open-ended annual CFC production does not provide a clear target for ending CFC production or incentive for CFC MDI manufacturers to switch to CFC-free alternatives. Parties might wish to consider a fixed timetable for CFC production at multiple facilities to avoid open-ended CFC production.

1.3.4 Remaining Stockpiles

Remaining stockpiles in non-Article 5 Parties and Article 5 Parties are a potential source of pharmaceutical-grade CFCs for about a third of business-as-usual demand for MDIs in 2010, but could not meet total demand based on reported plans unless the transition to CFC-free alternatives is accelerated with adequate funding and technical expertise. The reported stockpile at the end of 2008 in the United States was 830 tonnes. The stockpile in the United States may yet be used domestically to supply its requirements for CFC MDIs, but some could potentially remain at the end of its CFC MDI phase-out. The stockpile that remains in the European Community is of the order of about 100 tonnes. There may also be stockpiles available in Article 5 Parties that are completing their CFC MDI manufacturing phase-out or have large surplus for their own needs. Regulatory issues may need to be considered for export of surplus stockpiles.

1.3.5 Cease CFC MDI production at the end of 2009

This will become the default outcome[4] in many countries if Parties do not resolve the current CFC production uncertainties before the end of 2009.

1.3.6 A Coordinated Final Campaign Production

A coordinated final campaign production for essential MDI uses was recommended previously by the TEAP and its MTOC when it was understood that after 2009 only the CFC producer in Spain would be supplying the majority of CFCs needed for Article 5 Parties, and that China would supply itself. However, with changed circumstances and the current uncertainty of CFC supply, it is impossible to predict where any essential use CFCs approved by Parties will be sourced for 2010 and beyond. Therefore, it is uncertain whether a coordinated final campaign production would still be relevant or recommended. TEAP and

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[3] *ibid.*

[4] Except for the United States, which has an approved essential use exemption for 2010 and an operating facility to supply its own use.

its MTOC will continue to follow the developments concerning production and supply of pharmaceutical-grade CFCs, but is unable to provide Parties with a detailed response to Decision XX/4 until Parties clarify the CFC production situation.

1.4 Estimated CFC requirements for MDIs in 2010 and beyond

Information[5] available allows a global picture of estimated pharmaceutical-grade CFC requirements for MDIs to be developed for 2010 until phase-out (see Table 1). If approved by Parties, about 2,300 tonnes of essential use pharmaceutical-grade CFCs for MDIs would need to be produced for 2010, or sourced from stockpiles that would otherwise be destroyed, with a total estimated demand of about 6,000 tonnes until phase-out.

If there were a single supplier of CFCs after 2009, based on a *prima facie* consideration of projected CFC requirements alone[6], a final campaign production run might not be required until around 2014, after which CFC production might become less economical when dropping below a few hundred tonnes of CFCs per year. If there are multiple suppliers, then final campaign production runs may be needed when it becomes less economical at each individual plant. This indicates the difficulty in making predictions while uncertainty exists about future CFC production, but also points to the possibility that an organised final campaign production, as originally envisaged, may no longer be advantageous.

Storage Capacity

From available information, it appears that few CFC MDI manufacturers in Article 5 Parties have adequate capacity for storage longer than a few months of current production. This indicates that a final campaign production, if undertaken, might need to be carefully timed to optimise the use of available storage capacity, or alternatively off-site storage may need to be located such as at a CFC production facility[7].

[5] Including from essential use nominations for 2010, ExCom project proposals, reports from implementing agencies, and from the recent SEAP and South Asia Networks of ODS Officers, Chiang Mai, 8-10 October 2009. This information does not take into account whether the projected CFC requirements meet the essential use criteria.

[6] This does not take into account whether the projected CFC requirements meet the essential use criteria.

[7] For more information on storage and other detailed aspects of a final campaign production, see *Report of the Technology and Economic Assessment Panel, May 2008 Volume 1, Progress Report*, Chapter 2, Updated Response to Decision XVIII/16: Difficulties faced by some Article 5 Parties manufacturing metered-dose inhalers which use chlorofluorocarbons.

Table 1: Estimated CFC requirements[8] for MDIs 2010-2014+

Country	2010	2011	2012	2013	2014 +	Total
Algeria	11	8	0	0	0	19
Argentina	178	180	180	85	40	663
Bangladesh	157	100	75	50	0	382
China	972	748	650	400	345	3,115
Colombia	-	-	-	-	-	0
Cuba	-	-	-	-	-	0
Egypt	227	37	0	0	0	264
India	344	230	184	0	0	758
Indonesia	-	-	-	-	-	0
Iran	105	0	0	0	0	105
Mexico	-	-	-	-	-	0
Pakistan	35	35	35	0	0	105
Russia	212	100	0	0	0	312
Syria	45	30	0	0	0	75
Uruguay	-	-	-	-	-	0
Venezuela	-	-	-	-	-	0
Total	2,286	1,468	1,124	535	385	5,798

[8] Consumption in some countries appears as zero since they have indicated they will be producing from stockpile at least for 2010. Estimated requirements do not take into account whether these meet the essential use criteria.