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Third Progress Report and Final Progress Report

MP/CPR/04/131/- Development of CFCs Phase-Out Plan for the MDI Sector

Contract No. 05/192

In accordance with the contract and milestone of the "Development of CFCs Phase-Out Plan for the MDI Sector", the Third Progress Report containing the sector plan for CFCs phase-out in the MDI sector in China and the Final Report summarizing all activities and final version of the Sector Plan for CFCs phase-out in the MDI sector in China agreed by the Secretariat of the Multilateral Fund. For achieving these objectives, there are some activities that have been completed and developed. Since the Sector Plan for CFCs phase-out in the MDI sector in China was approved by the 56th Secretariat of the Multilateral Fund in Nov, 2008, which shows that the final goal of the contract was achieved, and the Third Progress Report and the Final Report were combined as one progress report. The progress made from the verification report submitted to UNIDO to the Sector plan approved by 56th Secretariat of the Multilateral Fund is showed as follows:

1. Progress made in year 2006

The Verification Report on ODS for MDIs in China was submitted to UNIDO in May 2006. At the end of May, 2006, UNIDO, NICPBP, SFDA and MEP/FECO visited some MDI enterprises in Wuxi and Shanghai, and found that the data collected during our visit at the manufactures were

different from the one in the Verification Report. Then the submission of MDI sector has been postponed to 2007, so that there is enough time to verify the consumption figures for MDI carefully.

2. Progress made in year 2007

In April 2007, the time table of MDI sector plan drafted was agreed by UNIDO, NICPBP, SFDA and MEP/FECO, decided to verify the related data, and visit larger CFCs consumption MDIs manufactures.

Through discussions among SFDA, SEPA and UNIDO, it was agreed to try our best to submit the MDI Sector Plan to the 53rd ExCom in November 2007, so that sufficient time could be left to the enterprises for their conversion.

SFDA and MEP/FECO, under the contract with UNIDO had jointly organized the data survey of all the MDI enterprises at end of June and early of July. From June 20, 2007 to July 2, 2007, representatives from NICPBP, SFDA, and MEP/FECO are divided into 5 groups to visit 21 enterprises with CFCs consumption in 2006.

In July 2007, Meetings on MDIs was concentrated on the analysis of the data collected, discussed the structure and main contents of the sector plan and to formulate the project document.

The draft sector plan for phase-out of CFCs consumption in MDI sector was submitted to UNIDO at the end of July. On mid August, final version of the sector plan for phase-out of CFCs consumption in MDI sector, together with the Endorsement Letter was submitted to UNIDO. Then, UNIDO submit the MDI Sector Plan to the 53rd ExCom in November 2007.

The sector plan for phase-out of CFCs consumption in MDI sector was

not approved by the 53rd ExCom in November 2007. Through discussions with UNIDO, CFCs consumption in 2007 of the MDI manufactures must be verified in order that higher grant could be approved.

3. Progress made in year 2008

On Mar.28, 2008, SFDA, NICPBP and MEP/FECO jointly organized the meeting to discuss the MDI sector plan preparation issue. Then, SFDA issued notice of verification for the CFCs consumption of the MDI manufactures organized by NICPBP. From April 12th to 19th, representatives from NICPBP, SFDA, and MEP/FECO are divided into 5 groups to visit 14 enterprises in Sichuan, Guangdong, Shanghai, Shandong, Chongqing provinces with CFCs consumption in 2007. The verification content includes CFCs consumption, CFCs purchased, used, storage, and the production, sales of the MDI products in 2007 by the related enterprise. In addition, the MDI manufactures refilled <Questionnaire for the ODS consumption by the pharmaceutical MDI manufactures>, which especially added the issue for industrial rationalization and the exemption of the active ingredients.

In 2007, total CFCs consumption for MDI sector is 322,475 kg, production of the MDI is 20,136,410 cans, which is increased by 22.85% and 16.43% respectively than that is in 2006. And there are some changes for the MDI manufactures compared with which in 2006, Guangdong Tongde pharmaceutical Co. ltd. (No.35), Harbin Hengcang pharmaceutical Co. ltd. (No.11) renew to produce CFCs MDI in 2007, and Henan Xinin pharmaceutical Co. ltd. (No.14), Henan Zhongfu pharmaceutical Co. ltd. (No.15), Pharmaceutical Factory of Shanxi Medical University (No.25) only produce one active ingredient of MDI because of raw material sources issue.

The sector plan for phase-out of CFCs consumption in MDI sector was

updated greatly by NICPBP, SFDA, MEP/FECO, and UNIDO according to the result of the site visit verification, and submitted to UNIDO and the 55th ExCom secondly in May 2008.

At the end of May, 2008, the ExCom of the Multilateral Fund raised issues for the revised MDI sector plan, which were discussed and addressed in detail by NICPBP, SFDA, MEP/FECO through two days' meeting.

On July 13th to 19th, 2008, representatives from NICPBP, SFDA, and MEP/FECO attended the 55th ExCom, and the sector plan for phase-out of CFCs consumption in MDI sector was not approved by the 55th ExCom in July 2008.

On August 27th, 2008, SFDA, NICPBP and MEP/FECO jointly organized the meeting to discuss the MDI sector plan preparation and MDI used CFCs exemption issue during the implementation period of the sector plan, and some MDI manufactures with larger CFCs consumption participated the meeting.

In September 2008, NICPBP, SFDA, MEP/FECO discussed and addressed in detail about the issues raised by Australian, and then sent the Reply to the Austria question to the Secretariat.

On Nov.13rd, 2008, SFDA, NICPBP and MEP/FECO jointly organized the experts' meeting to discuss the implementation plan for MDI used CFCs exemption issue in China.

The sector plan for phase-out of CFCs consumption in MDI sector was submitted thirdly and approved by 56th ExCom in November 2008 eventually.

Summary

In a whole, from Jan., 2006 to today, the contract of the "Development of CFCs Phase-Out Plan for the MDI Sector" has lasted for 3 years more, and the objective of the contract achieved finally, which is that Sector Plan for CFCs phase-out in the MDI sector in China was approved by the 56th Secretariat of the Multilateral Fund in Nov, 2008. In order to prepare and submit an implemented CFCs Phase-Out Plan for the MDI Sector in China, there are 4 times in Sep, 2005, May-June, 2006, June, 2007, and in April,2008 on site verification for yearly CFCs consumption of the related MDI manufactures organized by SFDA, NICPBP and MEP/FECO, and the sector plan for phase-out of CFCs consumption in MDI sector was updated and submitted to 53rd, 55th and 56th ExCom for 3 times, and the sector plan approved finally shows the efforts put by Excom, UNIDO, SFDA, NICPBP and MEP/FECO.

(b) To request UNEP, in future submissions on the CAP budget to continue:

(i) To provide detailed information on the activities for which the global funds would be used;

(ii) To expand the prioritization of funding between CAP budget lines to accommodate changing priorities; and to provide details on the reallocations made in its budget following decisions 47/24 and 50/26; and

(iii) To report on the current post levels of staff and to inform the Executive Committee of any changes therein particularly in respect of increased budgetary allocations.

(Decision 56/43)

(g) Investment projects

Metered-dose inhalers

Argentina: Phase-out of CFC consumption in the manufacturing of aerosol MDIs (World Bank)

182. Introducing document UNEP/OzL.Pro/ExCom/56/22, the representative of the Secretariat said that, on behalf of the Government of Argentina, the World Bank had submitted a project proposal for the phase-out of CFC consumption in the manufacturing of MDIs in Argentina through the conversion of production lines to isobutane and hydrofluoroalkane (HFA) technology. A number of policy and cost issues had been discussed during the project review process, including the eligibility for and sources of funding for the conversion of production lines, and essential use nominations for pharma-grade CFCs post-2010. The overall cost of the project was estimated at US $2.8 million, including a transition strategy.

183. The Government of Argentina, the Secretariat and the company concerned were commended for introducing an innovative technology that also had climate change benefits. One member urged that the desk study being carried out by UNEP take note of the technology so that it might be brought to wider attention.

184. The Executive Committee decided to approve the project for the phase-out of CFC consumption in the manufacturing of metered-dose inhalers in Argentina, at the amount of US$2,806,874 plus agency support costs of US $210,516 to the World Bank, on the understanding that:

(a) Laboratorio Pablo Cassará will cease consumption of CFCs for non-essential uses and convert to a non-ODS technology at its own cost if the selection of the isobutane technology proposed by the enterprise is not approved by the local health authorities; and

(b) The Government of Argentina will have flexibility in using the funding available for eligible activities it deems appropriate to achieve the complete phase-out of CFCs in the MDI sector and in accordance with relevant decisions and guidelines of the Fund.

(Decision 56/44)

China: Sector plan for the phase-out of CFC consumption in the MDI sector (UNIDO)

185. Introducing document UNEP/OzL.Pro/ExCom/56/24, the representative of the Secretariat said that, on behalf of the Government of China, UNIDO had submitted a sector plan for the phase-out of

322.5 ODP tonnes of CFCs used in the manufacturing of MDIs at a total cost to the Fund of US$18.85 million, plus agency support costs. The project had previously been submitted to the 53rd and 55th Meetings. The Secretariat, in reviewing additional information provided by the Government of China following consideration of the issue by the Executive Committee at its 55th Meeting, had concluded that the methodology proposed at that Meeting for determining the incremental cost of the sector plan was still valid. Using that methodology the total level of proposed funding would be US$12.49 million, on the understanding that the Government of China would have flexibility to use the funding available for eligible activities it deemed appropriate to achieve complete phase-out of CFCs in the MDI sector. This proposal had not been accepted by the Government of China. The Executive Committee decided to refer consideration of the matter to a contact group.

186. After having heard the report of the contact group, the Executive Committee decided to approve the sector plan for phase-out of CFC consumption in the MDI sector in China at a total cost of US $13.5 million plus agency support costs of US $1,012,500 for UNIDO, on the understanding that:

(a) The Government of China would have flexibility in using the funding available for eligible activities it deemed appropriate to achieve the complete phase-out of CFCs in the metered-dose inhaler (MDI) sector and in accordance with the relevant decisions and guidelines of the Fund; and

(b) That no more funding would be approved by the Executive Committee for the phase-out of CFCs in China.

(Decision 56/45)

Colombia: Phase-out of CFCs in the manufacturing of MDIs (UNDP)

187. The representative of the Secretariat said that UNDP had submitted a project proposal on behalf of the Government of Colombia for phasing-out use CFCs in the manufacture of MDIs by assisting the sole locally owned enterprise producing CFC-MDIs to convert its production line to HFA technology by 2012. The total cost of the project was less than US $1.1 million before any adjustments required by relevant decisions. In discussions with UNDP, the Secretariat had raised several issues, all of which had been resolved. The total cost of the project had been agreed at US $409,359, after having taken into account a deduction of US $30,500 from the total to eliminate double-counting of funds provided under the national phase-out plan and almost US $490,000 provided as a counterpart contribution by the enterprise.

188. The Executive Committee decided to approve the project to phase-out use of CFCs in the manufacture of MDIs at the amount of US $409,359 plus agency support costs of US $30,702 for UNDP.

(Decision 56/46)

India: National strategy for transition to non-CFC MDIs and plan for phase-out of CFCs in the manufacture of pharmaceutical MDIs (Italy, UNDP, UNEP)

189. The representative of the Secretariat said that UNDP as the lead implementing agency had submitted, on behalf of the Government of India, a national strategy for transition to non-CFC MDIs and a plan to phase-out CFCs in the manufacture of pharmaceutical MDIs. The total estimated cost of the project was US $61.7 million. However, India was requesting US $26.7 million after deducting the foreign ownership component of one enterprise, adjustments due to 4.9 per cent in exports of MDIs to non-Article 5 countries and 57 per cent in counterpart contributions by the enterprises. The Secretariat had proposed an alternative method for determining the incremental cost of the project on the basis of its

PROJECT COVER SHEET – MULTI-YEAR PROJECTS

COUNTRY: **China**

PROJECT TITLE	BILATERAL/IMPLEMENTING AGENCY
Sector Plan for Phase out of CFCs Consumption in China's MDI Sector	UNIDO

NATIONAL CO-ORDINATING AGENCY: State Environmental Protection Administration (SEPA)
State Food and Drug Administration (SFDA)

LATEST REPORTED CONSUMPTION DATA FOR ODS ADDRESSED IN PROJECT

A: ARTICLE-7 DATA (ODP TONNES, 2005, AS OF SEMPTEMBER 2006)

Annex A, Group I	13,549.81	Annex B, Group II	963.936
Annex A, group II	1,176.9	Annex E, MeBr	

B: COUNTRY PROGRAMME SECTORAL DATA (ODP TONNES, 2005, AS OF SEPTEMBER 2006)

ODS	Foam	Refrigeration	Aerosol
CFC-11	6,085.29	606.38	101.96
CFC-12	108.00	4,598.03	374.26

CFC consumption remaining eligible for funding (ODP tonnes)	423.2

CURRENT YEAR BUSINESS PLAN: Total funding: US$ 3,225,000 total phase-out: 101 ODP tonnes.

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PROJECT DATA		2007	2008	2009	2010	Total
CFCs (ODP tonnes)	Montreal Protocol limits	8,672.8	8,672.8	8,672.8	0	n.a.
	Annual consumption limit	7,400	550	550	0	n.a.
	Annual phase-out newly addressed	0	0	280.9	0	280.9
TOTAL ODS CONSUMPTION TO BE PHASED OUT		0	0	280.9	0	280.9
Total ODS consumption to be phased-in (CFCs)		0	0	0	0	0
Project costs (US $):						22,316,189
Support costs (US $))						1,673,714
TOTAL COST TO MULTILATERAL FUND (US $)						**23,989,903**
Project cost effectiveness (US $/kg): 79.45						

FUNDING REQUEST: Approval of the MDI Sector CFCs Phase out Plan for China and its total project funding of **US$ 22,316,189** plus support cost of **US$1,673,714** as indicated above.

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EXECUTIVE SUMMARY

This sector plan will assist China to phase out all CFC consumption of MDI sector in China. The funding request targets the eligible consumption of 280.9 ODP tonnes (236.7 tonnes of CFC11, 40.9 tonnes of CFC12 and 3.3 tonnes of CFC114). The sector plan will be implemented through a series of technical assistance, legislative and investment activities starting in 2008. The sector plan was prepared on the basis of a detailed analysis of MDI manufacturing enterprises in China, and covers all enterprises and production lines. The sector plan proposes a mix of approaches including change to other type of pharmaceutical products, (for example to DPI, if mature MDI substitutes are not available), conversion to non-ODS substitute processes where economically feasible, and closure of production where other approaches are not feasible. The sector plan will include policy actions to ensure that the phase out proceeds on schedule, and that the ineligible enterprises, which are not financed under the project, will stop using ODSs as propellant or dispersant of MDI production.

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Prepared by: **SFDA/SEPA and the UNIDO** **Date: 20 August 2007**

Contents

Chapter I Introduction

1. **Montreal Protocol and achievement of CFCs phase out in China**. In September 1989, China joined the worldwide effort to protect the ozone layer by ratifying the Vienna Convention on the Protection of Ozone Layer. China deepened its commitments by signing the Montreal Protocol and its London Amendment in June 1991 and ratifying its Copenhagen Amendment in April 2003. To implement the phase out of Ozone Depleting Substances (ODS), China has been meeting its obligations to these international agreements by implementing the Country Program for Phase out of Ozone Depleting Substances (CP), which the government approved in January 1993 and updated in November 1999. By 1 July 2007, China successfully completed the Accelerated Phase-out Plan for CFC and Halon Production and Consumption in China, that is two and a half years earlier than the requirements of the Montreal Protocol. Excluding CFCs used in MDI sector, all CFCs consumption has been phased out, thus the phase out of CFCs in the MDI sector represents the main challenge for China to complete the total phase out of CFCs production and consumption.
2. **Institutional arrangements for management of ODS phaseout.** To monitor and manage the CP implementation, China established a National Leading Group (NLG) for Ozone Layer protection. The NLG provides strategic guidance and inter-sectoral coordination for ODS phase-out. The State Environmental Protection Administration (SEPA) leads the NLG, which includes the Ministry of Foreign Affairs, Ministry of Finance, Ministry of Science and Technology, National Development and Reform Commission, Ministry of Public Security, Ministry of Information Industry, State Food and Drug Administration (SFDA) and selected government departments responsible for the industrial sector. For the day-to-day management, China has established an Implementation Office for Compliance with the Montreal Protocol (IOC for MP, the former Project Management Office) hosted by SEPA. There are nine special working groups in the IOC, which consist of staff from SEPA and other ministries, commissions and sector industrial associations.
3. **Policy and Regulation**. China issued and implemented a number of national and sectoral policies for ODS phase out during the past ten years. The key policies include: (1) Air Pollution Prevention and Control Act, which is the basis for the ODS regulatory system in China; (2) Circular on the ban of establishment of new production facilities producing or consuming ODS, (ODS production control); (3) Management Measures on the Import and Export of ODS. (4) The Guiding Catalogue of Industrial Structure Regulation (2005) (issued by the National Development and Reform Commission at the end of 2005, which classifies over 1,000 industries into the categories of encouragement, restriction and elimination. The ODS industries were classified into the latter two categories).

4. **Efforts made for phase-out of CFCs in the MDI sector.** The Chinese Government and the stakeholders of the country's MDI sector have attached great importance to the CFCs phase-out tasks, which are to be undertaken with active yet careful attitude in the MDI manufacturing sector. They carried out preparations for alternative technology identification, exchange of information with experts from home and abroad, and conducted two rounds of preliminary surveys. In March 1995 and December 1998, entrusted by SEPA, the Aerosol Newsletter (a professional magazine of China's aerosol sector), organized two International MDI Technology Workshops in Beijing. Experts from international companies and Chinese MDI enterprises, research institutes and government agencies participated in these workshops. In 1997, SEPA established the MDI Sector Technical Team for CFCs Phase-out, which was composed by experts from research institutes, national testing centres and MDI producers. In December 2003 and during the preparation of this proposed sector plan, SEPA and SFDA established a special technical expert team, which is composed of the Chinese Academia: Chinese Academy of Engineering, Chinese Academy of Medical Sciences, MDI aerosol researchers from universities and research institutes, experts from factories, etc. Since then, the technical expert team carried out a comprehensive study of alternatives as well as other options to phase-out CFCs in MDI sector.
5. **Development of the MDI CFC Phase-out Sector Plan (MDISP).** Funding of US$ 90,000 was approved at the 43rd ExCom meeting in July 2004 to prepare the Sector Plan for Phase-out of CFCs Consumption in China MDI Sector. As the leading agency for the implementation of Montreal Protocol, SEPA in cooperation with SFDA selected National Institute for the Control of Pharmaceutical and Biological Products (NICPBP) to prepare this sector plan. The development of MDISP started in early 2005 under the auspices of SEPA and SFDA. The first draft of MDISP was completed in April 2007 endorsed at a national workshop in August 2007.
6. **Main contents of the sector plan and the impact of the project on the country's Montreal protocol obligations.** This sector plan address the MDI sector in terms of: (1) data survey and analysis, (2) current regulations and policies governing the sector, (3) technical options, (4) strategy of phase out and policy framework, (5) incremental costs analysis, (6) operating mechanism, and (7) action plan. Upon approval of this Sector Plan with the requested funding of US$ 22,316,189 (without agency support cost) the Chinese Government will ensure the phase out of all the remaining eligible unfunded CFC consumption in the MDI sector amounting to 280.9 ODP tonnes /year, including the phase out of all CFC consumption at 38 enterprises, producing 25 types of MDIs (104 product licenses).

Chapter II Sector Baseline

A Development of MDI in China

7. The first pharmaceutical aerosols were from sulfamido compound aerosols developed in 1942, while the first metered dose inhaler (MDIs) aerosol was born in Riker Laboratories and came to the market in 1956. The medical aerosol industry in China started fairly late. In 1964, an anti-asthmatic aerosol, the first Chinese medicinal aerosol product, had been developed and produced jointly by Shanghai Institute of Pharmaceutical Industry, Shanghai Sine Pharmaceutics Factory, Wuxi First Pharmaceutics Factory and Chongqing Seventh Pharmaceutics Factory. However, during the first 20 years after the initiating stage of the production, i.e. until the 1980s, the development of medicinal aerosol in China was comparatively slow due to the scarcity of can, valve and satisfactory metering device. Great progress was made along with the solutions of all these technical problems after 1980s. Up to 2006, 104 MDI production licences were approved in China. These are used by 38 producers manufacturing 25 types of CFC MDIs, based on 22 chemical active ingredients and 3 MDIs based on Chinese traditional medicines.

Table 1 Basic information on production licences and producers

	Product licenses	Types of products	Producers	Remarks
All registration licences issued for CFC-based MDI products	104	25	38	Including those with registration licences but no production
Currently produced CFC-based MDI products	40	17	17	

8. MDI has irreplaceable advantages in curing asthma and COPD: easy to carry, low dose, fast relieve and control the symptoms like dyspnoea of the patients.

B Asthma and COPD in China

9. According to the Global Initiative for Asthma (GINA) asthma is a chronic inflammatory disorder of the airways. Chronically inflamed airways are hyperresponsive; they become obstructed and airflow is limited (by bronchoconstriction, mucus plugs, and increased

inflammation) when airways are exposed to various risk factors.

10. The common risk factors for asthma symptoms include exposure to allergens (such as those from house dust, mites, animals with fur, cockroaches and pollens.), occupational irritants, tobacco smoke, respiratory (viral) infections, exercise, strong emotional expressions, chemical irritants, and drugs (such as aspirin and beta blockers).
11. A stepwise approach to pharmacologic treatment to achieve and maintain control of asthma should take into account the safety of treatment, potential for adverse effects, and the cost of treatment required to achieve control.
12. Asthma causes recurring episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. Unfortunately asthma is one of the most common chronic diseases worldwide. The prevalence of asthma symptoms in children varies from 1 to more than 30 percent in different populations and is increasing in most countries, especially among young children. Fortunately asthma can be effectively treated and most patients can achieve good control of their disease through treatment and medication.
13. Development of anti-asthma drugs is targeting the inflammatory factors as leukotriene, the platelet-activating factor - thromboxane A2, cytokines, phospholipase A2-inhibitor, tachykinin, in view of the complicated mechanism of the occurance. Anti-inflammation has become the front line treatment, mainly including carbohydrate corticosteroid and antagonists against inflammatory mediators. Although the side effects of inhaled treatment are dramatically decreased compared with the systematic treatment with carbohydrate corticosteroid, the safety of the long term treatment is still widely disputed, especially when it has been found that the incidence and mortality still can not be lowered by long term treatment of inhaled carbohydrate corticosteroid. Thus the research about antagonists against inflammatory mediators is more and more becoming the hotspot of asthma treatment.
14. The incidence of asthma in China is rising during the past few years: in 2000 the number of annual incidence of asthma among the Chinese residents amounted to 15.6 million, or 1.2%, which shows an increase of 75% (with a rate of 4% per year), compared with the data in 1980. The incidence of asthma is highest in the population of children under 14 years of age. Based on a medical report, the incidence is ranging between 0.5 and 3.6%. the second highest incidence is 2.6% among people more than 60 years old. The incidence is higher in the regions of coastal and south China, with a highest 3.03% in Fujian province and 2.53% in Guangzhou. North and inland region of China is lower, with 0.5% in Shandong province and 0.11% in the Tibet autonomous region.

C Treatment of Asthma and COPD in China

15. Based on old habits of treatment, some doctors and patients still many times choose less effective oral medicine or injections instead of MDI to relieve or cure asthma. Some

patients also take Chinese traditional medicine. Based on an incomplete investigation, only about 10% of the patients are using MDI, but the numbers are growing fast along with the rapid development of the country.

16. The of asthma treatment was classified by the Coordination Group of Asthma Treatment under the Chinese Medical Association on Respiratory Diseases and the classification was published in *"The Directory of prevention and control of Bronchial Asthma"*. Seven kinds of treatment were recommended in the directory, which could be classified into 3 kinds of drug delivery manners:

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Table 2 The Recommended Treatment Methods for Preventing and Control of Bronchial Asthma

Drug type	Drug Delivery	Drug Name	Remarks
Glucocorticoids	Inhalation	BeclometasoneDipropionate	
		Budesonide	
		FluticasonePropionate	
	Oral	Prednisone	
		Prednisolone	
		Methyl Prednisone	
	Intravenous injection	Succinic Hydrocortisone	
		Methyl Prednisolone	
		Dexamethasone	
β -adrenergic receptor agonists (not suitable for severe cases)	Inhalation	Ssalbutamol	
		Terbutalin	
		Fenoterol	
		Formoterol	Long-acting
		Salmeterol	Long-acting
	Oral	Salbutamol	
		Terbutalin	
		Procaterol	
		Bambuterol	
	Injection		High incidence of systematic adverse reactions
Theophyllines	Oral	Aminophylline	
		Controlled (Sustained)Released Theophylline	
	Intravenous	Aminophylline	
		Doxofylline	
		Bis 2-Hydroxylpropylene Theophylline	
Anticholinergic	Inhalation	Ipratropium Bromide	

Drug type	Drug Delivery	Drug Name	Remarks
		Atropine oxybromide	
		Tiotropium bromide	
Leukotriene regulators	Oral	Zafirlukast	
		Montelukast	
		Ibudilast	
Noncortical hormone (slight asthma)	Inhalation	Sodium Cromoglycate	
		Nedocromil sodium	
Antihistamine	Oral	Ketotifen fumarate	
		Loratadine	
		Astemizole	
		Azelastine	
Antiallergic drugs	Oral	Tranilast	
		Repirinast	
Chinese traditional medicine	Oral Inhalation	Guilong Kechuanming Aerosol,, Hajie Dingchuan Aerosol, Huashanshen Aerosol, Zhichuanling Aerosol	

17. China Asthma Alliance (CAA) was set up in June 2005. It is led by the Coordination Group of Asthma Treatment under Chinese Medical Association on Respiratory Diseases. CAA aims to disseminate the standard treatments of asthma, and improve the control and research level of asthma in China, by ways of strengthening the cooperation with other asthma control organizations throughout the country.
18. For the time being, 26 provinces (including municipalities directly under the central government) have their own asthma alliances. The activities to propagate the standard treatment and to develop the doctor training programme with the help of asthma control organizations should follow the directives of GINA and "*The Directory of Prevention and Control of Bronchial Asthma in China*". Accordingly, MDI should be recommended by the doctors as the first choice to treat asthma.
19. Based on the statistics derived from the report of "*Market investigation of anti-asthma drugs*", published recently by the south China Institute of Medical Economic Research, which is an affiliated organization of SFDA, more than 70% percents of the asthma drug was sold in hospitals. The market has been increasing steadily from 2004 to 2006.

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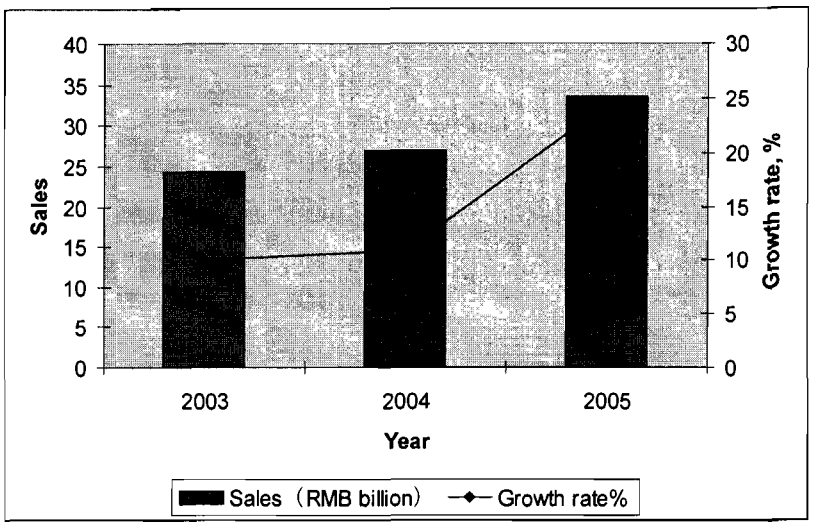

Fig. 1: The Sales of MDI Products in China

20. It is expected that MDI will be used more and more to treat the asthma.

D Production process of MDIs

21. As other medicines, MDIs should be registered at SFDA prior the start of their production. The detailed registration process is described in Section A, chapter III.
22. The MDI production process is simply described on the following figure.

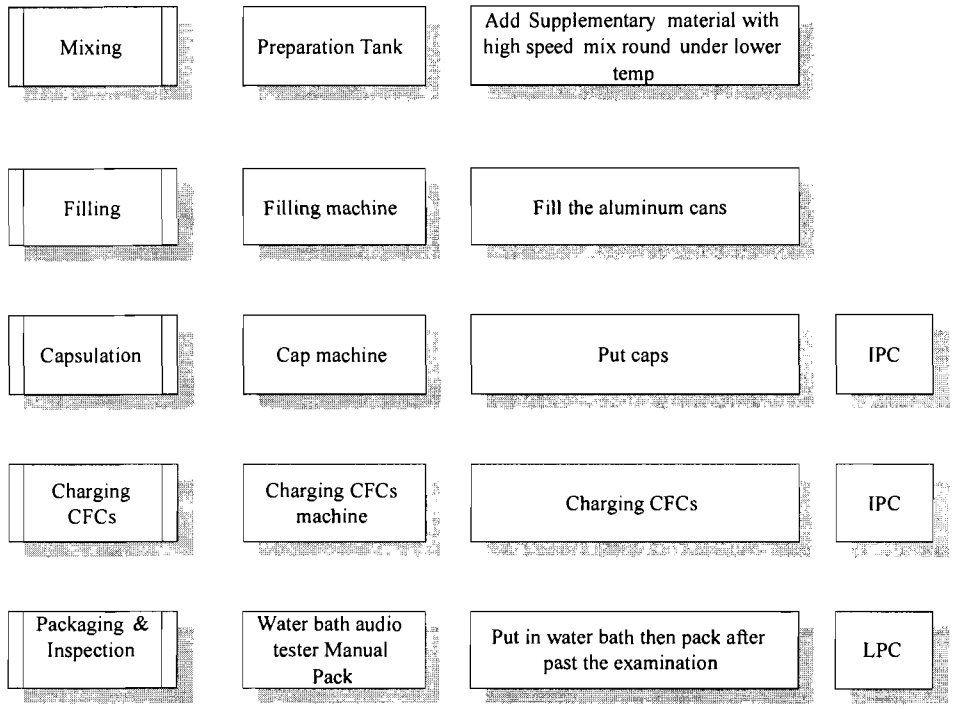

Fig. 2 The production process for Salbutamol Aerosol (suspension)

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E Date Survey

23. NICPBP was entrusted by SFDA, SEPA and UNIDO to carry out MDI sector investigation and prepare the sector plan to phaseout CFCs in the MDI sector of China.
24. The date survey process is shown in following figure 3.
25. The data survey was planned to be conducted by the following ways:

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A. Search all the MDIs manufacturers in the drug registration system;

B. Send a comprehensive questionnaire to related enterprises for completion;

C. Visit enterprises to verify the CFC consumption;

D. Verify all data again during consultation on the draft sector plan.

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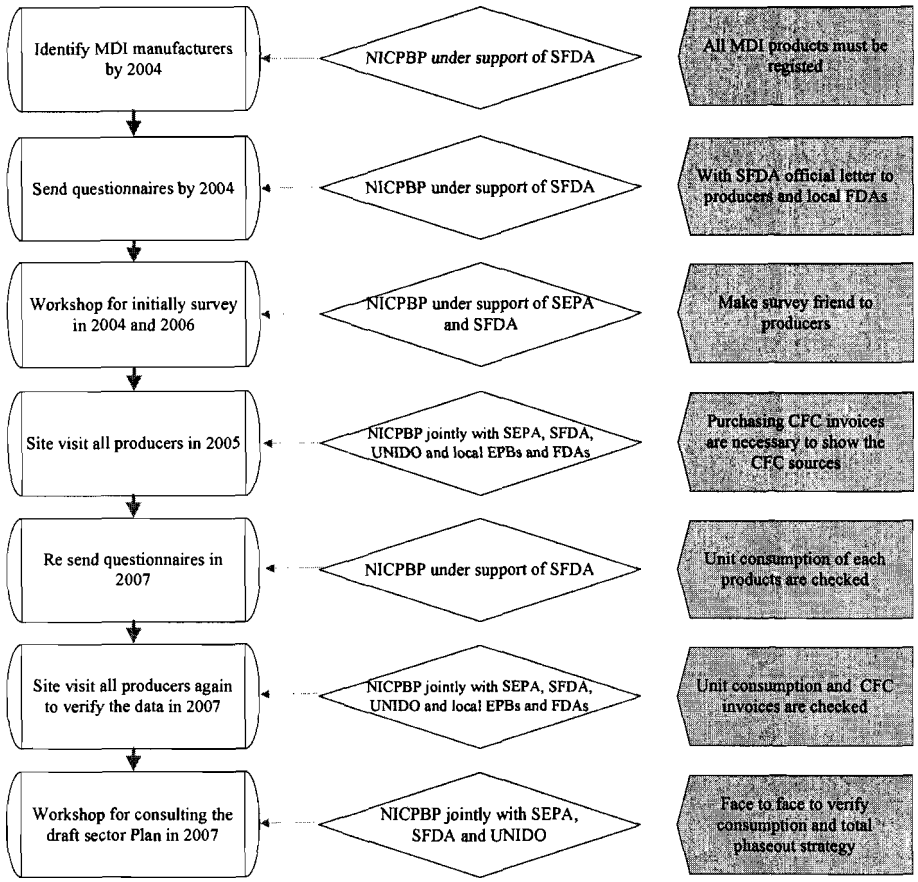

Fig. 3 Data survey process

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26. The actual chronology of events was as follows:

a. SFDA and NICPBP identified all MDI producers;

b. SFDA, SEPA and NICPBP prepared a questionnaire to collect the consumption, production and technical data under supported of UNIDO;

c. The questionnaire was distributed to all the MDI producers in China;

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d. Up to the November 2004, SFDA received feedback from 57 companies;

e. In August 2004, SEPA, NICPBP and SFDA carried out field investigations at three pharmaceutical aerosol producers, namely: S&P Pharmaceutical Co., Ltd., Xinjiang

Biochemistry Pharmaceutical Co., Ltd., and Xinjiang Pharmaceutical Factory.

f. In September 2005, SFDA and NICPBP visited 38 producers to collect and verify the required information.

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g. In March, 2006, SFDA requested local Food and Drug Bureaus through-out the country to confirm the status of MDI enterprises and their products.

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h. In April 2006, SFDA organized a meeting to initially discuss the plan of CFCs phase-out; this was attended by all MDIs enterprises. During the meeting, all the enterprises confirmed their data once again.

i. In May-June 2006 UNIDO reviewed the outcomes of the first surveys and plan with SEPA, SFDA and NICPBP in Beijing and visited several major producers in Hangzhou, Shanghai and Wuxi to verify the data.

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j. In May 2007, SEPA, NICPBP re-visited three enterprises which showed the biggest consumptions of CFCs in the years 2003 to 2005.

k. In June 2007, SEPA, NICPBP, and SFDA re-visited all the above mentioned 21 enterprises to collect MDI production and CFCs consumption data for the year 2006 and verify the data of previous years.

l. UNIDO has organized several meeting through the recent years to harmonise the data collection exercise, discuss the status of the preparation of the Sector Plan and advise on various issues of concern.

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F Enterprise information, CFC Consumption in the MDI Sector

27. Currently there are totally 25 types of MDIs (including three Chinese traditional medicine) produced in China by 38 companies (including 5 with foreign ownership). In the period 2003-2006 23 companies produced 17 types of MDIs using CFCs. Due to market reasons 8 types of MDIs were not produced during 2003-2006. The companies and their CFC consumptions are listed as follows:

Table 3 Products and CFC Consumption by enterprises

Company Code	Company Name	Product Code	Product Name (active ingredient)	CFC Consumption (g/can)	CFC Consumption (kg), 2004	CFC Consumption (kg), 2005	CFC Consumption (kg), 2006
01	AstraZeneca Pharmaceutical Co., Ltd.	B13	Terbutaline Sulfate Aerosol	17.5	4,240.0	4,559.0	5,536.0
01	AstraZeneca Pharmaceutical Co., Ltd.	B04	Budesonide Aerosol	9.9	3,262.0	3,494.0	4,538.0
01	AstraZeneca Pharmaceutical Co., Ltd.	B13	Terbutaline Sulfate Aerosol	9.9	4,010.0	2,901.0	3,129.0
02	Beijing Haiderun Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol	11.0	0.0	0.0	6,424.0
02	Beijing Haiderun Pharmaceutical Co., Ltd.	B22	Isoprenaline Hydrochloride Aerosol	11.0	0.0	0.0	2,915.0
02	Beijing Haiderun Pharmaceutical Co., Ltd.	B23	Iprartropium Bromide Aerosol	11.3	0.0	0.0	27.0
03	Beijing Shengdelaibao Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol	21.9	504.6	745.9	
03	Beijing Shengdelaibao Pharmaceutical Co., Ltd.	B01	Beclometasone Dipropionate Aerosol	22.0	270.5	180.3	
05	GlaxoSmithKline (Tianjin) Co., Ltd.	B01	Beclometasone Dipropionate Aerosol	27.3	12,203.1	0.0	
05	GlaxoSmithKline (Tianjin) Co., Ltd.	B01	Beclometasone Dipropionate Aerosol	20.4	2,733.6	0.0	
06	GlaxoSmithKline (Chongqing) Co., Ltd. *	B15	Salbutamol Aerosol	25.5			
06	GlaxoSmithKline (Chongqing) Co., Ltd.*	B01	Beclometasone Dipropionate Aerosol	27.3			

Company Code	Company Name	Product Code	Product Name (active ingredient)	CFC Consumption (g/can)	CFC Consumption (kg), 2004	CFC Consumption (kg), 2005	CFC Consumption (kg), 2006
06	GlaxoSmithKline (Chongqing) Co., Ltd.*	B26	Beclomethasone Dipropionate Aerosol	13.1			
06	GlaxoSmithKline (Chongqing) Co., Ltd.*	B01	Beclometasone Dipropionate Aerosol	19.8			
08	Guangzhou Dongkang Pharmaceutical Co., Ltd.	B22	Isoprenaline Hydrochloride Aerosol	12.5	2,370.0	2,010.0	1,341.0
08	Guangzhou Dongkang Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol	12.5	250.0	400.0	219.0
09	Guiyang Dechangxiang Pharmaceutical Co., Ltd.	B24	Zhichuanling Aerosol	12.0	393.6	30.0	130.8
11	Harbin Hengcang Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol	22.5	172.1	179.5	0.0
14	Henan Xinxin Pharmaceutical (Group) Co., Ltd.	B11	Huashanshen Aerosol	9.8	0.0	0.0	300.0
15	Henan Zhongfu Pharmaceutical Co.,Ltd.	B15	Salbutamol Aerosol	14.7	670.3	1,380.3	2,205.0
16	Heilongjiang Tanglong Pharmaceutical Co.,Ltd.	B15	Salbutamol Aerosol	13.9	27.8	0.0	
18	Jinan Weimin Pharmaceutical Co.,Ltd.	B15	Salbutamol Aerosol	13.2	22,560.1	29,676.2	33,652.0
18	Jinan Weimin Pharmaceutical Co.,Ltd.	B22	Isoprenaline Hydrochloride Aerosol	13.2	24,492.6	26,574.2	30,134.0
19	Penglai Nuokang Pharmaceutical Co.,Ltd.	B15	Salbutamol Aerosol (solution)	11.3	12,219.0	12,395.0	16,025.0
19	Penglai Nuokang Pharmaceutical Co.,Ltd.	B22	Isoprenaline Hydrochloride Aerosol	11.3	12,028.0	10,618.0	12,769.0

Company Code	Company Name	Product Code	Product Name (active ingredient)	CFC Consumption (g/can)	CFC Consumption (kg), 2004	CFC Consumption (kg), 2005	CFC Consumption (kg), 2006
19	Penglai Nuokang Pharmaceutical Co.,Ltd.	B16	Salbutamol Aerosol (suspension)	20.9	7.5	7.4	41.7
19	Penglai Nuokang Pharmaceutical Co.,Ltd.	B14	Sodium Cyomoglicate Aerosol	25.3	0.0	0.0	50.5
19	Penglai Nuokang Pharmaceutical Co.,Ltd.	B07	Compound Isoprenaline Hydrochloride Aerosol (suspension)	20.9	0.0	0.0	41.7
21	Jewim Pharmaceutical (Shandong)Co., Ltd.	B16	Salbutamol Aerosol (suspension)	17.2	37,405.7	79,163.9	70,000.0
21	Jewim Pharmaceutical (Shandong)Co., Ltd.	B01	Beclomethasone Dipropionate Aerosol	23.2	7,288.5	16,526.3	22,950.0
21	Jewim Pharmaceutical (Shandong)Co., Ltd.	B15	Salbutamol Aerosol (solution)	16.2	2,947.4	9,801.2	20,250.0
21	Jewim Pharmaceutical (Shandong) Co., Ltd.	B14	Sodium Cyomoglicate Aerosol	16.9	2,109.9	6,902.0	7,378.0
24	Shandong Lunan Beite Pharmaceutical Co., Ltd.	B04	Budesonide Aerosol	49.4	3,459.0	2,344.5	3,210.0
24	Shandong Lunan Beite Pharmaceutical Co., Ltd.	B25	Salbutamol Aerosol Compound Salbutamol Sulfate Aerosol	22.4			100.0
24	Shandong Lunan Beite Pharmaceutical Co., Ltd.	B17	Salmeterol Xinafoate Aerosol	3.3			10.0
25	Pharmaceutical Factory of Shanxi Medical University	B16	Salbutamol Aerosol (suspension)	19.5	1,003.0	858.0	689.0

Company Code	Company Name	Product Code	Product Name (active ingredient)	CFC Consumption (g/can)	CFC Consumption (kg), 2004	CFC Consumption (kg), 2005	CFC Consumption (kg), 2006
25	Pharmaceutical Factory of Shanxi Medical University	B01	Beclomethasone Dipropionate Aerosol (suspension)	19.5	62.0	90.0	19.0
28	Shanghai Pharmaceutical (Group) Co., Ltd Prescription Drug Business Unit	B15	Salbutamol Aerosol (solution)	15.6	2,617.1	7,222.2	7,035.0
28	Shanghai Pharmaceutical (Group) Co., Ltd Prescription Drug Business Unit	B16	Compound Salbutamol Aerosol (suspension)	19.5	4,767.8	6,233.8	7,289.0
28	Shanghai Pharmaceutical (Group) Co., Ltd Prescription Drug Business Unit	B12	Ribavirin Aerosol	15.0	0.0	1,851.0	3,193.0
28	Shanghai Pharmaceutical (Group) Co., Ltd Prescription Drug Business Unit	B09	Ketotifun Fumarate Aerosol	20.1	0.0	0.0	1,271.0
28	Shanghai Pharmaceutical (Group) Co., Ltd Prescription Drug Business Unit	B04	Budesonide Aerosol	20.9	198.0	435.0	289.0
28	Shanghai Pharmaceutical (Group) Co., Ltd Prescription Drug Business Unit	B22	Isoprenaline Hydrochloride	15.6	165.0	200.0	165.0
28	Shanghai Pharmaceutical (Group) Co., Ltd Prescription Drug Business Unit	B01	Beclometasone Dipropionate Aerosol	23.3	0.0	0.0	79.0

Company Code	Company Name	Product Code	Product Name (active ingredient)	CFC Consumption (g/can)	CFC Consumption (kg), 2004	CFC Consumption (kg), 2005	CFC Consumption (kg), 2006
28	Shanghai Pharmaceutical (Group) Co., Ltd Prescription Drug Business Unit	B14	Sodium Cyomoglicate Aerosol	21.9	0.0	0.0	113.0
28	Shanghai Pharmaceutical (Group) Co., Ltd Prescription Drug Business Unit	B17	Salmeterol Xinafoate Aerosol	15.0	33.6	0.0	0.0
29	Tianjin Century Pharmaceutical Co.,Ltd.	B22	Isoprenaline Hydrochloride Aerosol		0.0	0.0	0.0
29	Tianjin Century Pharmaceutical Co.,Ltd.	B15	Salbutamol Aerosol	9.8	0.0	0.0	0.0
31	Weifang Zhongshi Pharmacy Co.,Ltd.	B15	Salbutamol Aerosol (solution)	11.6	3,150.0	1,350.0	900.0
31	Weifang Zhongshi Pharmacy Co.,Ltd.	B16	Salbutamol Aerosol (suspension)	15.0	0.0	0.0	0.0
32	No.1 Pharmaceutical Co., Ltd. of Wuxi Shanhe Group	B15	Salbutamol Aerosol	11.5	7,570.0	6,755.0	4,840.0
32	No.1 Pharmaceutical Co., Ltd. of Wuxi Shanhe Group	B22	Isoprenaline Hydrochloride Aerosol	11.5	1,470.0	1,245.0	0.0
36	Chongqing Kerui pharmacy Co.,Ltd.	B16	Salbutamol Aerosol (suspension)	16.8	5,550.0	7,530.0	7,376.5
37	Zigong Chengguang Pharmaceutical Co.,Ltd.	B05	Dimethicone Aerosol	25.2	307.1	22.2	70.0
38	Jiangsu Tianji Pharmaceutical Co.,Ltd.	B12	Ribavirin Spray	9.0			4,202.0

批注 [G1]: Please insert the name of MDI

Table 4 CFC Consumption of MDI Sector in China 2004 - 2006 (unit: tons ODP)

Year	2004	2005	2006
CFC-11	152.6	200.9	236.7
CFC-12	27.1	40.1	40.9
CFC-114	2.9	2.7	3.3
CFCs	182.5	243.7	280.9
Of which consuming by 5 foreign companies	30.4	13.2	14.1
Of which consumption by 18 domestic companies*	152.1	230.5	266.8

* There are 15 domestic companies which have registered MDI products but have no production during 2003-2006.

** The ODP terms of CFC-11, CFC-12 and CFC-114 are same as the metric tonnes.

Table 5 Production of CFCs MDI in China 2004 - 2006

Year	2004	2005	2006
Output (Cans)	12,027,255	15,871,614	18,857,763

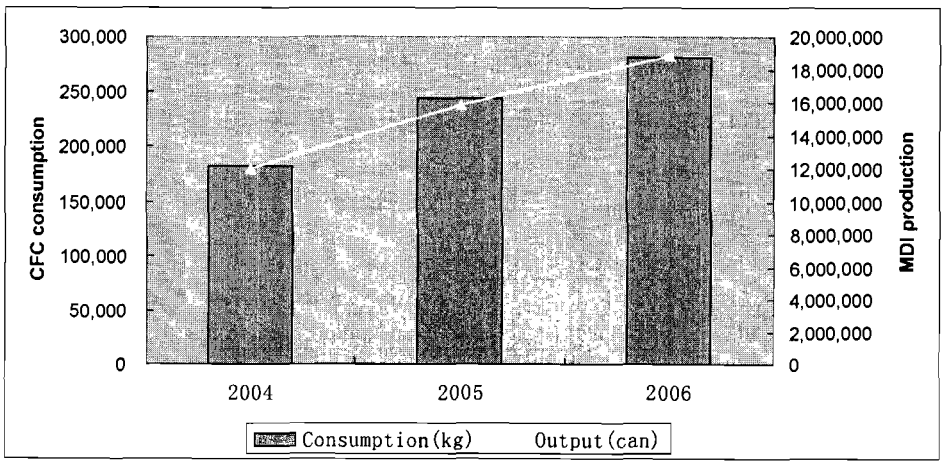

Fig. 4 CFC Consumption and MDI production during 2004 - 2006

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Table 6 General Information of the MDI Manufacturing Enterprises

Company Code	Company Name	Year of Establishment	Chinese share of ownership	No. of Production Lines	Number of Licenses	Type	CFC Consumption 2006 (kg)	2006 Output (ampul)
1	AstraZeneca Pharmaceutical Co., Ltd.	1992	0%	1	4	B04, B13	13,203	1,084,726
2	Beijing Haiderun Pharmaceutical Co., Ltd.	1978	100%	1	3	B15, B22, B23	9,366	851,400
3	Beijing Shengdelaibao Pharmaceutical Co., Ltd.	1991	0%	1	7	B01,B12,B14, B15	0	0
4	Beijing Double-Crane Modern Medicinal Technology Co., Ltd.	1991	100%	0	3	B19, B23, B23	0	0
5	GlaxoSmithKline (Tianjin) Co., Ltd.	1991	0%	1	2	B01	0	0
7	Guangzhou Baiyunshan Hejigong Pharmaceutical Co., Ltd.*	1994	100%	0	4	B01, B15,B20, B22	0	0
8	Guangzhou Dongkang Pharmaceutical Co., Ltd.	1988	100%	1	3	B01,B15, B22	1560	124,800
9	Guiyang Dechangxiang Pharmaceutical Co., Ltd.	1979	100%	1	1	B24	131	10898
10	Harbin Guangji Pharmaceutical Factory*	n.a.	100%	0	2	B15, B16	0	0
11	Harbin Hengcang Pharmaceutical Co., Ltd.	1993	100%	1	2	B14,B15	0	0
12	Harbin Huili Pharmaceutical Co., Ltd.	1998	100%	0	1	B17	0	0
13	Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd.*	1994	100%	0	1	B01	0	0
14	Henan Xinxin Pharmaceutical (Group) Co., Ltd.	1982	100%	1	1	B11	300	30000
15	Henan Zhongfu Pharmaceutical Co., Ltd.	1992	100%	1	1	B15	2,205	150,000 -
16	Heilongjiang Tianlong	1997	100%	2	3	B14,B15	0	0

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Company Code	Company Name	Year of Establishment	Chinese share of ownership	No. of Production Lines	Number of Licenses	Type	CFC Consumption 2006 (kg)	2006 Output (ampul)
	Pharmaceutical Co., Ltd.							
17	Jilin Xiuzheng Pharmaceutical (Group) Co., Ltd.*	n.a	100%		1	B01	0	0
18	Jinan Weiming Pharmaceutical Co., Ltd.	1979	100%	2	3	B15, B22	63,786	4,832,300
19	Penglai Nuokang Pharmaceutical Co.,Ltd.	1993	100%	2	5	B07, B14, B15, B16, B22	28,928	2,552,299
20	Qiqihar Pharmaceutical Factory*	n.a	100%		1	B15	0	0
21	Jewim Pharmaceutical (Shandong) Co., Ltd.	1993	100%	1	6	B01, B14, B15, B16	120,578	6,704,000
22	Shandong Linuo Kefeng Pharmaceutical Co., Ltd.	1991	100%		3	B15, B18, B22	0	0
23	Shandong Lukang Cisen Pharmaceutical Co., Ltd.	1992	100%		2	B01, B22	0	0
24	Shandong Lunan Beite Pharmaceutical Co., Ltd.	2001	100%	1	3	B04,B17,B25	3,320	114,560
25	Pharmaceutical Factory of Shanxi Medical University	1994	100%	1	3	B01, B16,B18	708	35,554
26	Shanghai Boehringer-Ingelheim Pharmaceutical Co., Ltd.	1990	100%	0	3	B08, B23	0	0
27	Shanghai Fuxing Zhaohui Pharmaceutical Co., Ltd.	1988	100%		3	B02, B15, B16	0	0
28	Shanghai Pharmaceutical (Group) Co., Ltd Sine Pharma Laboratory	1982	100%	1	14	B01, B04, B07,B09,B10,B12 B14, B15, B16, B17 ,B21,B22	19,434	1,132,455
29	Tianjin Century Pharmaceutical Co., Ltd.	1981	100%	1	2	B15, B22	0	0
30	Tonghua Baishan Pharmaceutical Co., Ltd.	2001	100%		1	B06	0	0
31	Weifang Zhongshi Pharmaceutical Co., Ltd.	1993	0%	1	4	B01,B15, B16	900	3280

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Company Code	Company Name	Year of Establishment	Chinese share of ownership	No. of Production Lines	Number of Licenses	Type	CFC Consumption 2006 (kg)	2006 Output (ampul)
32	No.1 Pharmaceutical Co., Ltd. of Wuxi Shanhe Group	1965	100%	1	2	B15, B22	4,840	313,689
33	Xi'an Lisheng Pharmaceutical Co., Ltd.*	n.a.	100%		1	B15	0.	0
34	Xinjiang Pharmaceutical Factory	1975	100%	1	1	B15	0	0
35	Zhanjiang New Ton Tex Pharmaceutical Co., Ltd.	1987	100%	1	2	B15, B16	0.	0
36	Chongqing Kerui Pharmaceutical Co., Ltd.	1975	100%	1	4	B15,B16,B20,B22	7,377	448,800
37	Zigong Chenguang Pharmaceutical Co., Ltd.	1981	100%	1	1	B05	70	2,020
38	Jiangsu Tianji Pharmaceutical Co., Ltd.	1992	100%	1	1	B12	4,202	466,982
	Total						**280,908**	**18,677,763**

Note:

1. Companies marked with * don't produce anymore.
2. Companies with no MDI lines are using contract fillers to fill their products.

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28. The summary of information on enterprises for the year 2006 is as follows:

Table 7 Summary of information of enterprises for 2006

	Producers	Number of Licences	Number of Licences in production
Number of MDI producers	38	104	40
Of which producing CFC-MDI ownership by domestic	15	51	36
Of which with idling capacities ownership by domestic	18	36	0
Of which producing CFC-MDI with foreign ownership	4	17	4
Of which doesn't exist	1	*	*
Consumption (tons):			
CFC-11	236.7		
CFC-12	40.9		
CFC-114	3.3		
Total consumption	280.9		
Of which consumed by five foreign companies	14.1		
Of which consumed by 15 domestic companies*	266.8		

* One of foreign companies stoped producing in Chongqing and shifted its registered products to its sister company in Tianjin.

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29. The CFC consumption data survey did not show the expected rapid growth of CFC based MDI production and CFC consumption. The reason is that from late 1990's, SEPA began to conduct public awareness raising activities on CFCs phase out. Currently, a large amount of imported DPI and CFC-free MDIs are on the Chinese market.

30. According to the discussion with enterprises during the site visits, MDI manufacturing enterprises in China face many problems and difficulties in the process of CFCs replacement. Up to now, only one product form one enterprise got approval from SFDA for clinical tests. All the other enterprises have no clear ideas on the ways to phase out CFCs.

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Chapter III Regulation and Policy for the MDI Sector and CFC Phaseout

A Regulatory framework for Drug, especially for MDI

31. CFCs are used as an inactive carrier substance (excipient) in the production of MDI. According to the laws, regulations and policies concerning drug management in China, strict procedures must be followed when formulation of the drug including the excipient is changed. The main laws, regulations and policies governing the drug management are as follows:

Drug Administration Law of the People's Republic of China (took effect on 1 December 2001)

32. This law is a national law to be observed strictly by all pharmaceutical products related production enterprises and institutions. The stipulations of the Drug Administration Law of PRC is used as the guiding principle in this Sector Plan of CFCs Phase out in the MDI Sector. This law aims to strengthen drug administration, guarantee drug quality, safeguard the safety of use of drugs in human body, safeguard human health, and protect legal rights to use the drug. As specified in its Clause 2, this law must be observed strictly by any unit or individual functioning in R&D, production, operation, use, and supervisory administration of drugs within Chinese territory. The MDI aerosol is one kind of drugs, and thus its supervisory administration (including the substitution of excipient/propellant and the modification of the form of drug) shall comply with various regulations of *Drug Administration Law of PRC*. Some clauses related to the MDI sector plan include, but not limited to:

a) Control over Manufacturers. Article 9 states that "drug manufacturers shall conduct production according to the Good Manufacturing Practices for Pharmaceutical Products (GMP) formulated by the Drug Administration Department under the State Council on the basis of this Law. The drug regulatory department shall inspect drug manufacturers on their compliance with the GMP requirements and issue a certificate to the manufacturers passing the inspection. The specific measures and schedule for implementing the GMP shall be formulated by the Drug Administration Department under the State Council."

b) Control over Drugs. Article 29 states that the dossier on a new drug research and development, including the manufacturing process, quality specifications, results of pharmacological and toxicological study, and the related data and the samples shall, in accordance with the regulations of the Drug Administration Department under the State Council, be truthfully submitted to the said department for approval, before clinical trial

is conducted. Measures for verifying the qualifications of clinical study institutions for drugs shall be formulated jointly by the drug regulatory department and the administration department for health under the State Council. When a new drug has gone through clinical trials and passed the evaluation, a New Drug Certificate shall be issued upon approval by the Drug Administration Department under the State Council.

c) Control over Production. Article 31 states that "A drug manufacturer may produce the drug only after an approval number (production license) is granted to it."

Regulation on Drug Registration revised recently by SFDA (No. 28, effective as of 1 October 2007)

a) Article 12 states that "a new drug application means a registration application for a drug that has not been marketed in China. A drug that has been marketed in China, for which an application is made for a change in dosage form, or route of administration of medicaments, addition of new indication shall be treated as a new drug application." ..... "Supplementary application means an application for the change, addition, or cancellation of any item or content in the existing registration approval of a new drug, or of a drug already with national standards *(approved for an other company)*, or import drug."

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b) Article 18 stipulates, that regarding a drug or its formulation, manufacturing process and indication etc. the applicant shall submit documents to explain the patent status and ownership rights in China. If patent(s) related to the above is valid in China the applicant shall submit a letter of guarantee to declare that the drug will not infringe the patent rights of others and that the applicant assumes liability for any possible infringement. If any disputes on patent occurs in the process of registration, the related parties shall try to resolve the matter according to relevant laws, regulations.

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c) Article 113 requires that if there is a change a.) in drug registration standards, b.) excipient, or c.) the production process, which may affect product quality a supplementary application should be processed. The application should be submitted to the FDA of the Province, Autonomous Region or Municipality under the Central Government, who shall review the application and submit recommendations to SFDA for approval. Then applicant will be notified subsequently.

d) Article 150 authorises SFDA to administer the technical review during the drug registration process in accordance with the following requirement:

i) Complete approval procedure in 90 days for a drug to apply new clinical study, complete approval procedure in 80 days if a drug meets the requirements under Article 48 of this Regulation;

ii) Complete approval procedure in 150 days for production of new drug, complete approval procedure in 120 days if a drug meets the requirements under Article 48 of this Regulation;

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iii) Complete approval procedure in 160 days for an imitated drug already with national standards, or a change in dosage form.

iv) Complete approval procedure in 40 days for supplemental application if a technical review is needed.

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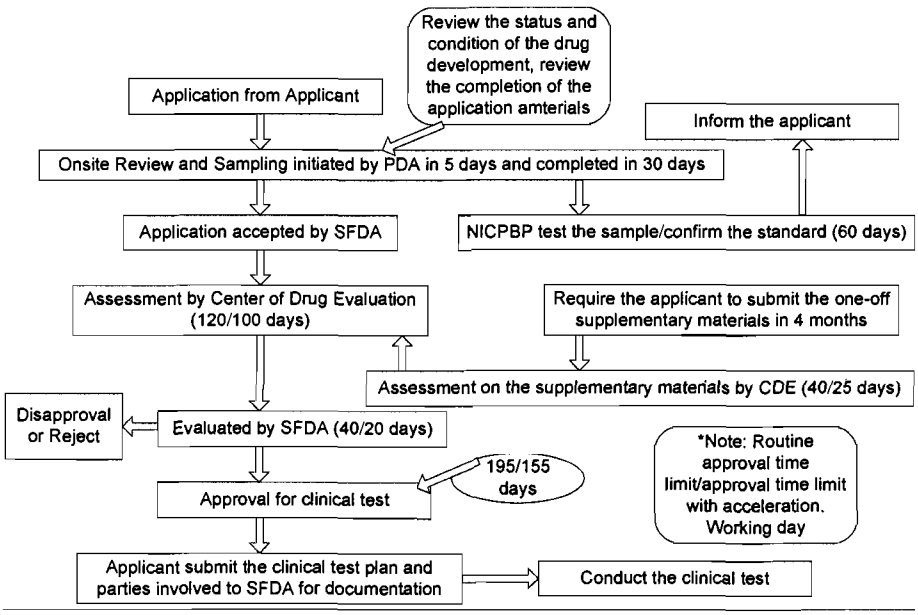

Fig. 5 Approval Procedure for Clinical Test of the New Drug

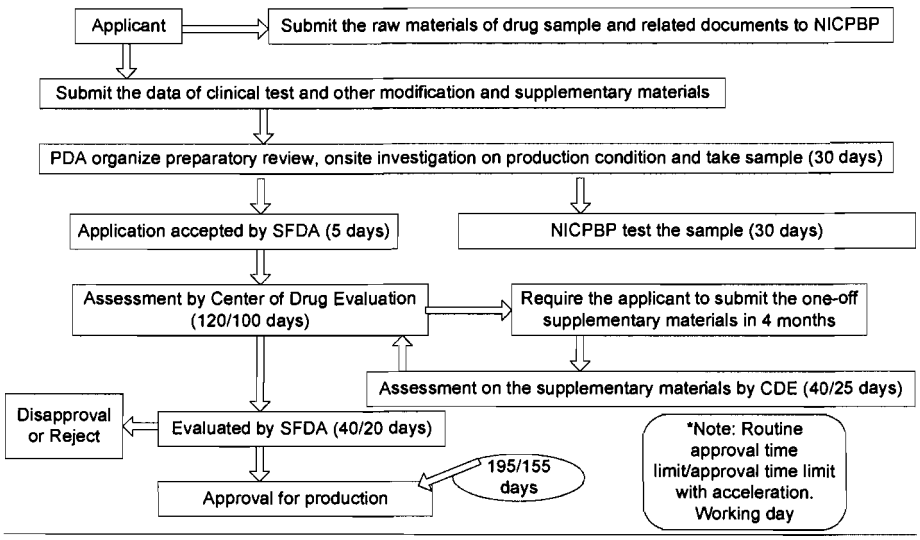

Fig. 6 Approval Procedure for the Production of New Drug

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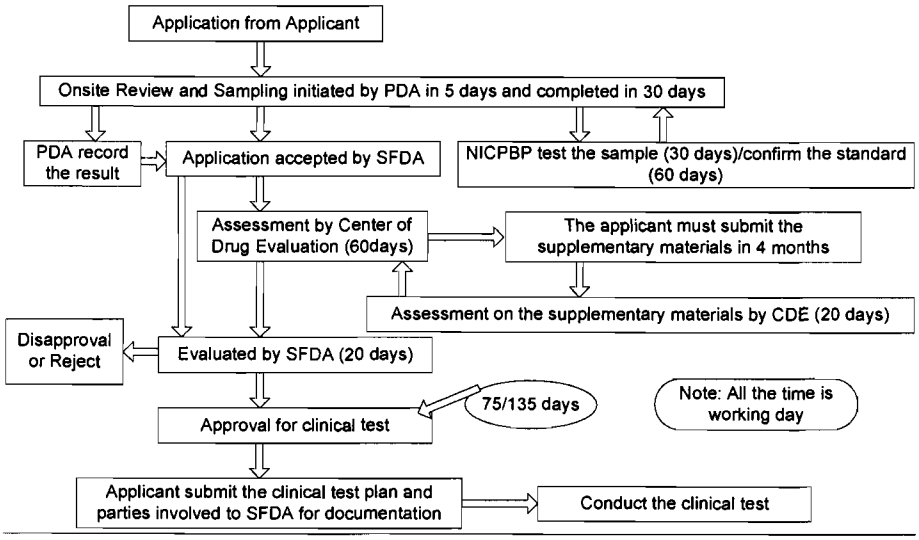

Fig. 7 Approval Procedure for Clinical Test for Change to Existing Drug

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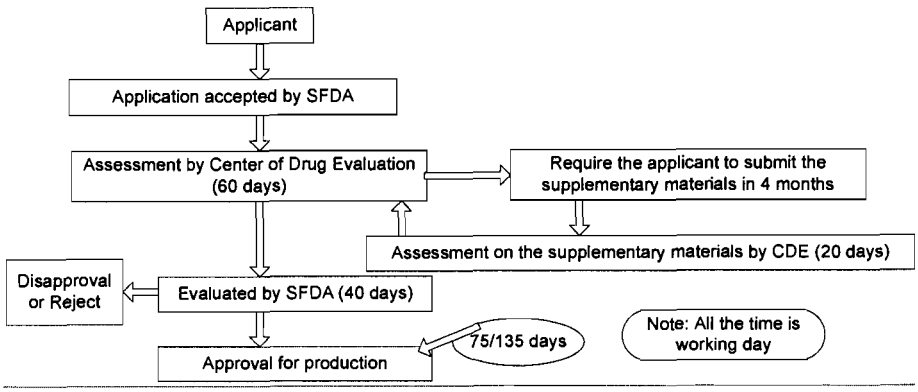

Fig. 8 Approval Procedure for Production for Change to Existing Drug

B Policies Related to CFC Phaseout

33. **Notice on Terminating the Use of Chlorofluorocarbons (CFCs) as Excipient for Medical Aerosols** (Guo Si Yao Jian Zhu No. [2006] 279): This notice issued by SFDA on 22 June 2006, specified the following relevant matters in order to accomplish the commitment of the Chinese Government and guarantee the smooth phase out of CFCs in line with accelerated CFC Phase-out Plan of China:

a) China stopped using CFCs as pharmaceutical excipient in the production of external-use aerosol from 1 July 2007. The external-use aerosols produced with CFC based excipient before this date can be circulated and used until the expiration of their validity date. China will stop using CFCs as pharmaceutical excipient in the production of metered dose inhalant aerosols from 1 January 2010, and the CFC based metered inhalant aerosol produced before 1 January 2010 can be circulated and used until the expiration of their validity date.

b) China stopped importing the CFC based external-use aerosol from 1 July 2007, and the external aerosols imported before this date can be circulated and used until the expiration of their validity date. China will stop importing the CFC based metered inhalant aerosol from 1 January 2010, and the inhalant aerosol imported before this date can be circulated and used until the expiration of their validity date.

c) China stopped examining and approving registration applications for CFC based external-use aerosols (including that for imported ones) from 1 July 2007 and that of CFC based metered inhalant aerosol (including that of imported ones) from 1 January 2010.

d) To eliminate CFCs in line with the Sectoral Phase out Plan, drug producers shall, according to the relevant requirements of the Regulations on Drug Registration, apply for modification of the pharmaceutical excipient or drug form of pharmaceutical aerosols.

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Chapter IV Technical Options

A Potential Ways to Phaseout CFCs in the MDI Sector

34. There are two major issues to be considered when converting CFCs based MDIs to non-ODS alternatives:

1) find the substitute excipient to replace CFCs,

2) adopt other drug delivery system to e.g. compressed air atomizer, ultrasonic atomizer, two-phase system, self-pressurising system or dry powder inhalation.

Table 8 Comparison of Different Types of Asthma Treatment Drugs

Type of inhaler	Advantages	Disadvantages
Metered dose inhalers (MDI)	1. Simple actuation system 2. Reliable accurate dose regardless of the patient's breathing capacity 3. Compact and portable 4. Easy to use 5. Economical 6. Good resistance to moisture	1. Mostly use CFCs as propellants 2. The method of pressing and breathing requires coordination between actuation and breathing (breath-actuated systems do not have this drawback). 3. Dosage accuracy may be dependant on the formulation. 4. Complex manufacturing process.
Dry Power Inhalers (DPI)	1. No propellant used	1. Drug release depends on the patients breathing capacity. 2. The inhaled fraction is reduced if the patient breath is directed into the system. 3. Relatively expensive.
Nebulisers	1. No special breathing coordination required. 2. Works with patients using mechanical ventilation. 3. Useful to administer new or less used drugs.	1. Not portable. 2. Depends on an electric supply. 3. Expensive. 4. Operation takes a long time. 5. Requires the use of preservatives to reduce risk of bacteria contamination.

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35. For the time being, the potential substitutes of CFCs used for MDI are HFA 134a and HFA 227.

B Alternative excipient - Hydrofluoroalkanes (HFA)

36. HFA have similar properties as CFCs, however their chemical stability and polarity are slightly lower than that of CFCs. The table below shows the comparison between HFA and CFCs in terms of the physical and chemical characteristics and their environmental properties.

Table 9 Comparison of Properties between Fluoroalkanes and CFCs

Property	CFC-11	CFC-12	CFC-114	HFA-134a	HFA-227
Chemical formula	$CFCl_3$	CF_2Cl_2	CF_2ClCF_2Cl	CF_3CFH_2	F_3CHFCF_3
Vapour pressure (kPa,21.1℃)	92.4	484	88.9	569(20℃)	3.99
Boiling point (℃)	-24	-30	4	-26.5	-17.3
Density (g / ml)	1.49	1.33	1.47	1.22	1.41
ODP	1	1	1	0	0
GWP	4,000	8,500	9,300	1,300	2,900
Life circle of the atmosphere (year)	75	111	7200	15	33

Table 10 Advantages and Disadvantages of using HFA for MDIs

	Advantages	Disadvantages	Comments
HFA	- Low inhalation toxicity - Higher chemical stability - High purity - No harm to ozone layer	- Bad solvent, low polarity - High GWP - greenhouse effect - Higher cost	- HFA may be used by the MDI aerosol producers in China as a potential substitute to CFCs

C Alternative Technologies

37. In recent years, international MDIs producers did intensive research on the technology of substitution of CFCs and change of drug formulation. The substitute propellants currently used in the world are mainly HFA-134a and HFA-227a. Except for terbutaline, the CFCs

used with all the other active ingredients could be replaced by HFA. The leading companies in the world such as Boehringer, Fisons, 3M, Glaxo and Riker have obtained relevant formulation patents, which cover the propellant system including components, co-solvent, hydrocarbon surfactant and fluoro-surfactant.

38. In contrast with the above, the results of our sector investigation show that Chinese MDI manufacturing enterprises possess only preliminary idea instead of actual action plans on the process of CFCs replacement. It is reported that many issues still have to be resolved for introduction of Hydrofluoroalkane as propellants for MDIs:

- **Co-solvent with Low Boiling Point.** Both tetrafluoroethane (HFA-134a) and heptafluoropropane (HFA-227a) have higher vapour pressure and are in gaseous state under normal atmospheric temperature. No Hydrofluoroalkane is available, which has the same high boiling point as CFC-11 does. Therefore, it brings challenges to design the formulation and production process. One of the solutions is to seek for proper solvents without toxicity or irritation but with certain volatility and good compatibility with Hydrofluoroalkane. Today, the commonly used co-solvents include low-molecular-weight alkane (e.g propane and butane) and low-molecular-weight alcohols (e.g ethanol and isopropanol).

- **Surfactant Selection.** Surfactant is used to disperse medicament particles and lubricate the valve. As Hydrofluoroalkane has lower polarity than CFCs, it can not dissolve majority of surfactants. One solution is to identify surfactants with good solubility and compatibility with medicaments. Another solution is to add a co-solvent which can dissolve the surfactant.

- **Drug Characteristics.** Some medicaments easily form solvates in the new propellant system, thus increasing the tendency of crystal growth. Some poly-crystalline drugs (such as steroid hormone) are easier to have crystalline transformation and promote crystal growth. Thus, drug characteristics should be taken into account in formulation design, particularly in the design for suspended aerosols.

- **Valve Selection.** As Hydrofluoroalkane is chemically less stable than CFCs, valve components (e.g. airproof rubber and its additive) should be compatible with the new propellant. Similarly, valve components should not cause HFA to decompose. At present, several major valve companies such as Bespak, 3M and Valois conduct research on the valve system for Hydrofluoroalkane.

- **Alternative Actuator.** In case a medicament can not be formulated into suspended aerosol, it is generally made into solution aerosol. In general, solution aerosol has poorer atomisation effect. Decreasing vapour pressure of the canister results in bigger atomized particle size. Though increasing the pressure can reduce the particle size, it also causes majority of particulate medicaments to be accumulated at throat due to the

bumping of particles arising from the increase of initial speed. Thus, it is needed to design new actuators, which can both crash the particles and reduce the initial speed.

D Policy and Patent Issues

39. Phaseout of CFC is the commitment made by the government of China. The obstacles include lengthy and costly drug registration, lack of funds and technologies.

    a. Based on "*The Drug Administration Law of the People's Republic of China*", change of excipient leads to the re-registration of the drug. The preparation of the technical dossier required for the re-registration, in which a lot of pharmaceutical and pharmacodynamic studies must be done.

    b. Modification of production and market promotion of new drugs cost large amounts of money. It's a heavy burden for most of the MDI enterprises.

40. The patent issue is also a big obstacle to conduct CFC phaseout in MDI sector.
41. There are two major HFA MDI related patents in China. They cover the

    a. formulation, which use HFA134a, HFA227 and their mixture as propellant for all the applications currently produced in China, and
    b. co-solvent and surfactant as well.

42. The cost for the patent transfer is extremely high. It seems, however even more difficult and costly to develop new technologies. The detailed content of the patents are listed in the table below:

Table 11 MDI related patent in China

Patent Name	CFC-free aerosol to cure the diseases in the respiratory system	**Patent Number**	00133271.6
Publication Number	CN1296814	**Date published**	2001.05.30
Applicants	China Pharmaceutical University		
Inventor	Junshou Zhang, Li Ding, Yizhong You	**International Application**	
Patent Name	New aerosol reagent containing polarized fluoride molecules	**Patent Number**	**01815467.0**
Publication Number	CN1455663	**Date published**	2003.11.12
Applicants	AstraZeneca Co. Ltd.		
Inventor	P. Rogda	**International Application**	PCT/SE01/01606 2001.7.10

E Transitional Arrangement

43. Due to limited time before 1 January 2010 when the use of virgin CFCs have to be stopped in MDI manufacturing, it will be very difficult for quite a few MDI producers to complete the drug re-registration process. Thus, some CFC should be stockpiled to be used 2010 onwards.
44. For some enterprises, which have more than one applications, if the re-registration can not be completed before 1 January 2010 for some drugs, stockpiled CFC is also needed for the production of those applications.
45. Another concern is the high GWP of HFAs, even though, HFA used for MDI propellant is estimated to account for less than 0.02% of global greenhouse gas emission in 2010. The International Pharmaceutical Aerosol Confederation (IPAC) is persuading the parties to the Kyoto Protocol to allow maintaining the continuous use of HFA in MDI sector.

Chapter V Phase-out Strategy and Policy Framework

46. China will meet the phase out schedule of CFCs for protection of the Ozone layer and compliance with Montreal Protocol as indicated below. The phase out of CFCs in the MDI sector should not impose any negative impact on the clinical demand and supply situation for MDI products, i.e. it should enable China to maintain its MDI production at a level to meet the clinical demand by quality and quantity and at acceptable prices.
47. MDI sector plan is the last sector plan for phase out CFCs in China. China will insure that the domestic sale of freshly produced CFCs after 2008 will be limited to the MDI sector only. China will integrate the necessary requirements in the Agreement Between China and The Executive Committee for the CFCs/CTC/Halon Accelerated Phase-Out Plan (ANNEX XII.39 Policies, Procedures, Guidelines, Criteria) to set up future CFCs production plan.

A Objectives

48. The main objectives of this plan are:

1) To ensure that the phase out of CFCs in China's MDI sector meets the requirements stipulated in the Montreal Protocol and in Accelerated CFC Phase out Plan and/or other Agreements;
2) To maintain the phase-out momentum and to avoid risk in compliance with the Montreal Protocol for phase-out of CFCs;
3) To encourage new alternatives in China's MDI sector to improve technology innovation, and to maintain MDI production at the level to meet the clinical demands.

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B Phase-out Schedule

49. CFCs consumption in MDI sector: China will make efforts to phaseout CFCs consumption for MDI sector by end of 2009. The phase-out control targets for CFC consumption in MDI sector are listed in Table 12.

Table 12 The phase out control targets for CFC consumption in MDI sector (tons ODP)

	2006	2007	2008	2009	2010
Maximum Allowable CFCs consumption					
National level	13,500	7,400	550	550	0**
MDI sector	280.9		550	550	0
Max allowable CFCs production *	13,500	7,400	550	550	0

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* Appendix 2-A. The targets, and funding, AGREEMENT BETWEEN CHINA AND THE EXECUTIVE COMMITTEE FOR THE CFCS/CTC/HALON ACCELERATED PHASE-OUT PLAN, ANNEX XII.39 Policies, procedures, guidelines, criteria.

** Except the essential use agreed by the parties.

50. CFCs production during 2008-2010: the CFCs productions for domestic sale are limited for MDI sector and possible essential use only during 2008-2010. Based on the current survey, the maximum consumption for the whole MDI sector will be 300 MT/annul (including CFC-11/CFC-12) during 2007-2009; however, considering ongoing conversion consumption requirement after 2009, the maximum consumption quota issued for the sector will be 550 tons and 550 tons in 2008 and 2009 respectively.

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C Policies and Measures

51. ***Adaptation of ODS licensing system to control CFCs consumption in the MDI sector***. To propose, based on current ODS licensing system, a monitoring and evaluation plan for CFCs consumption control in the MDI sector, including review of enterprise information, issuance of CFCs licenses and quotas for consumption, as well as regular site supervision. The key points of the licensing system include (1) no trade in CFCs is allowed between the licensed enterprises and the non-licensed ones; (2) no change of licenses from one type of CFC to another one is allowed between the enterprises holding licenses for different ODS substances; (3) no purchase of CFCs from other licensed enterprises is allowed exceeding the issued quota; (4) all transactions and trade must be approved by SEPA, and (5) all transaction and trade process must be entered into the information management system.
52. ***Issue CFCs consumption ban for MDI sector***. The National Leading Group of Ozone Layer Protection under the State Council will issue the ban on CFCs consumption to ensure that all the CFC producers and consumers are informed and prepared. The date of issuance of the CFC ban for the MDI sector will follow the date of approval by the ExCom of the MDI sector plan.
53. ***Strengthen supervision and capacity of sector plan implementation***. A monitoring system will be developed for the implementation of the MDI sector plan. It will track the implementation of the sector plan by (1) review of CFCs consumption data and information reported by the enterprises, (2) review of transactions and trade processes of

CFCs, and (3) timely adjustment of CFCs quotas and its license holders. A supervisory and monitoring team will be established.

54. ***Strengthen formulation of technical standards for the CFCs alternatives.*** China will revise the relevant technical standards and codes of CFCs alternatives based on its production and alternative technology development and the progress of CFC phaseout in MDI sector.
55. ***Policies Ranging over the Transition Period (after 2010)***. China will stop using CFCs as excipients for MDI as of 1 January 2010. That means that there are no virgin CFCs produced for the MDI sector. After this date, given the limited timeframe, MDI manufacturers have to use stockpiled CFCs before they can obtain from SFDA the approval numbers for their new products. However, using of stockpiled CFCs would be under stringent supervision of the government. SFDA will make transitional arrangement. When receiving the application form the manufacturers for using CFCs in storage during the transition period, SFDA and SEPA will review and approve the applications.
56. ***Public awareness and education***. China will continue to strengthen the education and training for enterprises, public, and those who are responsible for implementation of ODS policies, especially stakeholders in the MDI sector.
57. ***Supervision after 2010***. After 2010, SFDA and SEPA will monitor non-CFCs aerosol products so as to guarantee its safety and efficacy of clinical application.

Chapter VI Incremental Cost Calculation

58. The incremental costs for the MDI sector have been calculated taking into consideration:

1) MLF guidelines,
2) Activities identified for conversion of CFCs based technologies to no-CFC based ones;
3) Remaining eligible consumption of CFCs in the sector;
4) Enterprise level incremental conversion costs for all the identified eligible enterprises, according to their activities:
5) Identified Technical Assistance activities

A Incremental Cost Identified

Incremental Cost at Enterprise Level

59. The conversion activities at enterprise level include seven items:

1) Research & Development of non-CFC MDIs (including technology screening and formulation development);
2) Registration of the new products;
3) Modification of existing facilities;
4) Training to meet the new production requirements;
5) Validation of new production process ;
6) Incremental operating cost of materials and utilities for production;
7) Promotion of new products on the market.

60. In order to reduce the cost of the project to the Multilateral Fund two kinds of costs of the conversion process, were excluded from the IC requested from MLF and will be paid by the beneficiaries as their counterpart contribution, namely:

1) Cost for Research & Development of non-CFC MDIs (including technology screening and formulation development), and
2) Cost for marketing and promotion of new products.

The relationship between conversion activities at enterprise level and the IC requested from MLF are shown as follows:

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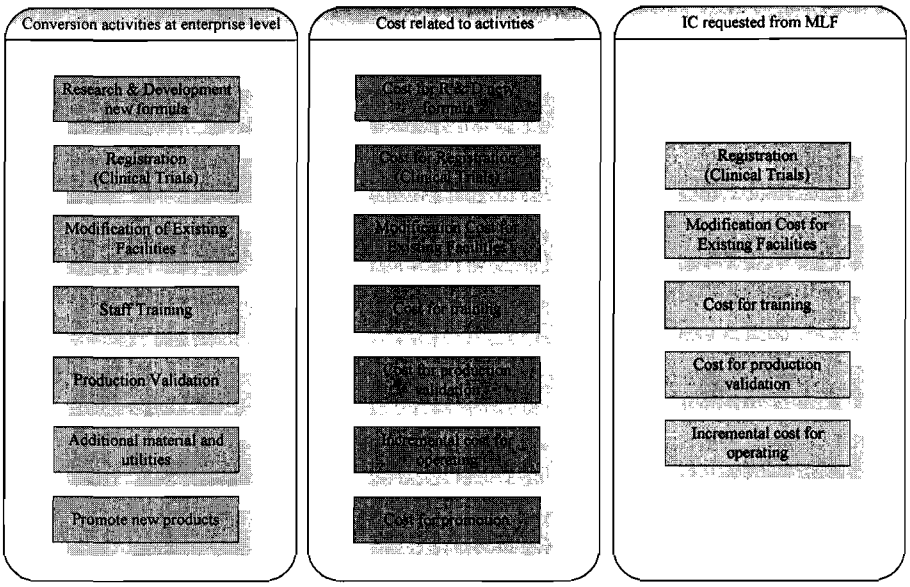

Fig. 9 The relationship between conversion activities at enterprise level to the incremental cost items requested from MLF

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61. ***Cost for research & development of new formulation.*** Since research and development of the new formulations of MDI would be done by the MDI producers themselves, or would be bought from the patentees, the cost for the new formulation could be very different. If the MDI producers buy the technologies from the patentees, royalty fee may be required based on their annual production. Therefore, it is very difficult to estimate the cost for Research & Development of the new formulation of MDIs.
62. ***Cost for marketing and promotion of new products.*** CFC-MDIs are familiar to the patients and have been widely used in China. The non-CFC MDIs have some different properties, thus in addition to the normal advertisement and sales promotion, extra efforts are needed from the MDI producers to promote their non-CFC-MDI products to the market. This campaign has to address both the doctors and the patients. However, these kinds of costs are difficult to be estimated at enterprise level.

Incremental Cost for Technical Assistance

删除的内容: **Incremental cost for technical assistance**

63. Beside the enterprise level costs, as described in Section 4.3, there are a series of activities of technical assistance nature, like: capacity building, training, data collection, public awareness, development and implementation of policies, progress monitoring, performance verification, and supervision.

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B Basic Assumptions for the Incremental Cost Calculation

Eligibility Criteria for Incremental Cost Calculation

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64. There are three factors impacting eligibility: (1) the installation date of the production facility; (2) ownership of the company; (3) export ratio of MDI production; and (4) idle production facilities.

i. **The installation date of the production facility**. The cut-off date of 25 July 1995 normally applied for other CFC consuming sectors should not be applied to the MDI sector, because:
   1) in 1995 no alternative technology was available;
   2) as in many other countries, even until 2006 it was not yet clear for SFDA if CFC consumption in MDI production could be phased out in China at all.

   Therefore, it is suggested to apply as cut-off date 30 November 2004, when the preparatory assistance project for the MDI sector plan was approved.

ii. **Ownership of the company.** There were four enterprises with foreign ownership in 2006, which were not considered in the calculation of the incremental costs. The baseline consumption (2006) of these enterprises with foreign ownership is 14.1 ODP tonnes ODP.

iii. **Export ratio of MDI production.** As mentioned in Section F, Chapter II, China imports and exports MDI products. The export ratio is high at the four foreign ownership enterprises, due to their partnership arrangements. However, others, especially the 100% domestic ownership enterprises, export very small amounts of MDIs (well below 10%) due to the limitations of registrations of their medical products in foreign countries. Therefore, the deduction of export ratio of MDI production is considered in the deduction of ownership of the said companies.

iv. **Idle production facilities.** A few eligible manufacturers have not been in production for years. However, as long as they have MDI product approval numbers issued by SFDA, they have legal rights to resume production depending on the market demand. Therefore, for those manufacturers, which had no CFC consumption in 2006, only the cost for preparation of technical dossier for registration purposes are considered as eligible incremental cost.

Key Assumptions for Incremental Operating Cost Calculation

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65. There are several factors, which have bearing on the incremental cost, e.g. (1) the alternative technology selected; (2) the period for calculation of incremental operating cost.

i. **Alternative technology**. According to the survey, the majority of Chinese MDI manufacturers may use HFAs (e.g. HFC-134a, HFC-227) as CFCs alternatives after screening a variety of technologies. As discussed in Chapter IV, based on the sector survey and the literature review of international experience, HFC-134a will be the first choice for most MDI producers. Besides, conversion to HFA is financially more feasible in China than the DPI route, because in case of conversion to DPI or other dosage forms, the whole production facility would have to be changed and the registration of the new drug at SFDA would take much more time and would cost much more than the replacement of propellant. It is also to be noted that DPI cannot be universally used for all patients, since a certain group of patients cannot inhale DPIs.

ii. **Period for calculation of incremental operating cost**. In the approved MLF projects different periods are used for the calculation incremental cost. In order to reduce the total cost of the project only 1 year was used in the calculation of the incremental operating cost.

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C Incremental Investment Cost for Conversion of MDI manufacturers

Preparation of Technical Dossier Required for non-CFC MDI Registration

66. On the basis of preliminary screening tests, the aerosol producer shall determine the substitution route according to the specific conditions (such as the properties and cost of alternative product), and apply for approval of modification of the medical excipient according to the Law of Drug Administration of PRC, the *Regulations on Drug Registration*, and the use requirement of the substitute. According to the *Regulations on Drug Registration*, different sets of technical documents shall be submitted corresponding to the following two cases of modification of medicinal adjuvant:

1) the excipient was already approved in China for medical applications;
2) new medicinal excipient to be used first time in China (to register as new medicinal adjuvant, and determine the application type according to the actual conditions of the aerosol producers).

67. Table 13 lists the content of the dossier for application for change of excipient to a new one, already within the National Standards.

Table 13 Technical Documents on Registration Application for Changing the Adjuvant of Medical Aerosol to a new one, already within the National Standard

Modification Item	Document Required
Excipient of medical requirement approved for other products	1. Copy of drug approval certification documents and their appendix
	2. Certification documents
	3. Sample of revised *Package Insert* enclosed with detailed revision illustrations
	4. Sample of revised package/ label enclosed with detailed revision illustrations
	5. Documents of pharmacological research
	6. Real sample of drug
	23.Research documents & literature of genital toxicity research
	24.Research documents & literature of carcinogenesis research
	25.Domestic and relevant foreign overview of clinical trial documents
	26.Plan & scheme of clinical trial
	27.Clinical researcher manual
	28. Sample of Informed Consent, and approval document of Ethics Committee.
	29.Clinical Trial Report

Table 14 lists the content of dossier for Drug Registration Application for the Use of New Excipients.

Table 14 Technical Documents required for Registration Application for Modifying the Adjuvant of Medical Aerosol

Modification Item	Document Required
New medicinal adjuvant	1. Name & naming basis of medicinal adjuvant
	2. Certification documents
	3. Objective & basis of topic establishment
	4. Summary & assessment of main research results
	5. Sample of *Package Insert*, drafting illustrations, and latest reference
	6. Design sample of package & label
	7. Overview of pharmacological research documents
	8. Research documents & literature of production process
	9. Research documents & literature verifying chemical structure or compositions
	10. Research documents & literature of quality research work
	11. Research documents & literature of drug-related compatibility
	12. Standard draft and drafting illustrations, with standard product or control product
	13. Inspection Report on 3 continuous batches of samples
	14. Research documents & literature of stability research

	15. Selection basis & quality standard of packing materials and containers in direct contact with medicinal adjuvant
	16. Overview of pharmacological & toxicological research documents
	17. Research documents & literature of pharmaco-dynamics influence on to-be-applied drug
	18. Research documents & literature of general pharmacological research
	19. Research documents & literature of acute toxicological research
	20. Research documents & literature of long-term toxicological research
	21. Research documents & literature of main local/systemic administration -related special safety test, such as allergy (local, systemic, and light), hemolysis, and local irritability (blood vessel, mucosa, muscle)
	22. Research documents & literature of mutagenesis research
	23. Research documents & literature of genital toxicity research
	24. Research documents & literature of carcinogenesis research
	25. Domestic and foreign relevant overview of clinical trial documents
	26. Plan & scheme of clinical trial
	27. Clinical researcher manual
	28. Sample of Informed Consent, and approval document of Ethics Committee.
	29. Clinical Trial Report

68. Table 15 lists the dossier for Drug Registration Application for Change in Dosage Form.

Table 15 Technical Documents for Registration Application for Modifying the Drug Dosage Form of Medical Aerosol

Modification Item	**Document Required**
Modification of dosage form of drugs already sold on the Chinese market, not modifying their administration route	1. Drug name
	2. Certification documents
	3. Objective & basis of topic establishment
	4. Summary & assessment of main research results
	5. *Package Insert*, drafting illustrations, and relevant reference
	6. Design sample of package & label
	7. Overview of pharmacological research documents
	8. Research documents & literature of production process for raw drugs, and research documents & literature of prescription and process for preparation
	9. Research documents & literature verifying chemical structure or compositions
	10. Research documents & literature of quality research work
	11. Drug standard and drafting illustrations, with standard product or control product
	12. Inspection Report on samples

	13. Origin, quality standard, and Inspection report of raw drugs and adjuvant
	14. Research documents & literature of drug stability research
	15. Selection basis & quality standard of packing materials and containers in direct contact with drug
	16. Overview of pharmacological & toxicological research documents
	17. Research documents & literature of special safety test, such as allergy (local, systemic, and light), hemolysis, and local irritability (blood vessel, mucosa, muscle)
	18. Research document & literature other than clinical pharmacokinetics research
	19. Domestic and foreign relevant overview of clinical trial documents
	20. Plan & scheme of clinical trial
	21. Clinical researcher manual
	22. Sample of Informed Consent, and approval document of Ethics Committee.
	23. Clinical Trial Report

69. The cost of preparation of the technical dossier will depend on the application of the selected propellant and the production process. It can not be accurately calculated at the current stage. Therefore, Table 17 is the best estimate based on past experience. Six key items are included for the estimation, though there are some other items as well, which were not included.

70. In accordance with the relevant regulations, each manufacturer has to make registration and get its license for their new MDI aerosol product based on its formulation and production process, though some products may also be produced by multiple manufacturers. Therefore, enterprises have to make re-registration application for new licenses for a total of 77 MDIs (Excluding 17 application in foreign enterprises and 10 applications in domestic enterprises, which confirmed that they do not to produce MDIs any longer. Referring to Table 7, Section F in Chapter II for the 36 licenses in production in 2006 the US$ 195,000 will be requested from MLF, as detailed in Table 16. For licenses not in production in 2006 only the most important activities will be compensated at the level of US$ 85,000, the remaining will be borne by the enterprises.

Table 16 Cost of Preparation of Technical Dossier for Registration

No.	Application Materials	For Licences in Production in 2006 (US$ $)	For Licences Not in Production in 2006 (US$ $)
1	Study of Production Process	12,500	7,500
2	Study of Quality	7,500	7,500
3	Pharmacological Study	20,000	0
4	Toxicological Study	20,000	0
5	Special safety Test	15,000	0
6	Clinical Test	120,000	70,000
	Subtotal	*195,000*	*85,000*
	Number of License with Production in 2006	36	41
	Sub - Total	7,020,000	3,485,000
Grand Total		**10,505,000**	

Cost of Modification of Existing Production Facilities

71. The requested incremental cost for modification of existing facilities shown in Table 17 is based on the assumption that these manufacturers will convert to HFA-134a excipient. As HFA-134a is not compatible with the hermetic seals and materials and some components of the existing facilities, it is necessary to modify or replace the existing pumps, pipes, hermetic pipe fittings, valves as well as the filling & charging equipment and associated instruments.

72. Based on information in Table 7, Section F in Chapter II, currently, 17 enterprises produced CFC based MDIs in baseline year 2006, among which only 15 enterprises with 17 production lines are of 100% Chinese ownership. The cost of conversion of these 17 production lines in the 15 Chinese enterprises will be requested from the MLF.

73. The cost for converting/replacing of the drug mixing tank, piping, valves, sealings, labour etc. for the enterprise with annual CFC consumption of
   - more than 100 tonnes, will be calculated at USD 800,000/line.
   - less than 100 tonnes and more than 10 tonnes, cost for the modification of the same items will be compensated at the level of as USD 420,000/line.
   - less than 10 tonnes, the compensation for these changes are calculated as USD 100,000/line.

74. The cost of conversion/replacement of filling/crimping line equipment is also classified into three categories:
   - USD 520,000 for those with production more than 5 million cans/year;
   - USD 260,000 for those with production less than 5 million and more than 1 million cans/year;
   - USD 100,000 for those with production less than 1 million cans/year.

Table 17 Cost of Modification of Existing Facilities

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Company Code	Company Name	CFC Consumption 2006 (kg)	2006 Output (can)	Cost for Mixing Tank and Related (US$)	Cost for Filling/ Crimping Line (US$)	Total (US$)
2	Beijing Haiderun Pharmaceutical Co., Ltd.	9,366	851,400	100,000	100,000	200,000
8	Guangzhou Dongkang Pharmaceutical Co., Ltd.	1560	124,800	100,000	100,000	200,000
9	Guiyang Dechangxiang Pharmaceutical Co., Ltd.	131	10898	100,000	100,000	200,000
14	Henan Xinxin Pharmaceutical (Group) Co., Ltd.	300	30000	100,000	100,000	200,000
15	Henan Zhongfu Pharmaceutical Co., Ltd.	2,205	150,000	100,000	100,000	200,000
18	Jinan Weiming Pharmaceutical Co., Ltd.	63.786	4,832,300	420,000	260,000	680,000
19	Penglai Nuokang Pharmaceutical Co.,Ltd.	28,928	2,552,299	420,000	260,000	680,000
21	Jewim Pharmaceutical (Shandong) Co., Ltd.	120,578	6,704,000	800,000	520,000	1,320,000
24	Shandong Lunan Beite Pharmaceutical Co., Ltd.	3,320	114,560	100,000	100,000	200,000
25	Pharmaceutical Factory of Shanxi Medical University	708	35,554	100,000	100,000	200,000
28	Shanghai Pharmaceutical (Group) Co., Ltd Sine Pharma Laboratory	19,434	1,132,455	420,000	260,000	680,000
32	No.1 Pharmaceutical Co., Ltd. of Wuxi Shanhe Group	4,840	313,689	100,000	100,000	200,000
36	Chongqing Kerui Pharmaceutical Co., Ltd.	7,377	448,800	100,000	100,000	200,000
37	Zigong Chenguang Pharmaceutical Co., Ltd.	70	2,020	100,000	100,000	200,000
38	Jiangsu Tianji Pharmaceutical Co., Ltd.	4,202	466,982	100,000	100,000	200,000
	Grand Total	**280,908**	**18,677,763**			**5,560,000**

Validation Process

75. *Provisions on Quality Management for Pharmaceutical Production* (SFDA #9,) was issued by SFDA in 1998 and is effective as of 1 August 1998. Article 57 stipulates that validation of pharmaceutical production shall consist of

a. validation of the workshop,

b. validation of installation of facilities and equipment,

c. validation of facility operation and performance, and

d. validation for products.

76. Article 58 states that re-validation shall be carried out in case of a change of main quality related factors such as production process, quality control method, main excipients and production facility.

77. In accordance with *Guidance of Validation of Pharmaceutical Production* (2004), Drug production validation includes prospective validation, concurrent validation, retrospective validation and revalidation. Due to the replacement of propellant or change of dosage form, new production equipment, production technology and product application will be introduced.

78. Therefore, it is necessary to carry out prospective validation before commercial production could start. The purpose of prospective validation is to evaluate and confirm the reproducibility and reliability of production process.

79. Concurrent validation has to be conducted after the start of commercial production in order to obtain data from the actual process operation, so as to prove that it fulfils the expected requirements.

80. After normal production for a certain period of time of normal commercial production retrospective validation is to take place to collect statistical data and make trend analysis, thus discovering the worst conditions for the process operation and indicating the risk of potential malfunction.

81. Revalidation includes compulsive validation, alternate validation and regular validation

Validation for Changing Excipient (Alternative Propellant)

82. Changing of excipients requires prospective validation, concurrent validation, retrospective validation and revalidation. The validation includes:

i) validation of workshop;
ii) validation of public utilities;
iii) validation of computer system;

iv) validation of production equipment;
v) validation of production process;
vi) validation of personnel;
vii) validation of other relevant items.

i. Validation of Workshop, Public Utility System and Computer System

a. Validation of workshop is needed to confirm that 1)the reconstructed workshops is in compliance with design standards; 2) the flow of people and materials is proper; 3) workshop cleanliness is up to the level of 300,000 grade.
b. Validation of public utilities consists of six items, namely, heating, ventilation, air conditioning, discharging system, cooling system and propellant supply system.
c. Validation of computer system consist of four items, namely, batch record/SOP management system, material management system, lab system and the management system for production/engineering spare parts.

ii. Validation of Production Equipment

d. Validation of production equipment comprises six items, namely, weighing scales, containers, valve cleansing equipment, and compound vessel system, filling equipment, weight inspection system and spray inspection system.

iii. Validation of Production Process

e. Validation items for dispensing preparation includes: temperature of liquid product in compound vessels, particle sizes and homogenization of the drug liquid.
f. Validation of cleaning effect of containers: various impurities placed into the container should be totally removed by cleaning.
g. Validation items for filling process include appearance, filling weight and leakage. At least three batches shall be inspected. Samples shall be taken from different places to check the appearance, filling weight, active ingredient and leakage.
h. Validation items for weighing equipment include weighing accuracy and elimination of under-weighed and over-weighed samples.
i. Validation items for timing of product inspection include leakage and shot weight per actuation. Different inspection times shall be selected to test the leakage and the shot per actuation so as to find out the best inspection time.
j. Validation item for spray inspection include the performance of spray and elimination of samples that don't spray or don't spray constantly.
k. Validation of metered aerosols is done based on the product quality standards. The items include validation of appearance, active ingredient per actuation, quantity of actuation per canister, shot weight per actuation, spray distribution, microbes, etc. At least three batches of samples shall be inspected with validated sampling and analysis methods to

ensure that finished products are produced steadily in compliance with product delivery standards.

l. Validation items for cleanliness include the cleanliness of compound vessels and filling lines. There shall be no cross-contamination between different batches. After cleaning of the filler, the contents of raw medicinal material, water and solvent shall be measured, to make sure that no active medicinal material or solvent remained.

iv. Validation for Personnel and Other Relevant Items

m. Validation for personnel consists of establishment of filing system for each person engaged in aerosol production, including records for training, health, safety and personnel performance, etc.

n. Validation for other relevant items includes document recording, instrument calibration, preventative maintenance, production areas and area for changing clothes as well as waste cleansing and sterilization.

Validation for Change in Dosage Form

83. For change in dosage form, it is required to conduct prospective validation, concurrent validation, retrospective validation and revalidation. The validations are basically the same as those for Part A, except that there are some differences in validation items for finished product. Validation for metered aerosol includes appearance, total times of actuation per canister, shot weight per actuation, active ingredient per actuation, spray distribution, variation of filling amount (filling amount) and microbes, etc. At least three batches of samples shall be inspected with validated sampling and analysis methods to ensure that finished products are produced steadily in compliance with product delivery standards.

84. There are 17 eligible production lines in 15 eligible enterprises, which had MDI production in 2006. Cost for production validation is detailed in Table 18.

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Table 18 Cost of Production Validation

SN	Item	Content	Expenses (US$)
1	Equipment	Scales, Containers, Valve Cleansing Equipment; Compound Vessel System; Filling &Charging Equipment; Weight Checking System; Spray Checking System	12,500
2	Production process	Liquid Drug Processing, Cleaning effectiveness for Containers; Filling Process; Weight Checking System; Product Checking Time; Spray Checking; Finished Products; Cleaning Effectiveness.	20,500
3	Others	Workshop; Public Utilities; Computer System; Others	7,000
	Subtotal for one production line		*40,000*
	Number of production lines with baseline production		17
	Grand Total, Validation		**680,000**

Staff Training

85. Due to the introduction of new substitutes, it is necessary to provide training for the staff of the manufacturers. Those people who should receive training include quality control technicians, operators, recorders, engineers, management staff and those working for procurement, transportation and maintenance. It is estimated that each manufacturer has 20 for production and 40 for the other areas.

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Table 19 Cost for Staff Training

	Production Staff	Other Staff	Public Training
Number of Trainees	20	40	10,000
Unit cost (US$/person)	125	375	
Subtotal (US$)	2,500	15,000	
Subtotal of one production line (US$)			*27,500*
Number of Eligible Enterprises			15
Grand Total, Training (US$)			**412,500**

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D Incremental Operating Cost

86. The calculation is based on the consumption, production and cost data collected from manufacturers during the survey undertaken by NICPBP, SFDA, SEPA and UNIDO. Calculation of IOC is based on the ExCom guidelines and using Incremental Operating Cost for a period of one year. In this project, IOC is calculated based on the CFC

consumption and production output of the year preceding the submission of the document, i.e. in 2006. The price differences for HFA products and CFC products are shown in Table 20.

Table 20 Price difference for HFA products and CFC products

Item	Original Product (CFC as propellant)		Product after Conversion (HFA-134a as propellant)	
	US$/kg	Unit Cost (US$/can)	US$/kg	Unit Cost (US$/can)
1. propellant	3.43		7.38	
2. Packaging				
Canister		0.16875		0.19507
Valve		0.04813		0.19287
Subtotal for packaging		0.21688		0.38793

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87. The foreign ownership enterprises were excluded in the process of IOC calculation.
88. Literature reviews indicate that on average, HFA MDI uses 30% less propellant than a CFC MDI.
89. The calculation for each enterprises based on the above parameters is shown below in Table 21. The total IOC is US$3,502,689.

Table 21 Enterprise level IOC Calculation

Company Code	Company Name	Year of Establ.	CFC Consumption in 2006, (kg)	IOC, Propellant, US$	Output in 2006, (cans)	IOC, Can, US$	Total IOC (US$)
2	Beijing Haiderun Pharmaceutical Co., Ltd.	1978	9,366	16,259	851,400	145,632	161,891
8	Guangzhou Dongkang Pharmaceutical Co., Ltd.	1988	1,560	2,708	124,800	21,347	24,055
9	Guiyang Dechangxiang Pharmaceutical Co., Ltd.	1979	131	227	10,898	1,864	2,091
14	Henan Xinxin Pharmaceutical (Group) Co., Ltd.	1982	300	521	30,000	5,132	5,652
15	Henan Zhongfu Pharmaceutical Co., Ltd.	1992	2,205	3,828	150,000	25,658	29,485
18	Jinan Weiming Pharmaceutical Co., Ltd.	1979	63,786	110,732	4,832,300	826,565	937,297
19	Penglai Nuokang Pharmaceutical Co., Ltd.	1993	28,928	50,219	2,552,299	436,571	486,790
21	Jewim Pharmaceutical (Shandong) Co., Ltd.	1993	120,578	209,323	6,704,000	1,146,719	1,356,043
24	Shandong Lunan Beite Pharmaceutical Co., Ltd.	2001	3,320	5,764	114,560	19,595	25,359
25	Pharmaceutical Factory Shanxi Medical University	1994	708	1,229	35,554	6,082	7,311
28	Sine Pharma Laboratory of Shanghai Pharmaceutical (Group) Co., Ltd	1982	19,434	33,737	1,132,455	193,706	227,444
32	No.1 Pharmaceutical Co., Ltd. of Wuxi Shanhe Group	1965	4,840	8,402	313,689	53,657	62,059
36	Chongqing Kerui Pharmaceutical Co., Ltd.	1975	7,377	12,806	448,800	76,767	89,573
37	Zigong Chenguang Pharmaceutical Co., Ltd.	1981	70	122	2,020	346	467
38	Jiangsu Tianji Pharmaceutical Co., Ltd.		4,202	7,295	466,982	79,877	87,172
Grand Total, IOC			**266,804**	**463,172**	**17,769,757**	**3,039,517**	**3,502,689**

E Contingency of incremental capital cost

90. Contingency is calculated as 10% of the cost of modification of the production facilities.

F Technical Assistance (TA)

91. In order to implement the sector plan smoothly, it is necessary to undertake TA activities. The total fund requested for Technical Assistance is 1.1 million US dollars covering the following activities:

a. Workshops for aerosol manufacturers, equipment manufacturers and technical experts during the implementation of the sector plan;

b. Training of responsible staff of government agencies such as local Food and Drug Administration Bureaus and Environmental Protection Bureaus on the implementation of the phase out policies in the MDI sector;

c. Legislative support activities;

d. Preparation and appraisal of feasibility study reports to decide on the group of eligible enterprises and the funding needs;

e. Technical support and harmonisation of product and process conversion activities;

f. Development of a MIS system, monitoring and management of the Sector Plan, verification of performance indicators;

g. Auditing of CFCs consumption annually for pharmaceutical aerosol manufacturers;

h. Study tours;

i. Public awareness promotion activities;

j. General training of doctors, patients and pharmacists, environmental and health officials, the medical community, clinics, pharmaceutical companies and non-governmental organizations

k. Other TAs as necessary.

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G Summary

92. The total costs requested from the MLF, includes the one time investment cost and the one year operating cost for the eligible producers as well as the cost of technical assistance activities required for the implementation of this sector plan. The incremental cost will be used to phase out of 280.9 ODP tonnes/year CFCs in the MDI sector of China .

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Table 22 Summary of incremental costs

Item	Incremental Cost (US$)
Preparation of Technical Dossiers Required for non-CFC MDI Registration	**10,505,000**
Modification of Existing Production Facilities	**5,560,000**
Production Validation	680,000
Staff Training	412,500
Incremental Operating Cost	3,502,689
Technical Assistance	1,100,000
Contingency*	556,000
Total	**22,316,189**
Implementing Agency Support Cost	**1,673,714**
Total Funding Requested	**23,989,903**
Cost Effectiveness, US$/kg	**79.45**

* The contingency is calculated as 10% of Cost of Modification of Existing Production Facilities.

Chapter VII Operating Mechanism

A Agreement between SEPA and UNIDO

93. Following approval of the Sector Plan by the ExCom, SEPA and UNIDO will sign an agreement, which will indicate that UNIDO entrusts SEPA to implement the Sector Plan under UNIDO's supervision. According to the Agreement, UNIDO will disburse grants to SEPA based upon (a) submission of a detailed Work Plan on the implementation for the Sector Plan, hereafter referred to as the Work Plan and (b) satisfactory performance of implementation and (c) meeting the agreed performance indicators.
94. The Work Plan will include the key activities and schedule for conversion of enterprises, the amount of CFC elimination, conditions and amount of fund disbursement, the necessary technical assistance activities and their schedules.
95. After signing the Agreement with UNIDO, SEPA and SFDA will jointly establish a special working group (SWG). SWG will organize, manage and monitor the implementation of the sector plan in close cooperation with the recipient companies.
96. Based on the satisfactory progress report of SEPA and verified achievement of the phase-out target. UNIDO will disburse funds to a special account; ODS Special Account set up in SEPA after receiving SEPA's funding request.

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B Roles and Responsibilities

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97. The MDI Sector Plan will be executed by SEPA, acting on behalf of Chinese Government. The daily work will be done by FECO, one affiliated institution of SEPA. SEPA and SFDA will jointly set up the SWG, whose office will be located in FECO. SWG will be responsible for preparing the Work Plan. SEPA and SFDA will jointly select through a bidding process a domestic implementing agency (DIA) for the management of daily works during the implementation of the Sector Plan.
98. Roles and Responsibilities of each institution involved are described as follows.

UNIDO

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99. Will be responsible for overall implementation of the Sector Plan and accomplishment of its objectives as approved by the ExCom. UNIDO will:

a) Establish working and reporting arrangement with SEPA and SFDA;
b) Supervise SEPA, SFDA and the recipient companies to complete this Sector Plan;
c) Provide necessary technological and managerial support to SEPA and SFDA for the implementation of this Sector Plan;
d) Pay the fund of the Sector Plan to SEPA based on the agreed conditions;
e) Monitor the implementation of the Work Plan, conduct necessary audit and inspection, review bidding processes of selecting the DIA, eligible enterprises and the institutions undertaking the technical assistance projects; and
f) Report to the ExCom. on the implementation status of the Sector Plan.

SEPA

100. Will through PMO, be responsible for overall project management and coordination for the implementation of the Sector Plan. SEPA will:

a) Set up a SWG consisting of staff from PMO and SFDA, and selected technical experts from the industry jointly with SFDA;
b) Set up an ODS Special Account;
c) Select a DIA jointly with SFDA, supervise the work of DIA;
d) Review the funding request submitted by the Working Group and DIA, and approve the disbursement;
e) Review the CFC consumption quota submitted by the work group and issue the quota to the enterprises;
f) Submit progress report to UNDIO semi-annually;
g) Verify and ensure the realization of CFC phase out target of the Sector Plan, and the destruction of CFC equipment in enterprises involved; and
h) Prepare and issue the related regulations jointly with SFDA.

SFDA

101. Will cooperate with SEPA to implement this Sector Plan. SFDA will:

a) Help PMO to set up the SWG and select qualified technical experts for SWG;
b) Set up SWG office and facilitate its operation;
c) Select a DIA jointly with SEPA;

d) Coordinate the relationships among SEPA, SWG, DIA and counterpart enterprises;
e) Help SEPA to realize the CFC phase out target indicated in the Sector Plan,
f) Monitor the destruction of CFC equipment at the recepient enterprises according to MLF rules;
g) Provide support on sector policy and technology, lead MDI manufacturing enterprises to eliminate CFC consumption and prepare relevant regulations jointly with SEPA so that they can be issued and enter into force subsequently;
h) Design CFCs phase-out policies in MDI sector, in cooperation with SEPA;
i) Organize local FDAs to implement phase-out policies and undertake irregular spot check to the MDI manufacturers;
j) Supervise CFCs consumption of MDI aerosol manufacturers;
k) Ensure adequate clinical supply of MDI products.

SWG

102. Will, with the backstopping of SEPA and SFDA, be responsible for implementing the Work Plan and undertake the following activities:

a) Manage daily works of implementing the Sector Plan, coordinate the activities among all relevant parties;
b) Establish an implementing and monitoring mechanism as well as a computerized database in English, which should include the status of the implementation of the Sector Plan for all eligible and non-eligible CFC-based MDI manufacturers, so that SWG, SEPA/PMO, SFDA and UNIDO can easily learn each project's situation.
c) Select most cost-effective contractors to execute the conversion project;
d) Through bidding, select contractors of the technical assistance projects, and manage their implementation;
e) Review DIA's payment requests and submit them to PMO for disbursement;
f) Monitor DIA's work, submit progress report to PMO quarterly, timely report to PMO on technical, managerial, or implementation problems, which might arise;
g) Visit beneficiaries, inspect project implementation, take part in the destruction of their CFC equipment;
h) With the help of DIA, organize official project commissioning;
i) Help SEPA/PMO prepare quarterly and annual reports on the status of ODS Special Account, including budget revisions requested from PMO and UNIDO. With PMO's entrustment, prepare requests for replenishment of funds and submit it to UNIDO; and

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j) Provide assistance to verification audits as may be required by the Government, UNIDO and the ExCom.

DIA

103. With the backstopping of PMO, SFDA and SWG, DIA will be responsible for the project activities at enterprise level as follows:

a) Provide necessary managerial and technological assistance to SWG;
b) Conduct equipment and service procurement for beneficiary enterprises, help the enterprises in converting their production lines;
c) Prepare payment requests for beneficiaries, or review beneficiaries payment request before submitting it to PMO;
d) Submit regular report on project implementation to SWG, help SWG prepare progress reports on project implementation;
e) Verify and inform SWG and PMO on problems that might arise at enterprises; and
f) Organize official project commissioning.

C Audit and Reporting

104. SWG will execute the Work Plan; submit progress reports to PMO four times a year. PMO will submit semi-annual and annual reports to UNIDO. The reports will be prepared in a format agreed by SEPA, SFDA and UNIDO. UNIDO will report to ExCom on the progress of implementation and financial status of the project.

105. UNIDO will audit each year's project implementation. UNIDO will supervise implementation of the Work Plan, including spot check of project records and periodic check on enterprises.

106. SEPA will be responsible for conducting local annual audits according to regulations set for the ODS Special Account.

D Destruction of CFC Equipment and Certification

107. Confirmation of the destruction of CFC equipment and its certification should be obtained from an authorized organization in a form as specified in the ODS Phase out Contracts between SEPA and enterprises. SEPA will be responsible for preparing a completion

report for each enterprise confirming that all terms and conditions of the ODS Phase out contract, including the destruction of equipment, have been fulfilled. UNIDO will retain the right to carry out factory inspections.

Chapter VIII Action Plan

108. This Chapter presents the Action Plan and schedule for implementing CFCs phase-out for China's MDI sector. The proposed Action Plan is summarized in table 23.

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Table 23 Phase-out Targets and Funding Request from 2007 to 2010 in Action Plan

	2006 (Baseline)	2007 (Estimate)	2008	2009	2010
CFC Consumption Targets					
Maximum Allowable CFC Consumption/Production under the Accelerated CFC Phase out Plan (except for essential use consumption)			550	550	0
CFCs Consumption (newly produced CFCs)	280.9	310	310*	310*	0
CFCs from Stockpiled CFCs	0		0	0	n.a.**
Funding Request(USD'000)					
Enterprise-Level Activities	n.a.	21,216,189			
Technical Assistance Activities	n.a.	1,100,000			
Support Cost (7.5%)	n.a.	1,673,714			
Total MLF Cost	n.a.	23,989,903			
Actions					
Enterprise-Level Activities	n.a.		(1) sign CFC phase out contract with SFDA/SEPA	(1) Modification of Existing Facilities	
			(2) Identify alternatives by mid 2008.	(2)Validation and New Production	
			(3) Start Registration Application.	(3) Workshops, Trainings	
Technical Assistance Activities			(1) Workshops on alternatives, new processes, technical requirements, consumption quota, contract issues etc.;	(1) Workshops on alternatives;	(1) Workshops on new products and technical standards.
			(2) Survey on technical standards and other issues.	(2) Survey of conversion issues as necessary.	

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	2006 (Baseline)	2007 (Estimate)	2008	2009	2010
Policies and measures			(1) Issue and enforce consumption quota licenses to MDI producers;	(1) Enforcement of quotas and verification audit of CFCs consumptions	(1) Enforcement of quotas and verification audit of CFCs consumptions
			(2) Issue ban on use of CFCs for MDI production.	(2) Preparation of Progress Reports covering all sector plan activities.	(2) Preparation of Progress Reports covering all sector plan activities.
			(3) Verification audit of CFCs consumptions		
Indicators					
			(1) All eligible MDI producers signed contract for CFC phaseout.	(1) CFC production and CFC consumption quota are lower than 550 tones ODP respectively.	
			(2) Consumption quota system is established.	(2) several TA activity contracts are signed.	
			(3) Relevant TA activity contracts are signed.	(3) 5 producers completed conversion.	(1) CFC production and fresh CFC consumption quota for MDI are 0 ODP tonnes.
			(4) National CFC production and CFC consumption quota are lower than 550 tones ODP respectively.		
			(5) Ban on use of CFCs for MDI production is issued.		

* Maximum quota will be issued to allowed MDI producers stockpile CFCs as needed during the conversion.

** Use of stockpiled CFCs required in the ongoing process of conversion.

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Appendix 1

Chinese Producers & Varieties of MDI Products

Company Code	Company Name	Product Code	Product Name	Approval No.	Traditional Chinese Medicine
01	AstraZeneca Pharmaceutical Co., Ltd.	B04	Budesonide Aerosol (100d)	H20030410	
01	AstraZeneca Pharmaceutical Co., Ltd.	B04	Budesonide Aerosol	H20030411	
01	AstraZeneca Pharmaceutical Co., Ltd.	B13	Terbutalin Sulfate Aerosol (400 sprays)	H10930058	
01	AstraZeneca Pharmaceutical Co., Ltd.	B13	Terbutalin Sulfate Aerosol (200 sprays)	H10930059	
02	Beijing Haiderun Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol	H11021384	
02	Beijing Haiderun Pharmaceutical Co., Ltd.	B22	Isoprenaline Hydrochloride Aerosol	H11021180	
02	Beijing Haiderun Pharmaceutical Co., Ltd.	B23	Ipratropium Aerosol	H11022421	
03	Beijing Shengdelaibao Pharmaceutical Co., Ltd.	B01	Beclomethasone Dipropionate Aerosol (50μg)	H11020191	
03	Beijing Shengdelaibao Pharmaceutical Co., Ltd.	B01	Beclomethasone Dipropionate Aerosol (100μg)	H11020192	
03	Beijing Shengdelaibao Pharmaceutical Co., Ltd.	B01	Beclomethasone Dipropionate Aerosol (200μg)	H11020193	
03	Beijing Shengdelaibao Pharmaceutical Co., Ltd.	B01	Beclomethasone Dipropionate Aerosol (250μg)	H11020194	
03	Beijing Shengdelaibao Pharmaceutical Co., Ltd.	B12	Ribavirin Spray	H11020195	
03	Beijing Shengdelaibao Pharmaceutical Co., Ltd.	B14	Sodium Cromoglicate Aerosol	H11020196	
03	Beijing Shengdelaibao Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol	H11020197	

Company Code	Company Name	Product Code	Product Name	Approval No.	Traditional Chinese Medicine
04	Beijing Double-Crane Modern Medicinal Technology Co., Ltd.	B19	Isopropyl Scopolamine Bromide Aerosol	H1102216 8	
04	Beijing Double-Crane Modern Medicinal Technology Co., Ltd.	B23	Ipratropium Aerosol	H1102180 1	
04	Beijing Double-Crane Modern Medicinal Technology Co., Ltd.	B23	Ipratropium Aerosol	H1102180 2	
05	GlaxoSmithKline (Tianjin) Co., Ltd.	B01	Beclomethasone Dipropionate Aerosol (250ug/200 sprays)	H2005623 1	
05	GlaxoSmithKline (Tianjin) Co., Ltd.	B01	Beclomethasone Dipropionate Aerosol (50ug/200 sprays)	H2005625 9	
07	Guangzhou Baiyunshan Hejigong Pharmaceutical Co., Ltd.	B01	Beclomethasone Dipropionate Aerosol	H4402311 3	
07	Guangzhou Baiyunshan Hejigong Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol	H4402312 1	
07	Guangzhou Baiyunshan Hejigong Pharmaceutical Co., Ltd.	B20	Clenbuterol Hydrochloride Aerosol	H4402537 3	
07	Guangzhou Baiyunshan Hejigong Pharmaceutical Co., Ltd.	B22	Isoprenaline Hydrochloride Aerosol	H4402312 3	
08	Guangzhou Dongkang Pharmaceutical Co., Ltd.	B01	Beclomethasone Dipropionate Aerosol	H4402406 3	
08	Guangzhou Dongkang Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol	H4402021 7	
08	Guangzhou Dongkang Pharmaceutical Co., Ltd.	B22	Isoprenaline Hydrochloride Aerosol	H4402022 6	
09	Guiyang Dechangxiang Pharmaceutical Co., Ltd.	B24	Zhichuanling Aerosol	Z5202022 5	yes

Company Code	Company Name	Product Code	Product Name	Approval No.	Traditional Chinese Medicine
10	Harbin Guangji Pharmaceutical Factory	B15	Salbutamol Aerosol (liquid)	H2302056 1	
10	Harbin Guangji Pharmaceutical Factory	B16	Salbutamol Aerosol (suspension)	H2302068 4	
11	Harbin Hengcang Pharmaceutical Co., Ltd.	B14	Sodium Cromoglicate Aerosol	H2302341 3	
11	Harbin Hengcang Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol	H2302033 3	
12	Harbin Huili Pharmaceutical Co., Ltd.	B17	Salmeterol Xinafoate Aerosol	H1998010 5	
13	Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd.	B01	Beclomethasone Dipropionate Aerosol	H3302144 4	
14	Henan Xinxin Pharmaceutical (Group) Co., Ltd.	B11	Physochlaina infundibulris Kuang Aerosol	z41022146	yes
15	Henan Zhongfu Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol	H4102142 4	
16	Heilongjiang Tianlong Pharmaceutical Co., Ltd.	B14	Sodium Cromoglicate Aerosol	H2302036 9	
16	Heilongjiang Tianlong Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol	H2302037 0	
16	Heilongjiang Tianlong Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol	H2302037 1	
17	Jilin Xiuzheng Pharmaceutical (Group) Co., Ltd.	B01	Beclomethasone Dipropionate Aerosol	H2202341 1	
18	Jinan Weiming Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol	H3702065 3	
18	Jinan Weiming Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol (28mg,0.2%(g/g)	H3702065 3	

Company Code	Company Name	Product Code	Product Name	Approval No.	Traditional Chinese Medicine
18	Jinan Weiming Pharmaceutical Co., Ltd.	B22	Isoprenaline Hydrochloride Aerosol	H37020655	
19	Penglai Nuokang Pharmaceutical Co., Ltd.	B07	Compound Isoprenaline Hydrochloride Aerosol (suspension)	H37023690	
19	Penglai Nuokang Pharmaceutical Co., Ltd.	B14	Sodium Cromoglicate Aerosol	H20003867	
19	Penglai Nuokang Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol (liquid)	H37020545	
19	Penglai Nuokang Pharmaceutical Co., Ltd.	B16	Salbutamol Aerosol (suspension)	H37020544	
19	Penglai Nuokang Pharmaceutical Co., Ltd.	B22	Isoprenaline Hydrochloride Aerosol	H37020549	
20	Qiqihar Pharmaceutical Factory	B15	Salbutamol Aerosol	H23022108	
21	Jewim Pharmaceutical (Shandong) Co., Ltd.	B01	Beclomethasone Dipropionate Aerosol (250μg/100 sprays)	H20059866	
21	Jewim Pharmaceutical (Shandong) Co., Ltd.	B01	Beclomethasone Dipropionate Aerosol (250μg/200 sprays)	H20059867	
21	Jewim Pharmaceutical (Shandong) Co., Ltd.	B01	Beclomethasone Dipropionate Aerosol	H37022928	
21	Jewim Pharmaceutical (Shandong) Co., Ltd.	B14	Sodium Cromoglicate Aerosol	H37022929	

Company Code	Company Name	Product Code	Product Name	Approval No.	Traditional Chinese Medicine
21	Jewim Pharmaceutical (Shandong) Co., Ltd.	B15	Salbutamol Aerosol (liquid)	H19983227	
21	Jewim Pharmaceutical (Shandong) Co., Ltd.	B16	Salbutamol Aerosol (suspension)	H37022817	
22	Shandong Linuo Kefeng Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol (liquid)	H37022314	
22	Shandong Linuo Kefeng Pharmaceutical Co., Ltd.	B18	Isosorbide Dinitrate Aerosol	H37022845	
22	Shandong Linuo Kefeng Pharmaceutical Co., Ltd.	B22	Isoprenaline Hydrochloride Aerosol	H37023560	
23	Shandong Lukang Cisen Pharmaceutical Co., Ltd.	B01	Beclomethasone Dipropionate Aerosol	H37021846	
23	Shandong Lukang Cisen Pharmaceutical Co., Ltd.	B22	Isoprenaline Hydrochloride Aerosol	H37022070	
24	Shandong Lunan Beite Pharmaceutical Co., Ltd.	B04	Budesonide Aerosol	H20030987	
24	Shandong Lunan Beite Pharmaceutical Co., Ltd.	B17	Salmeterol Xinafoate Aerosol	H20052614	
24	Shandong Lunan Beite Pharmaceutical Co., Ltd.	B25	Salbutamol Sulfate Aerosol	H20060409	
25	Pharmaceutical Factory Shanxi Medical University	B01	Beclomethasone Dipropionate Aerosol	H14020317	
25	Pharmaceutical Factory Shanxi Medical University	B16	Salbutamol Aerosol (suspension)	H14020757	
25	Pharmaceutical Factory Shanxi Medical University	B18	Isosorbide Dinitrate Aerosol	H14023848	
26	Shanghai Boehringer-Ingelheim Pharmaceutical Co., Ltd.	B08	Compound Ipratropium Aerosol (5ml)	H20046117	

Company Code	Company Name	Product Code	Product Name	Approval No.	Traditional Chinese Medicine
26	Shanghai Boehringer-Ingelheim Pharmaceutical Co., Ltd.	B08	Compound Ipratropium Aerosol (10ml)	H20046118	
26	Shanghai Boehringer-Ingelheim Pharmaceutical Co., Ltd.	B23	Ipratropium Aerosol (Atrovent Aerosol, 10ml)	H20033863	
27	Shanghai Fuxing Zhaohui Pharmaceutical Co., Ltd.	B02	Beclomethasone Dipropionate Aerosol (suspension)	H31021090	
27	Shanghai Fuxing Zhaohui Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol (liquid)	H31021094	
27	Shanghai Fuxing Zhaohui Pharmaceutical Co., Ltd.	B16	Salbutamol Aerosol (suspension)	H31020802	
28	Sine Pharma Laboratory of Shanghai Pharmaceutical (Group) Co., Ltd	B01	Beclomethasone Dipropionate Aerosol	H31020770	
28	Sine Pharma Laboratory of Shanghai Pharmaceutical (Group) Co., Ltd	B04	Budesonide Aerosol	H20010552	
28	Sine Pharma Laboratory of Shanghai Pharmaceutical (Group) Co., Ltd	B07	Compound Isoprenaline Hydrochloride Aerosol (suspension)	H31022807	
28	Sine Pharma Laboratory of Shanghai Pharmaceutical (Group) Co., Ltd	B09	Ketotifun Fumarate Aerosol	H31022604	
28	Sine Pharma Laboratory of Shanghai Pharmaceutical (Group) Co., Ltd	B10	Carbochromen Aerosol	H31022283	
28	Sine Pharma Laboratory of Shanghai Pharmaceutical (Group) Co., Ltd	B12	Ribavirin Aerosol	H10970349	

Company Code	Company Name	Product Code	Product Name	Approval No.	Traditional Chinese Medicine
28	Sine Pharma Laboratory of Shanghai Pharmaceutical (Group) Co., Ltd	B14	Sodium Cromoglicate Aerosol	H3102068 1	
28	Sine Pharma Laboratory of Shanghai Pharmaceutical (Group) Co., Ltd	B15	Salbutamol Aerosol (liquid)	H3102060 6	
28	Sine Pharma Laboratory of Shanghai Pharmaceutical (Group) Co., Ltd	B16	Salbutamol Aerosol (suspension)	H3102056 0	
28	Sine Pharma Laboratory of Shanghai Pharmaceutical (Group) Co., Ltd	B17	Salmeterol Xinafoate Aerosol	H2001054 8	
28	Sine Pharma Laboratory of Shanghai Pharmaceutical (Group) Co., Ltd	B20	Clenbuterol Hydrochloride Aerosol	H3102280 9	
28	Sine Pharma Laboratory of Shanghai Pharmaceutical (Group) Co., Ltd	B21	Bromhexine Hydrochloride Aerosol	H3102260 7	
28	Sine Pharma Laboratory of Shanghai Pharmaceutical (Group) Co., Ltd	B22	Isoprenaline Hydrochloride Aerosol	H3102114 1	
28	Sine Pharma Laboratory of Shanghai Pharmaceutical (Group) Co., Ltd	B22	Isoprenaline Hydrochloride Aerosol	H3102285 8	
29	Tianjin Century Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol	H1202008 3	
29	Tianjin Century Pharmaceutical Co., Ltd.	B22	Isoprenaline Hydrochloride Aerosol	H1202008 4	
30	Tonghua Baishan Pharmaceutical Co., Ltd.	B06	Compound Danshen Aerosol	Z1095004 9	yes
31	Weifang Zhongshi Pharmaceutical Co., Ltd.	B01	Beclomethasone Dipropionate Aerosol	H3702215 2	
31	Weifang Zhongshi Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol (liquid)	H3702362 8	

Company Code	Company Name	Product Code	Product Name	Approval No.	Traditional Chinese Medicine
31	Weifang Zhongshi Pharmaceutical Co., Ltd.	B16	Salbutamol Aerosol (suspension)	H3702216 0	
31	Weifang Zhongshi Pharmaceutical Co., Ltd.	B16	Salbutamol Aerosol (suspension)	H3702216 1	
32	No.1 Pharmaceutical Co., Ltd. of Wuxi Shanhe Group	B15	Salbutamol Aerosol	H3202154 5	
32	No.1 Pharmaceutical Co., Ltd. of Wuxi Shanhe Group	B22	IsoprenalineHydrochlorideAerosol	H3202273 1	
33	Xian Lisheng Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol (liquid)	H6102094 6	
34	Xinjiang Pharmaceutical Factory	B15	Salbutamol Aerosol	H6502032 1	
35	Zhanjiang New Ton Tex Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol (liquid)	H4402366 9	
35	Zhanjiang New Ton Tex Pharmaceutical Co., Ltd.	B16	Salbutamol Aerosol (suspension)	H4402366 8	
36	Chongqing Kerui Pharmaceutical Co., Ltd.	B15	Salbutamol Aerosol (liquid)	H5002045 2	
36	Chongqing Kerui Pharmaceutical Co., Ltd.	B16	Salbutamol Aerosol (suspension)	H5002045 3	
36	Chongqing Kerui Pharmaceutical Co., Ltd.	B20	Clenbuterol Hydrochloride Aerosol	H5002166 0	
36	Chongqing Kerui Pharmaceutical Co., Ltd.	B22	Isoprenaline Hydrochloride Aerosol	H5002032 3	
37	Zigong Chenguang Pharmaceutical Co., Ltd.	B05	Dimethicone Aerosol	H5102190 6	
38	Jiangsu Tianji Pharmaceutical Co., Ltd.	B12	Ribavirin Spray	H2005950 2	

Table 8-1 Phase-out Targets and Funding Request from 2007 to 2010 in Action Plan

Line		Baseline (average of 04-06)	2008	2009	2010	2011
1	CFCs Consumption (newly produced CFCs)	300	300	300	0	0
2	CFCs from Stockpiled CFCs	0	1/	1/	1/	1/
3	Total CFCs Consumption	300	0	0	0	0
Funding Request(US$'000)						
4	Enterprise-Level Activities[1]					
5	Technical Assistance Activities					
6	Support Cost					
7	Total MLF Cost					

1/. Use of stockpiled CFCs as needed during the conversion.

Biennial Program

1). 2008-2009 Biennial Program: The following activities will be covered under this program:

Substitute screening. To support manufacturers to identify substitutes for their aerosol products before the first half year of 2009.

Registration Application. To support the registration for new CFCs-free aerosol products.

Modification of Existing Facilities, Validation and New Production.

Workshops, trainings and public awareness promotion.

Development of a MIS system and other TA activities as necessary.

Verification on CFCs consumption;

3). 2010-2011 Biennial Program: This will be submitted to the last ExCom meeting of 2010. It will consist of the following, but not limited to:

Registration Application. To support the registration for new CFCs-free aerosol products.

Modification of Existing Facilities, Validation and New Production.

Workshops, Trainings and public awareness promotion.

Verification on CFCs consumptions, including final verification of all phase out targets

under the sector plan.

Project Completion Report covering all sector plan activities will be prepared.

Implementation Schedule

Stage	Activities
Start-up	To complete policy development and substitute screening
Registration Application	To complete registration for new aerosol products. Registration applicatio initiated in the first year.
Production	To complete modification on the existing facilities, validation for product
Commissioning	To undertake project commissioning organized by SFDA and attended by original record, report and related documents should be retained.

Table 8-2 Implementation Schedule

	2008				2009				2010					
	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	
	X	X	X	X										
ation	X	X	X	X	X	X	X	X	X	X				
	X	X	X	X	X	X	X	X	X	X	X	X		
													X	