

Metered Dose Inhaler Transition Issues at the 24th Meeting of the Open-Ended Working Group of the Montreal Protocol

Geneva, Switzerland (13-16 July 2004)

INTRODUCTION

The International Pharmaceutical Aerosol Consortium (IPAC) appreciates the work of the Technology and Economic Assessment Panel (TEAP) in considering issues surrounding the transition to CFC-free metered dose inhalers (MDIs). In its May 2004 Report, TEAP made recommendations concerning essential use nominations for MDIs. The 2004 Report also (i) reviews the status of the MDI transition around the world; (ii) reports on TEAP's analysis of the potential impact of the phase-out in non-Article 5(1) countries on the availability of inhaled therapy in Article 5(1) countries; and (iii) provides TEAP's views on elements of Decision XV/5.

IPAC wishes to reiterate its commitment to a timely, effective transition to CFC-free products and, as detailed below, requests that the Parties take the necessary action to promptly progress the transition.

STATUS OF MDI TRANSITION

Transition in Non-Article 5(1) Countries

Last year, the Parties recognized the need to establish further Protocol-level measures to progress the transition and adopted Decision XV/5. The Decision acknowledges the "urgent need to accelerate the phase-out of CFC-containing metered dose inhalers" in developed countries, and IPAC believes that it is an important step toward a final transition roadmap. This is consistent with TEAP's prior assessment that the availability of CFC-free products alone will not lead to a timely completion of the transition and that additional steps are necessary for an effective transition – particularly "ceasing the

supply of CFC MDIs where alternatives exist." Therefore, IPAC has called for, and continues to strongly support: the cessation of essential use volumes for single-moiety salbutamol (albuterol) by end 2005 and the timely conclusion of the essential use process.

TEAP notes that two or more CFC-free salbutamol MDIs are available on the market in more than 30 non-Article 5(1) countries. The transition of salbutamol MDIs is critical to the overall transition given that these products represent at least half of the worldwide market. Completion of the salbutamol transition will significantly reduce CFC usage. For example, 70% of the 2006 US essential use nomination is for CFC single-moiety salbutamol MDIs, even though two CFC-free salbutamol MDIs have been on the market in the US for over two years.

The wisdom of TEAP's assessment that complete transition requires regulatory action to declare products non-essential can be seen by contrasting the current transition status in the major markets in the developed world. Canada, Australia, and Japan have set firm dates for phasing out CFC MDIs and thereby have been able to advance the transition to final closure. In addition, these three countries, as well as twelve countries in Europe, have declared the use of CFCs in salbutamol MDIs to be non-essential. As a result, neither Canada, Australia, nor Japan have requested essential use volumes for 2006, and the EU's request, which includes its need for export production, represents a substantial reduction from previous years. In the US, where no CFC products have yet been determined non-essential, despite two CFC-free salbutamol MDI products being available for over two years, more

than 90% of salbutamol MDIs still use CFCs. IPAC strongly urges the United States to follow the positive examples set by these countries and to declare single-moiety salbutamol CFC MDIs non-essential as of December 31, 2005.

In its 2002 Report, TEAP noted that although Decision XII/2 provides that all non-Article 5(1) Parties should develop and submit their national transition strategies by 31 January 2002, only 8 of 43 countries had done so. This year, TEAP reports that no additional countries have submitted strategies during the past two years. IPAC urges Parties that have not adopted national transition strategies to do so as soon as possible. IPAC would be pleased to serve as a resource during this process.

Transition in Article 5(1) Countries

In response to the Parties' request in Decision XV/5, TEAP undertook an assessment this year of the potential impacts of the phase-out of CFCs in non-Article 5(1) Parties on the availability of inhaled therapy in Article 5(1) Parties. TEAP notes that CFC MDIs are supplied to Article 5(1) countries via three main avenues: (i) importation from multinational pharmaceutical companies located in Europe or other developed countries; (ii) local manufacture in the Article 5(1) country; and (iii) local manufacture in the Article 5(1) country by a subsidiary of a multinational company that is headquartered in a non-Article 5(1) country. IPAC generally concurs with TEAP's assessment on these issues, and, in particular, agrees that the phase-out of CFC MDIs in non-Article 5(1) countries "need not have a significant impact on treatment availability in Article 5(1) countries."

TEAP has previously recommended that it is important for Article 5(1) countries to develop now national transition strategies. IPAC concurs with this recommendation and congratulates the countries (e.g., South Africa, Colombia and Malaysia) that have already done so.

Transition in Countries with Economies in Transition (CEIT)

TEAP's 2003 Report estimated that over 500 tonnes of CFCs are used for MDIs in CEIT.

TEAP notes this year that still only 2 of 17 CEIT have submitted national transition strategies to the Ozone Secretariat. TEAP has concluded that insufficient data exists in many CEIT to assess the status of the transition and make recommendations with regard to assuring an effective transition. IPAC concurs with the expectation that these circumstances may change as several CEIT joined the European Union in May and as others respond to Decision XV/5.

Implementation of Decision XV/5

Decision XV/5(9) requests that TEAP modify the *Handbook on Essential Use Nominations* to reflect the key elements of the decision, particularly the request that Parties include additional, more detailed data in their nominations. Specifically, Decision XV/5(2) requires Parties to "specify for each nominated use, the active ingredients, the intended market for sale and distribution and the quantity of CFCs required." IPAC generally supports this provision and believes that this increased detail and expanded mandate for TEAP should allow TEAP to better evaluate whether the volumes of CFCs requested meet the standard for essentiality set forth in Decision IV/25. IPAC acknowledges that TEAP and ATOC have noted some complexities and difficulties in implementing Decision XV/5. IPAC appreciates the important contributions of these expert panels in the essential use process and would be pleased to consult with them and the Parties on the most effective and efficient ways to accomplish the objectives of Decision XV/5.

IPAC strongly concurs with TEAP's conclusion that in the near-term additional data on intended markets and export versus domestic use is particularly important for salbutamol MDIs, and encourages Parties to provide this data consistent with the requirements of Decision XV/5.

Stockpiled Quantities of CFCs

TEAP's 2004 Report notes that the current CFC accounting frameworks provide only aggregate figures for a Party's stockpile of pharmaceutical-grade CFCs. However, as TEAP points out, individual companies "may hold a substantial and, perhaps, disproportionate

amount” of stockpiled CFCs and “the optimal management of [a Party’s] stockpile may be dependent on a clear knowledge of the individual holdings by various companies.” As TEAP notes, under Decision IV/25, production and consumption for an essential use should be permitted only if “the controlled substance is not available in sufficient quantity and quality from existing stocks of banked or recycled controlled substances ...”. TEAP has previously stated that a 12-month CFC supply constitutes a reasonable stockpile level.

IPAC concurs with TEAP’s assessment and therefore recommends that Nominating Parties submit, as part of their essential use nominations, sufficient information on individual companies’ CFC stockpiles. This will enable TEAP to determine whether an individual company’s stockpile is reasonable, so that TEAP can apply the above-quoted stockpile provision of Decision IV/25 in its assessment of essential use nominations.

Due Diligence on Research and Development

The TEAP Report points out that under Decision VIII/10, non-Article 5(1) Parties should request MDI companies to “demonstrate ongoing research and development of alternatives to CFC MDIs with all due diligence and/or to collaborate with companies with such efforts...”. TEAP cited an example where one Nominating Party had not complied in good faith with this provision, and asked for guidance from the Parties on the implications of this. As the original drafter and a strong supporter of the text that became Decision VIII/10 in 1996, IPAC shares TEAP’s assessment in its 1997 report that “[v]ague statements of commitment toward reformulation are not sufficient for [ATOC] to make evaluations...”. The Essential Use Handbook requires each Nominating Party to assure that **each company** has fully complied with this provision of Decision VIII/10. On numerous occasions in the past when a Nominating Party has not submitted information requested in the Essential Use Handbook, TEAP has declined to recommend approval of that Party’s essential use nomination.

IPAC strongly recommends that the Parties urge TEAP not to recommend approval of any nomination if the Nominating Party has not submitted information to assure TEAP that each company requesting essential use allocations has fully complied with Decision VIII/10’s provision to “demonstrate ongoing research and development of alternatives with all due diligence and/or collaborate with other companies in such efforts.”

Regulatory Approval and Reimbursement of CFC-free Treatments

It is important to keep in mind that in light of their responsibility to review and approve CFC-free therapies for patients, national health authorities play a critical role in the MDI transition. For this reason, Decision VII/11(2), requests national health authorities to expedite approval of such products. However, IPAC is not aware of how many countries have modified or expedited their approval processes to implement their global phase-out of CFC use. The Parties may wish to consider establishing a means for countries to report on what specific actions they have taken to expedite approval of products that will replace CFC MDIs. In addition, IPAC is aware that some Parties still favour CFC products over CFC-free products in purchasing and reimbursement decisions. IPAC urges the Parties not to discriminate against CFC-free treatments solely on the basis of cost.

ESSENTIAL USE NOMINATIONS

When considering Parties’ requests for “essential” CFCs, it is important to keep in mind that the essential use process established under Article 2A of the Protocol was designed as a *temporary* exemption, with strict criteria set by Decision IV/25, to allow the production of CFCs necessary for health and safety **only** when “there are no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of environment and health.” As TEAP has aptly noted, the availability of CFC-free alternatives alone will not lead to closure of the transition, and industry/government cooperation to define a firm date for the removal of CFC MDIs from the



marketplace is the most effective approach to achieving transition.

IPAC strongly concurs with these points and for these reasons, and as detailed below, believes that the Parties should not approve the CFC volumes requested for use in 2006 for single-moiety salbutamol MDIs intended for non-Article 5(1) countries.

United States

TEAP's May 2004 Report notes that the United States nomination for 1900 tonnes is unchanged from the quantity nominated for 2005. In its 2005 nomination, the US expressed hope that the transition on salbutamol "will proceed in a manner that obviates the need for the US to use the full amount requested [for 2005]." Yet, according to the US nomination for 2006, the significant majority of the US request for production in 2006 – approximately 70% – still is intended for production of single-moiety salbutamol MDIs, all for the US domestic market. As TEAP points out, two acceptable alternatives for single-moiety salbutamol have been on the US market for more than two years. Accordingly, the Aerosol Technical Options Committee (ATOC) correctly concludes that there "are no technical barriers, as defined under Decision IV/25, to the phase-out of CFC MDIs where salbutamol (albuterol) is the sole moiety."

It is also important to note that the criteria for non-essentiality defined by the United States' own MDI transition strategy have been or will be met by 2006. The US Stakeholders Group on MDI Transition ("the Stakeholders Group") – on behalf of a broad range of physician and patient organizations interested in respiratory diseases – has requested that the national health authority (FDA) remove single-moiety salbutamol CFC MDIs from the market effective December 31, 2005. IPAC fully supports the Stakeholders' positions and concurs that single-moiety salbutamol CFC MDIs should be declared non-essential and removed from the market by end-2005.

The United States has committed to concluding the domestic regulatory process to define the end date for the essentiality of salbutamol MDIs by March 2005. Indeed, meeting this self-imposed deadline is absolutely necessary to comply with the elements of Decision XV/5. Granting approval of essential use CFC volumes for salbutamol for 2006 is unnecessary and premature under the circumstances. TEAP has noted that it is currently uncertain whether salbutamol CFC MDIs will qualify as essential during 2006 but that "it is clear that an approximately three year supply of CFC will be available in 2005" if the full US nomination is approved by the Parties at MOP-16. Pursuant to Decision IV/25, essential use allocations should only be granted where CFCs are not available from existing stockpiles. With this level of stockpile, there should be no issue of CFC MDI availability for patients if the salbutamol portion of the 2006 US nomination is not approved by MOP-16.

European Community

TEAP notes that the European Community's 2006 nomination for 550 tonnes is approximately 30% lower than that requested for 2005 "continuing a steady downward trend for requests from the EC." IPAC congratulates the European Community's substantial efforts to progress the MDI transition. ATOC has requested that the EC provide additional data related to salbutamol CFC MDIs to facilitate the review of their 2006 request during 2005. IPAC agrees that the provision of such data would be useful and is consistent with the requirements of Decision XV/5.

In light of the above, IPAC requests that the Parties not approve the portion of the United States' and European Community's 2006 nominations intended for use in single-moiety salbutamol MDIs. IPAC requests that Parties approve those portions of the US and EU nominations that are intended for CFC MDI products other than single-moiety salbutamol.

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