

ADDENDUM (OCTOBER 2008)
ESSENTIAL USE NOMINATIONS FOR MDIS
REASSESSMENT

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1 Essential Uses

1.1 Executive Summary Essential Use Nominations for Metered Dose Inhalers

During the 28th Meeting of the Open Ended Working Group, representatives of the European Commission and United States' delegations held discussions with the co-chairs of the Medical Technical Options Committee about their essential use nominations for CFC metered dose inhalers for 2009 and 2010 respectively. After further deliberations, the European Commission submitted a revised nomination, which reduced its request from 38 tonnes to 22 tonnes of CFCs and provided additional information justifying its nomination. In addition, the United States submitted a revised nomination, which reduced its request from 182 tonnes to 92 tonnes and provided additional information justifying its nomination. This Report includes the Medical Technical Options Committee's assessment of, and recommendations for, the revised nominations from the European Community and the United States. The nomination from, and recommendation for, the Russian Federation for CFC metered dose inhalers for 2009, remains unchanged from the Technology and Economic Assessment Panel's May 2008 Report.

The following table summarises the recommendations of the Technology and Economic Assessment Panel (TEAP) and its Medical Technical Options Committee (MTOC) on the revised nominations for essential use production exemptions for chlorofluorocarbons (CFCs) for metered dose inhalers (MDIs) from the European Commission, the Russian Federation and the United States.

Table 1: Recommendations for essential use nominations

| | European Community | Russian Federation | United States |
|-------------|--|---|--|
| 2009 | Recommend exemption for CFCs for MDIs for 22 tonnes. | Recommend exemption for CFCs for MDIs for 248 tonnes (for single-moiety salbutamol to be sold within the Russian Federation). | |
| 2010 | | | Recommend exemption for CFCs for MDIs for 92 tonnes. |

The European Commission and the United States provided additional justification for their nominations. However, MTOC did not reach consensus to the validity of these lines of argument and did not universally accept that essentiality was demonstrated. Although MTOC did not unanimously regard the uses as essential, the remaining quantities represent less than 1 per cent of peak usage and MTOC agreed reluctantly to recommend the nominations for a final year to allow the last stage of transition to be effectively managed and completed at a local level, and thereby minimise any risk of impact to human health.

1.2 Essential Use Nominations for Metered Dose Inhalers

1.2.1 Criteria for Review of Essential Use Nominations for MDIs

Decision IV/25 of the 4th Meeting and subsequent Decisions V/18, VII/28, VIII/9, VIII/10, XII/2, XIV/5, XV/5, XVI/12, and XVIII/16 have set the criteria and the process for the assessment of

essential use nominations for MDIs for Parties not operating under paragraph 1 of Article 5 of the Protocol. Other essential use decisions relevant to these Parties are Decisions XIX/13, XVIII/7, and XVII/5.

1.2.2 Review of Nominations

The revised nominations were assessed according to the guidelines for essential use contained within the *Handbook on Essential Use Nominations* (TEAP, 2005) and subsequent Decisions of the Parties.

Concurrent with the evaluation undertaken by the MTOC, copies of all nominations are provided to the Technology and Economic Assessment Panel (TEAP). The TEAP and its TOCs can consult with other individuals or organisations to assist in the review and to prepare TEAP recommendations for the Parties.

1.2.3 Summary of Parties' Essential Use Nominations and Quantities for 2009 and 2010 (in tonnes)

| | European Community | Russian Federation | United States |
|-------------|---------------------------|---------------------------|----------------------|
| 2009 | 22 | 248 | - |
| 2010 | - | - | 92 |

1.2.4 Observations

1.2.5 Committee Evaluation and Recommendations

Quantities are expressed in metric tonnes.

1.2.5.1 European Community

| Year | Quantity nominated |
|-------------|---------------------------|
| 2009 | 22 tonnes |

Specific Use: MDIs for asthma and COPD

Active ingredients and intended markets for which the European Community nomination applies:

| Active Ingredients | Intended market |
|--|---|
| Salbutamol | Chile |
| Beclomethasone | Colombia, Venezuela, Pakistan, Argentina, Mexico, Chile |
| Salbutamol+Ipratropium bromide (combination) | European Community |
| Salbutamol+Flunisolide (combination) | European Community |

| | |
|--|---------------------------|
| Salbutamol+Beclomethasone dipropionate (combination) | European Community, Chile |
|--|---------------------------|

Recommendation: Recommend.

In August 2008, the European Commission submitted a revised nomination, which reduced its original request from 38 tonnes to 22 tonnes of CFCs and provided additional information justifying its nomination. Three active ingredients in the original nomination are no longer subject to the revised nomination: budesonide; cromoglycic acid; and isoproterenol HCl/phenylephrine HCl combination. About 60 per cent of the nominated quantity is intended for CFC MDI sale within the European Community (Italy) and the remaining 40 per cent is intended for export of CFC MDIs to Article 5 Parties.

Stockpile

In its original assessment in the May 2008 report, MTOC did not consider the portion of the nomination designated for export to Article 5 Parties to be essential, asserting that these quantities might be supplied from existing stockpiles in the European Community.

In June 2008, the European Commission conducted a survey of stocks of pharmaceutical grade CFCs available within the European Commission, including manufacturers no longer involved in nominating CFCs for MDIs. This survey provided comprehensive stockpile data for the revised nomination.

The survey data shows that companies that either no longer nominate CFCs but still manufacture MDIs from their stocks or no longer manufacture CFC MDIs hold about 98 per cent of the total stocks of CFCs. Quantities of post-1996 CFCs held by all companies amounted to 198 metric tonnes and pre-1996 stocks amounted to 66 metric tonnes. The survey found that some quantities held by companies no longer nominating CFCs would either be transferred to other companies or Article 5 Parties or be destroyed. Most of the CFC held in stocks by companies not nominating for 2009 is expected to supply the manufacture of CFC MDIs to be exported to Article 5 Parties.

The European Commission notes that it will maintain its efforts to facilitate the transfer of CFCs from companies holding stocks of CFCs to those nominating CFCs for 2009 in order to minimise the volumes to be licensed for 2009. However, it also notes that the use of stocks are manufacturing company's rights and therefore some quantities may be destroyed instead of being transferred due to business interests.

The European Commission gives assurances that, with 2009 being the final year for the production of CFC MDIs in the European Commission, its allocation process for the production of CFCs for MDIs for 2009 would optimise the use of remaining stocks declared available and minimise the production of new CFCs.

The survey data demonstrate to MTOC the inflexibility of stockpile transfers under an unregulated market system in meeting the objectives of the Montreal Protocol.

However, based on the data presented, the European Commission is making its best efforts to encourage stockpile transfers and minimise new production.

Active ingredients

In its original assessment in the May 2008 report, MTOC did not consider the portion of the nomination designated for combination products to be essential. MTOC has stated previously that combination products could not be considered essential when the individual components, or equivalents, are available as CFC-free alternatives.

The remaining active ingredients for combination products subject to the revised nomination are salbutamol/ipratropium bromide, salbutamol/flunisolide, and salbutamol/beclomethasone dipropionate. With regard to the CFC quantities nominated for combination MDI products to be sold in Italy, further justification for the volumes nominated and progress in the registration of alternative products were provided in the nomination, by one of the relevant companies and by the Agenzia Italiana del Farmaco (AIFA). The reasons given for the essential nature of these combination products to Italy include: better clinical outcome; better patient compliance; economical convenience from the purchase of one product with two active ingredients rather than two separate products; lower National Health Service costs; and reduced emissions of ozone-depleting CFCs or greenhouse gas HFCs into the atmosphere. MTOC members could not agree as to the validity of these arguments.

Information was also provided to show that salbutamol is widely available as an HFC MDI but that ipratropium bromide is not available either as an HFC or as a CFC MDI in the Italian market. It was also stated that flunisolide is not available as an HFC MDI but is still available as two CFC MDI products in the Italian market. However the manufacturing company has no plans to continue manufacturing or to reformulate the CFC MDI products. Despite this, elsewhere in the nomination, flunisolide is listed for Italy as a non-essential active ingredient for CFC MDIs in the group of inhaled steroids indicating the availability of adequate equivalent alternatives in that market.

No information was provided about DPI alternatives for any of these active ingredients. No information was provided about beclomethasone alternatives although MTOC understands that alternatives are available and notes that beclomethasone is listed for Italy as a non-essential active ingredient for CFC MDIs in the group of inhaled steroids, indicating adequate equivalent alternatives are available. Based on the information on alternatives, in MTOC's view only the salbutamol/ipratropium combination CFC MDI should be considered to be an essential use because ipratropium, or its equivalent, is not available in a CFC-free alternative.

The new information states that CFC-free alternatives to the three combination products are in the advanced stages of Phase 3 research and development. AIFA has given its assurances that with expedited procedures for assessing and authorising the reformulated products, Italy will not make any request for CFCs for MDIs after 2009.

Comments

MTOC was not universally convinced that the combination products were an essential CFC use as contended in the revised nomination: a few members believed that the products were an essential CFC use while most members did not. However there was reluctant consensus agreement that the nomination should be recommended on the basis of the progress with reformulation, the demonstrated inaccessibility of available stockpile, and given 2009 was the final year of nomination.

1.2.5.2 *Russian Federation*

Refer to the May 2008 TEAP Report.

1.2.5.3 *United States*

| Year | Quantity nominated |
|-------------|---------------------------|
| 2010 | 92 tonnes |

Specific Use: MDIs for asthma and COPD for the active ingredient epinephrine for use solely within the United States.

Recommendation: Recommend.

In September 2008, the United States submitted a revised nomination of CFCs for epinephrine MDIs only, reducing its original request from 182 tonnes to 92 tonnes of CFCs and providing additional information justifying its nomination.

Two active ingredients in the original nomination are no longer subject to the revised nomination: pirbuterol and triamcinolone. The United States notes that the revised nomination does not alter its view of the essentiality of any of the products identified in the original nomination or prejudge the final outcome of the two proposed US regulatory rulemakings relating to essentiality under US law.

Epinephrine

In its original assessment in the May 2008 report, MTOC did not consider CFCs for the active ingredients included in the original nomination to be essential due to the availability of suitable alternatives. For the active ingredient epinephrine, further justification for essentiality and for the volumes nominated, and an update on progress in the registration of alternative products were provided in the revised nomination.

The United States detailed the history and background to epinephrine use in its market and the uniqueness of its role as an over-the-counter (OTC) medication rather than as a prescription drug. While epinephrine is stated not to be the drug of choice for physicians treating patients with asthma, the product is argued to serve an important role for as many as 1.7 to 2.3 million asthma patients. Some of these patients are low-income and other patients without access to adequate health care.

The United States makes the distinction that salbutamol may be considered a suitable alternate bronchodilator to epinephrine from a clinical pharmacological standpoint

but is only available with a physician prescription whereas epinephrine is available OTC. On this basis, the United States maintains that CFCs for use in epinephrine MDIs is an essential use under Decision IV/25(1) because it is necessary for the health, safety and critical functioning of society and currently there are no technically and economically feasible alternatives available.

The United States provided additional information on progress with the clinical development program for a CFC-free replacement epinephrine inhalation aerosol, which the manufacturer, Armstrong, believes it can bring to market by the beginning of 2011. The revised nomination provides an expectation that this proposed timeline can be realistically and reasonably met.

Quantity Requested and Stockpile

In its original assessment in the May 2008 report, MTOC did not consider the original nomination to be essential, asserting that the nominated quantities might be supplied from existing stockpiles.

The United States notes that relying on aggregate stock amounts is not reflective of the manufacturing need of an individual company. While CFC stocks held by manufacturers is confidential business information which cannot be shared, the United States give its assurance that it applies appropriate calculation of CFC stocks on a manufacturer-by-manufacturer basis.

The May 2008 report mentions that Armstrong manufactures salbutamol and epinephrine MDIs and suggests that Armstrong consider using its existing stockpile originally designated for salbutamol to produce epinephrine CFC MDIs in 2010. The revised nomination notes that this is not entirely technically possible due to the different blends of CFCs used in epinephrine (CFC 12 and CFC 114) compared with salbutamol (CFC 12 and CFC 11). The projected Armstrong stock may not be adequate for its future needs according to the revised nomination. The United States gives its assurance that it has taken the different formulations and available stockpile into account.

In subsequent communication with the United States, MTOC requested additional information clarifying the request for 92 tonnes of CFCs for 2010. In the opinion of MTOC members, the quantity requested seemed higher than might be expected based on current demand, especially if the requested quantities were mainly for CFC 114 not available from stockpile. The United States explained that the nomination was not solely for CFC 114 and that the 92 tonnes requested were based on projected needs for epinephrine in 2010. The United States did not supply any further detail about production levels and associated CFC needs due to business confidentiality.

The revised nomination provides no information about the transferability and accessibility of stockpile between manufacturers. However, there might appear to be market inflexibility of stockpile transfers, as is the case for the European Commission, which would not favour meeting the objectives of the Montreal Protocol.

Comments

MTOC was not universally convinced that epinephrine MDI is an essential CFC use as contended in the revised nomination: some members believed that the product was an essential CFC use while others did not. A few members thought that the US should defer its nomination for 2010 until 2009 when the outcome of the US rulemaking process on epinephrine essentiality might be known. Some members noted that the sole use of a bronchodilator rescue aerosol (as is likely with inexpensive OTC epinephrine in a low-income population) runs contrary to current international guidelines for the treatment of asthma, which now emphasise regular controller therapy.

MTOC was most concerned to see the completion of development efforts by the beginning of 2011, as planned by Armstrong. Having had at least 15 years to develop a replacement product, MTOC is concerned whether Armstrong will ever succeed in these efforts. However there was reluctant consensus agreement that the nomination should be recommended on the basis of anticipated progress made with reformulation, the claimed inaccessibility of available stockpile, and given that 2010 is expected to be the final year when CFCs would be required for epinephrine. Further, MTOC was in agreement that 2010 would be the final year for which it would recommend a nomination for epinephrine CFC MDI.

