UNEP MAY 2012 REPORT OF THE TECHNOLOGY AND ECONOMIC ASSESSMENT PANEL VOLUME 1

PROGRESS REPORT

ADDENDUM (OCTOBER 2012) ESSENTIAL USE NOMINATIONS FOR MDIS ADDITIONAL INFORMATION FOR CHINA ESSENTIAL USE NOMINATION 2013

1 Essential Uses

1.1 Additional Information relating to the Essential Use Nomination for Metered Dose Inhalers from China for 2013

During the 32nd Meeting of the Open Ended Working Group, representatives of China's delegation held bilateral discussions with attending co-chairs of the Medical Technical Options Committee about China's essential use nomination for CFC metered dose inhalers for 2013. Subsequently, on 31st August, China provided additional information justifying its nomination for review by MTOC, specifically in relation to products containing Traditional Chinese Medicines as the active ingredients.

This Report includes the Medical Technical Options Committee's assessment of, and recommendations for, the nomination from China based on the additional information provided. The nominations from and recommendations for the Russian Federation for CFC metered dose inhalers for 2013 remain unchanged from the Technology and Economic Assessment Panel's May 2012 Report.

1.2 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, XVIII/16, XX/3, XXI/4, XXII/4, and XXIII/2 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 and Parties operating under paragraph 1 of Article 5 of the Protocol. Other essential use decisions relevant to these Parties are Decisions XVII/5, XVIII/7 and XIX/13.

1.3 Review of Nominations

Nominations are assessed according to the guidelines for essential use contained within the *Handbook on Essential Use Nominations* (TEAP, 2009) and subsequent Decisions of the Parties. Recommendations are made in accordance with Decision XV/5(3), which requests TEAP and its TOC to make recommendations on nominations for essential use exemptions for CFCs for MDIs with reference to the active ingredient of the metered-dose inhalers in which the CFCs will be used and the intended market for sale or distribution.

1.4 Committee Evaluation and Recommendation of China Essential Use Nomination relating to Traditional Chinese Medicines

Quantities are expressed in metric tonnes.

Year	Quantity nominated
2013	446.52 tonnes

Specific Use: MDIs for asthma and COPD

Active ingredients and intended markets for which the nomination applies:

Active Ingredient	Intended market	Quantity Nominated (Tonnes)
Beclomethasone	China	54.03
Beclomethasone/clenbuterol/ipratropium	China	0.7
Budesonide	China	11.18
Datura metel extract/clenbuterol	China	2.00
Dimethicone	China	0.2
Ephedra, ginkgo, sophora flavescens, radix scutellariae	China	7.00
Ipratropium/Salbutamol	China	0.745
Isoprenaline	China	33.4
Salbutamol	China	332.947
Sodium cromoglycate	China	4.312
Total		**446.52**

Recommendation: Recommend 386.82 metric tonnes of CFCs for the manufacture of MDIs for the active ingredients beclomethasone, beclomethasone/clenbuterol/ipratropium, budesonide, dimethicone, ipratropium/salbutamol, isoprenaline, salbutamol, sodium cromoglycate.

MTOC is unable to recommend 50 tonnes of CFCs for salbutamol, 9 tonnes for Traditional Chinese Medicines, and 0.7 tonnes for a company not undertaking active research and development (Changzhou Tracheitis Institute for beclomethasone/clenbuterol/ipratropium combination).

Additional information

The nomination includes 9 tonnes CFCs used to manufacture MDIs containing "Traditional Chinese Medicines" from two companies. GuiYang DeChangXiang Pharmaceutical Co. produces a combination CFC MDI with "datura metel extract" with clenbuterol. Datura is stramonium, a herbal form of an anticholinergic medicine (like ipratropium), and clenbuterol, a short-acting beta-agonist. LiaoNing HaiKangEn Natural Herb Pharmaceutical Co. produces a complex CFC MDI with four ingredients (ephedra, ginkgo, sophoroflavescens, radix scutellariae). Both inhalers are combination products. One of the active ingredients in each inhaler is a known bronchodilator (clenbuterol and ephedrine respectively).

MTOC stated in the TEAP report May 2012 that although the ingredients have been available as Traditional Chinese Medicines (TCMs) for a long time, they have been available in CFC inhalers only in more modern times. MTOC recognizes the fact that traditional Chinese medicine has its own rationale and mechanism that may not be subjected to the same scientific discipline as modern western medicine. However, there are many CFC-free formulations of TCMs, including oral and injectable forms, used for the treatment of asthma and respiratory disease. MTOC did not find evidence in China's initial nomination that demonstrates the improved efficacy of these TCM CFC inhaler products compared with other forms of TCM treatment.

China provided additional information relating to these TCM products only (see Appendix 1 for a substantive extract of the information provided). The review and subsequent discussion therefore only focus on these products.

Datura metel extract/clenbuterol

The information provided for the Datura metel extract/clenbuterol (or otherwise known as the Amazing Anti-Asthmatic Aerosol in the information provided) summarises a clinical study of its effectiveness as an anti-asthmatic drug, based on clinical criteria set out in the additional information and using aminophylline tablet as the control. Aminophylline is an oral anti-asthmatic drug with significant gastrointestinal side effects, which is the most commonly used asthma treatment in China. It is not an oral TCM. It is administered in the study in very low quantities, which MTOC believes is unlikely to have any significant clinical effect. Generally, oral aminophylline has lower bronchodilator efficacy than commonly used inhaled treatments such as salbutamol[1].

The additional information provided suggests that the Datura metel extract/clenbuterol inhaler is more effective than the control according to the clinical criteria used for this research. However, no information was provided to say whether this TCM inhaler is more effective than available oral or injectable alternative forms of TCMs. Based on MTOC's own technical knowledge, the short-acting beta-agonist, clenbuterol, alone is likely to be effective compared to the low-dose aminophylline control. The dose of clenbuterol for each inhalation is 20ug, which, in a small trial[2], has similar efficacy and safety to 200ug of salbutamol (i.e. 10 times the potency dose-for-dose). This dose of clenbuterol would provide substantial bronchodilation alone, with fewer side effects than the oral aminophylline. No evidence was presented to differentiate the effectiveness of the different ingredients, or to suggest that the inhaled herbal component is of any additional value over and above the known bronchodilator, clenbuterol. Moreover, no evidence was presented that shows the combination product to be superior or even equivalent to more common asthma treatments, such as the bronchodilator salbutamol.

[1] Shim CS, Williams MH Jr., Bronchodilator response to oral aminophylline and terbutaline versus aerosol albuterol in patients with chronic obstructive pulmonary disease, *Am J Med.* 1983 Oct; 75(4):697-701.

[2] Baronti A, Grieco A, Vibelli C., A comparison between inhaled clenbuterol and salbutamol in chronic bronchitis with reversible airway obstruction, *Eur J Respir Dis*. 1980 Jun; 61(3):143-50.

Ephedra, ginkgo, sophora flavescens, radix scutellariae

The information provided for the inhaler containing ephedra, ginkgo, sophora flavescens, and radix scutellariae summarises the pharmacological, toxicological and clinical studies for its use as an anti-asthmatic drug. Ephedra is a Chinese herbal medicine. The main active ingredients of ephedra are ephedrine hydrochloride and pseudoephedrine hydrochloride, which are both bronchodilators, the latter being less effective than the former. The clinical studies use "Reshen Aerosol" as the control. "Reshen" is a Chinese herbal medicine, also named "Funneled Physochlaina Root", with the corresponding name in English being *p*-cymene. However, *p*-cymene is not the active ingredient of "Reshen Aerosol". The active ingredients of the control are the tropane alkaloids, scopolamine, hyoscyamine, hyoscyamus niger L, which have anticholinergic effects. *p*-Cymene is generally used as a chemical in the manufacture of perfumes, and is considered an irritant by inhalation. MTOC does not believe that *p*-cymene would have any therapeutic value in asthma treatment.

The study suggests that the TCM inhaler is more effective as an anti-asthma treatment than the control, *p*-cymene. However, no information was provided to say whether this TCM inhaler is more effective than the readily available oral or injectable alternative forms of TCMs. In traditional Chinese medicine, the effectiveness of a drug is investigated as a whole, with each component thought to have its own special efficacy and difficult to elaborate by modern western medical theory. Based on MTOC's own technical knowledge, ephedrine (ephedra) alone is likely to be effective compared to the control. China provided information that 25 per cent of the active ingredient of this inhaler is ephedra, but it is not possible from this information to determine the effective beta-agonist dose. No evidence was presented to differentiate the effectiveness of the different ingredients, or to suggest that the remaining inhaled herbal components have any additional value over and above the known bronchodilator, ephedra (ephedrine). Moreover, no evidence was presented that shows the combination product to be superior or even equivalent to more common asthma treatments, such as the bronchodilator salbutamol.

The key question that MTOC has considered in its assessment is whether TCM CFC inhalers can be considered essential under the Montreal Protocol when compared with other TCM treatment forms, such as oral or injectable. Oral or injectable TCM treatment forms have been available as affordable asthma treatments in Chinese medicine for a long time, and could be considered suitable available alternatives under Decision IV/25. MTOC argues that oral and injectable forms of TCMs are suitable alternatives. No evidence has been presented to refute this view.

MTOC Comments

Based on the information provided, MTOC is unable to find reason to reverse its decision not recommending the exemption. MTOC did not find evidence in China's initial nomination, or in the additional information, that demonstrates the improved efficacy of TCMs in a CFC inhaler compared with other forms of TCMs. MTOC does not consider CFCs for this use to be essential according to the criteria of Decision IV/25, due to the availability of suitable alternatives, and is unable to recommend CFCs for these products.

For 2013 China may wish to consider allocating CFCs for these products from within its authorised quantity to allow time for transition of patients from the TCM CFC inhalers to suitable alternative asthma treatments, which may include oral TCMs, with the same or similar efficacy.

Recommended quantities in accordance with Decision XV/5(3):

Active Ingredient	**Intended market**	**Quantity (Tonnes)**
Beclomethasone	China	54.03
Beclomethasone/clenbuterol/ipratropium	China	0.0
Budesonide	China	11.18
Datura metel extract/clenbuterol	China	0.00
Dimethicone	China	0.2
Ephedra, ginkgo, sophora flavescens, radix scutellariae	China	0.00
Ipratropium/Salbutamol	China	0.745
Isoprenaline	China	33.4
Salbutamol	China	282.947
Sodium cromoglycate	China	4.312
Total		**386.82**

2 Appendix 1

This Appendix includes the relevant information provided by China. This information was used by MTOC to review its assessment of the essential use nomination of CFCs for TCM MDIs made by China for 2013.

The clinical studies were completed in the 1990s, and the clinical criteria were based on "the new medicines (traditional Chinese medicine) treatment of bronchial asthma clinical research guidelines" in China.

Clinical criteria were as follows:

1) Normal lung function judged for "clinical controlling".
2) If the increase of FEV1 for lung function is greater than 30%, the patient will be judged for "markedly effective".
3) If the increase of FEV1 for lung function is between l0% and 30%, the patient will be judged for "effective".
4) If the increase of FEV1 for lung function is less than l0%, the patient will be judged for "ineffective".

The total effective rate is the total proportion of patients which were judged for "clinical controlling", "markedly effective" and "effective" in the treatment.

Details are as follows:

1. Summary of clinical studies of Amazing Anti-asthmatic Aerosol (the research report see Annex 1) {Note, Annex 1 was not included in the translated summary}

Amazing Anti-asthmatic Aerosol（License Number: Z52020225） which used in the treatment of bronchial asthma is manufactured by Guiyang De Chang Xiang pharmaceutical Co. LTD. To test the effect and the safety of the drug, it has been clinically proved according to "Clinical Testing Plan of Amazing Anti-asthmatic Aerosol in Treating Bronchial Asthma" by Affiliated Hospital of Guiyang Medical College, MCH Hospital. Specialist clinic of Traditional Chinese Medicine of The People's Hospital in Guiyang Yunyan District, using the Aminophylline tablet produced by Hunan pharmaceutical Co.LTD as the control drug. By observing 400 patients, which contain the treatment group of 300 patients, using Amazing Anti-asthmatic Aerosol produced by De Chang Xiang pharmaceutical Co. LTD, and the control group with 100 patients, taking 100mg once, three times a day, children under the age of 12 taking 70mg per time (2/3 tablet), three times a day, l week for a treatment course. The patients were randomized to observation, the results showed that:

(1) Amazing Anti-asthmatic Aerosol is highly effective in all kinds of asthma according to western medicine clinical classification as well as heat-asthma syndrome and cold-asthma syndrome according to traditional Chinese medicine syndrome differentiation. The total effective rate is of 90.66%, it is significantly better than control group of aminophylline which rate is 66.00% ($P < 0.01$).
(2) The comparison between Drug onset time and Drug maintain efficacy time shows that, 272 patients of "markedly effective" and "effective" (contain cured) results of treatment group show onset time (min) is 14.14 + /-3.42, and maintain efficacy time (h), 7.684 3.51; while 66 patients of the results of the control group show onset time

(min) is 21.24 + /-4.17, and maintain efficacy time (h) is 4.84 + /-2.27. Obviously, the onset time and maintain efficacy time in the treatment group is significantly better than that in control group.

(3) In the treatment group of 300 patients, l7 patients appeared dry mouth, mouth numbness and dizziness to varies degrees, but without any treatment or special processing, the symptoms will eliminate, and do not affect curative effect; The symptoms of dry mouth and mouth numbness may relate to misuse of inhaling drugs that results in drugs stay in the mouth.

2. Summary of pharmacological and clinical research of Yinhuang Pinchan MDI (the research report see Annex 2) {Note, Annex 2 was not included in the translated summary}.

Yinhuang Pinchan MDI (License Number: Z10910033) is developed by Jilin Provincial Academy of TCM, and obtained the production licence in 1991. It is an herbal compound recipe aerosol containing ephedra, ginkgo, flavescens, sophora flavescens ait, scutellaria baicalensis georgi. The product is a pale yellow clear liquid, producing a specific aroma and tasting bitter first and was sweet when spraying. The usage of this product is simple and the course is short. Yinhuang Pinchan MDI has multiple effects such as, antiasthma, cough relieving, expelling phlegm, and can be used for asthma therapy (including bronchial asthma, asthmatic bronchitis, and other asthma).

Pharmacology studies showed that, Yinhuang Pinchan MDI can against the asthma induced by acetylcholine and histamine in guinea pigs, showing the role of anti-asthma and relaxing smooth muscle; It can release the cough induced by sulfur dioxide in mice, showing significant antitussive effect; It can promote the excretion of phenolsulfonphthalein, showing some expectorant effect; It also can inhibit paw swelling induced by carrageenan, showing inhibition effects of many common pathogenic bacterium, especially pneumococcal. The results indicated this product has anti-inflammatory effects and plays an essential role in clinical therapeutic effects.

Toxicological studies on rodents showed that, after inhaling this product for 21 consecutive days, even the maximum daily inhalation dose is 32g/kg, no abnormal changes were found in body weight, behavior, blood, and liver and kidney function of rats. Comparing with the control group, no significant difference was found in pathological examination, and no significant effect was found in immune function and phagocytic activity in mice.

On the basis of the pharmacological experiments, seven clinical units including the People's Hospital of Jilin Province, Changchun College of TCM, NO.208 Hospital of Chinese People's Liberation Army had carried out systemic clinical research of Yinhuang Pinchan MDI from 1983 to 1990. By observation and verification, 315 cases of asthma patients used Yinhuang Pinchan MDI (treatment group), 105 cases of asthma patients used P-Cymene Aerosols(control group), the clinical efficacy of Yinhuang Pinchan MDI was superior to P-Cymene Aerosols.

(1) The clinical observation showed that the total effective rate was 94.92% in treatment group, and was 80.95% in control group. After medication, the sputum, cough, asthma symptoms was better in treatment group than control group.

(2) The improvement of lung ventilation in treatment group was also surpassed the control group. After treatment, the number of patients with FEV1 appreciation> 30% was 23 cases in the treatment group, while only 1 case in the control group.

(3) The onset time and effective duration in the treatment group and control group were 3.76, 3.67 hours and 4.66, 2.88 hours, respectively. Therefore, comparing with the control group, the treatment group has faster onset time and longer effective duration.

At the same time, through clinical observation, though there was a tendency of reduction of blood pressure and heart rate followed by the relief of symptoms of asthma, but all of them are in the normal range of fluctuation, indicating Yinhuang Pinchan MDI has no side effects on blood pressure and heart rate. Liver and kidney function test results showed that the product had no side effects on liver and kidney function. For its pharmacologic effects of antiasthma, cough relieving, expectorant and anti-inflammatory, this product can be used to the treatment of bronchial asthma, asthmatic bronchitis, and other asthma. This product has a rapid onset time (3-5 minutes), long duration (3-5 hours), easy to use, safe, less of side effects and has no damaging effects on heart, liver and kidney function and immune function. The total effective rate of this product was 94.92%, has significant effect on the relief of symptoms and signs.
