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COMITE EXECUTIF
DU FONDS MULTILATERAL AUX FINS
D'APPLICATION DU PROTOCOLE DE MONTREAL
Cinquante et unième réunion
Montréal, 19 – 23 mars 2007

Addendum

PROPOSITION DE PROJET : RÉPUBLIQUE POPULAIRE DE CHINE

Le présent document comprend les observations et la recommandation du Secrétariat du Fonds pour la proposition de projet suivante :

Aérosols

• Élimination de la consommation de CFC dans le secteur des aérosols pharmaceutiques (programme biennal 2007-2008)	Banque mondiale

FICHE D'ÉVALUATION DE PROJET – PROJETS PLURIANNUELS
RÉPUBLIQUE POPULAIRE DE CHINE

TITRE DU PROJET	AGENCE BILATERALE/AGENCE D'EXÉCUTION
Élimination de la consommation de CFC dans le secteur des aérosols pharmaceutiques (programme biennal 2007-2008)	Banque mondiale

ORGANISME NATIONAL DE COORDINATION :	Administration nationale de protection de l'environnement

DERNIERES DONNEES DECLAREES SUR LA CONSOMMATION A ELIMINER GRACE AU PROJET

A : DONNEES RELATIVES A L'ARTICLE 7 (TONNES PAO, 2005, EN DATE DE FÉVRIER 2007)

CFC	13 321,7		

B : DONNÉES SECTORIELLES DU PROGRAMME DE PAYS (TONNES PAO, 2006, EN DATE DE SEPTEMBRE 2006)

SAO	Aérosols	Mousses	Réfrigération	SAO	Solvants	Agents de transformation	Fumigènes
CFC-11	112,725						
CFC-12	372,366						

Consommation restante de CFC admissible au financement (tonnes PAO)	

PLAN D'ACTIVITÉS DE L'ANNÉE EN COURS : Financement total : 13,63 millions $ US : Élimination totale : 386,0 tonnes PAO

DONNÉES RELATIVES AU PROJET		**2006**	**2007**	**2008**	**2009**	**2010**	**Total**
CFC (tonnes PAO)	Limites du Protocole de Montréal	4 471,5	**4 471,5**	4 471,5	4 471,5	À dét.	
	Consommation maximale pour l'année	8 385,57	**8 385,57**	8 385,57	8 385,57	À dét.	
	Élimination annuelle des projets en cours	485,1	**485,1**	0	0	0	485,1
	Élimination annuelle nouvellement ciblée						
	Élimination annuelle non financée						
CONSOMMATION TOTALE DE SAO À ÉLIMINER		485,1	**485,1**	0	0	0	485,1
Consommation totale de SAO à introduire (HCFC)							
Coûts finals du projet ($ US) :							
Financement pour l'agence principale: Banque mondiale		0	**8 793 520**	0	3 509 474	0	12 302 994
Financement total du projet		0	**8 793 520**	0	3 509 474	0	12 302 994
Coûts d'appui finals ($US) :							
Coûts d'appui pour l'agence principale : Banque mondiale		0	**659 514**	0	236 211	0	922 725
Total des coûts d'appui		0	**659 514**	0	236 211	0	922 725
COÛT TOTAL POUR LE FONDS MULTILATÉRAL ($US)		0	**9 453 034**	0	3 772 685	0	13 225 719
Rapport coût-efficacité final du projet ($US $ US/kg)							

DEMANDE DE FINANCEMENT : Approbation du financement pour la première tranche (2007) (comme ci-dessus).

RECOMMANDATION DU SECRÉTARIAT	À venir

DESCRIPTION DU PROJET

1. Au nom du gouvernement de la République populaire de Chine (Chine), la Banque mondiale a présenté de nouveau pour examen par le Comité exécutif à sa 51e réunion un plan sectoriel visant l'élimination de la consommation de CFC dans le secteur des aérosols pharmaceutiques de la Chine (Plan pour les aérosols pharmaceutiques), à un coût total de 12 302 994 $ US pour le Fonds multilatéral, plus des coûts d'appui d'agence de 922 725 $ US.

Données générales

2. À sa 50e réunion, le Comité exécutif avait examiné pour la première fois le plan pour les aérosols pharmaceutiques (UNEP/OzL.Pro/ExCom/50/28, paragraphes 1 à 35). Le coût du plan présenté était de 15 926 838 $US, plus des coûts d'appui d'agence de 1 194 513 $ US pour la Banque mondiale.

3. En présentant la proposition de projet au Comité exécutif, le Secrétariat a souligné les principaux problèmes exigeant un examen, notamment l'aide à certaines entreprises établies après la date de cessation du 25 juillet 1995, le financement d'autres entreprises qui n'avaient pas déclaré de consommation de référence de CFC, la sélection du HFC-134a au lieu des aérosols de la catégorie des hydrocarbures (HC) comme produit de remplacement du CFC comme propulseur, et le rapport coût-efficacité global du projet qui, à 32,83 $ US/kg, était plus de sept fois le seuil pour le secteur des aérosols (4,40 $ US/kg). Le Secrétariat a aussi informé le Comité exécutif que la Banque mondiale avait soutenu qu'on ne devrait pas tenir compte de la date de cessation de 1995 parce que la technologie de remplacement n'était pas disponible en Chine à ce moment, et aussi qu'on ne devrait pas non plus tenir compte du seuil de coût-efficacité pour le secteur des aérosols.

4. Par la suite, la Banque mondiale a indiqué que le plan avait exigé un travail supplémentaire, et demandé que le projet soit retiré et présenté de nouveau à la 51e réunion du Comité exécutif.

Résumé du projet

5. La plan révisé pour les aérosols pharmaceutiques est basé sur le remplacement du CFC par du HFC-134a à utiliser comme propulseur dans 41 produits pharmaceutiques en aérosol (28 produits en aérosol pour la peau et 13 produits en aérosol pour cavité), fabriqués par 23 entreprises admissibles.

6. Le coût total du plan pour les aérosols pharmaceutiques est basé sur les coûts suivants :

Élément	Coût unitaire ($ US)	Unités	Coût total ($ US)
Assistance technique	1 100 000	1	1 100 000
Produits de remplacement pour examen	43 750	41	1 793 750
Dossier technique des aérosols pour la peau	75 000	28	2 100 000
Dossier technique des aérosols pour cavité	93 750	13	1 218 750
Modifications de l'usine (circuit des aérosols pour la peau)	63 750	13	828 750
Modifications de l'usine (circuit des aérosols pour cavité)	38 750	7	271 250

Élément	Coût unitaire ($ US)	Unités	Coût total ($ US)
Validation de la production (par circuit de production)	37 500	20	750 000
Programme de formation (par circuit de production)	17 500	20	350 000
Coût d'exécution	3 509 474	1	3 509 474
Imprévus	841 250	1	841 250
Ajustement (propriété étrangère)	(460 223)	1	(460 223)
Total			12 303 001

7. Une copie de la proposition de projet révisée est jointe au présent document.

OBSERVATIONS ET RECOMMANDATION DU SECRÉTARIAT

OBSERVATIONS

8. La proposition de projet comprenait d'autres renseignements sur l'admissibilité des entreprises ayant une consommation de CFC faible ou nulle. Elle couvre le droit de propriété des herbes médicinales traditionnelles, les ingrédients des médicaments à base chimique, les procédures requises lors du changement de propulseur dans un médicament enregistré, l'utilisation d'autres mécanismes de libération ou de propulseurs de remplacement, et une description détaillée du procédé de production (y compris les données de référence pour les équipements) de 17 entreprises.

9. Le plan pour les aérosols pharmaceutiques est basé sur la même technologie et les mêmes éléments de coût que le plan présenté à la 50e réunion. Il a seulement exclu onze entreprises dont la consommation de CFC était faible ou nulle et qui n'avaient pu présenter un plan de production pour 2007, ce qui a réduit la demande de financement de 3 002 350 $ US. Les problèmes indiqués dans la proposition présentée à la 50e réunion sont donc toujours actuels. Ces problèmes et les réponses reçues de la Banque mondiale sont présentés ci-dessous.

Admissibilité au financement

Décision 17/7

10. Un financement de 704 000 $ US est demandé pour la reconversion de deux entreprises établies après la date de cessation du 25 juillet 1995 (Tableau 1). Si l'on se rapporte au libellé de la décision 17/7, c'est-à-dire (« étant donné l'évolution des technologies, aucun projet de conversion visant à reconvertir une capacité à base de SAO installée après le 25 juillet 1995 »), ces entreprises sont inadmissibles for financement :

Tableau 1
Entreprises établies après le 25 juillet 1995

Nom de l'entreprise	Circuits	CFC (kg)	N° de produit
17. Shandong Bencao Pharmaceutical	1	428	A26 A38
26. Huayi Pharmaceutical	1	380	A41
Total	**2**	**808**	

11. Quant à la date de cessation du financement, la réponse de la Banque mondiale a été :

a) La décision 17/7 ne devrait s'appliquer qu'aux secteurs des mousses et de la réfrigération ainsi qu'au secteur général des aérosols, et non au secteur des aérosols pharmaceutiques. Pour cette raison, le Comité exécutif n'avait pas approuvé un seul projet pour les aérosols pharmaceutiques avant 1995;

b) Selon la Loi sur l'administration des médicaments en Chine, il est obligatoire de présenter à l'organisme de réglementation toute modification à un médicament approuvé avant de commencer à le produire. Obtenir l'approbation de l'organisme de réglementation prend habituellement de trois à quatre ans; la recherche-développement des applications des aérosols pharmaceutiques approuvées en juillet 1999 doit donc avoir commencé au moins en 1995;

c) Les technologies de remplacement n'étaient pas disponibles en 1995 dans le secteur pharmaceutique en Chine. En fait, les aérosols pharmaceutiques étaient précisément exclus des CFC interdits dans les règlements de 1997 de la Chine visant les SAO.

12. Le Secrétariat désire toutefois prendre note que :

a) Des technologies de remplacement des CFC pour les aérosols pharmaceutiques étaient disponibles avant 1995. Par exemple, en raison des interdictions imposées par le gouvernement des États-Unis quant à l'utilisation de CFC dans les aérosols à compter du 31 mars 1978, l'industrie des aérosols (y compris les aérosols pharmaceutiques) est passée à une technologie aux hydrocarbures. Aucun problème n'a été associé à l'utilisation de propulseurs à base d'hydrocarbures, et les formulateurs de produits pharmaceutiques ont facilement commencé à les utiliser. Au moment de la transition vers les HC, le HFC-134a n'était pas disponible sur le marché;

b) Le Comité exécutif a approuvé cinq projets d'investissement en vue de l'élimination des CFC utilisés dans la production d'aérosols pharmaceutiques dans trois pays. Le problème de la disponibilité des technologies de remplacement avant 1995 n'a été soulevé dans aucun projet;

c) Le spécialiste de l'industrie qui a aidé le Secrétariat à examiner la proposition a développé plusieurs aérosols pharmaceutiques pour des propulseurs à base d'hydrocarbures afin de servir d'agents de remplissage dans certains pays (Argentine, Colombie, et Israël). Des produits similaires servent au remplissage dans plusieurs autres pays (Algérie, Australie, Brésil, Mexique, Afrique du Sud, et Tunisie).

Entreprises sans aucune consommation de CFC

13. Deux autres entreprises faisant partie du plan pour les aérosols pharmaceutiques et établies avant 25 juillet 1995 avaient déclaré ni consommation de référence de CFC, ni consommation de CFC, tel que l'indique le tableau 2 ci-dessous. Ces entreprises ne sont donc pas admissibles au financement.

Tableau 2

Entreprises sans consommation de référence de CFC, ni consommation de CFC*

Nom de l'entreprise	N° du produit
2. Beijing Haiderun Pharmaceutical	A25, A28, A30
8. Xinyi Pharmaceutical General Factory (Shanghai Pharmaceutical Group)	A06, A24, A35

(*) Tel que l'indique le Tableau 2-3 de la proposition de projet.

14. La Banque mondiale a déclaré que même si les deux entreprises n'avaient déclaré aucune consommation de référence de CFC, cela ne signifiait pas qu'elles ont abandonné la production d'aérosols, car la production dépend de la demande du marché ainsi que des ententes de production. Sur la base du dernier examen de la proposition, les deux entreprises avaient déclaré avoir produit une petite quantité en 2006. Afin de conserver ses droits de production, le gouvernement de la Chine demande un financement associé au dépistage et à l'enregistrement.

Conclusion

15. Selon l'analyse ci-dessus, le Secrétariat conclut que les 17 entreprises indiquées au tableau 3 ci-dessous sont admissibles au financement puisqu'elles étaient établies avant le 25 juillet 1995, qu'elles ont une consommation de référence de CFC, et qu'elles utilisent actuellement des CFC.

Tableau 3

Liste des entreprises admissibles au financement

Nom de l'entreprise	Circuits	CFC (kg)*	Produit pour la peau	Produit pour cavité
1. Wuxi Shanhe Group No. 1 Pharmaceutical	2	823	A10, A23	
5. Guiyang Dechangxiang Pharmaceutical	1	13		A07
7. Beijing Tongrentang Technology Development	1	14	A35	A21, A34
9. Fujian Nanshaolin Pharmaceutical	1	10 684	A22, A33	
11. Penglai Nuokang Pharmaceutical	1	3 491	A23	
13. Hubei Nanyang Pharmaceutical	1	34 575	A29	
14. Shenyang Jingcheng Pharmaceutical	1	28 859	A17	
16. Pharmaceutical Factory of Hunan Bencao Pharmacy	1	1 300	A16	
18. Shandong Jewim Pharmaceutical BlueBox	1	12 080	A23	A38, A39
19. Suizhou Pharmaceutical (Wuhan Jianmin Group)	1	13	A14, A19	
20. Guizhou Antai Pharmaceutical	1	20 827	A02, A08	
21. Guizhou Xinyi Pharmaceutical Corporation	1	229	A13	
23. Xinjiang Biochemistry Pharmaceutical	1	2 592		A05
24. Yunnan Baiyao Group Corporation	1	273 333	A45	

Nom de l'entreprise	Circuits	CFC (kg)*	Produit pour la peau	Produit pour cavité
27. Zhanjiang Xintongde Pharmaceutical	1	29 397	A11, A22 A23, A27, A32	A38, A40
29. Guizhou Hongyu Pharmaceutical	1	1 231	A36	A01
32. Shanghai Yishengyuan Pharmaceutical	1	112	A11, A23	
Total	**17**	**419 573**		

* Consommation admissible totale de CFC après déduction de 30 et 50 pour cent de la propriété étrangère des entreprises 13 et 14 respectivement.

16. La Banque mondiale juge que les quatre entreprises suivantes sont aussi admissibles au financement : Beijing Haiderun Pharmaceutical (n°2) Xinyi Pharmaceutical General Plant, Shanghai Pharmaceutical Group (n°8), Shandong Bencao Pharmaceutical (n° 17), et Huayi Pharmaceutical (n°26).

Sélection du propulseur de remplacement

17. Sur la base d'une analyse des propriétés du méthoxyméthane, des HC et du HFC-134a comme propulseurs de remplacement et d'un examen de la documentation technique, le plan pour les aérosols pharmaceutiques a provisoirement conclu que :

a) Le HFC-134a, le HFA-227, le méthoxyméthane, les HC et le gaz comprimé (comme le dioxyde de carbone) sont tous considérés comme des propulseurs de remplacement possibles. Chaque propulseur possède des propriétés physico-chimiques tout à fait uniques et chaque application d'aérosol a un procédé de production différent et une formulation différente. L'essai portant sur l'évaluation générale des produits de remplacement est effectué dans le but de sélectionner le propulseur de remplacement optimal du point de vue médical;

b) Le prix des propulseurs n'est pas le seul facteur qui détermine la sélection d'un produit de remplacement. La sélection du propulseur de remplacement doit aussi tenir compte du médicament, de son efficacité et de son effet sur la sécurité, de sa compatibilité avec tous les ingrédients, des modifications à la technique de production, des équipements et des matières premières, ainsi que de la sécurité et de l'efficacité;

c) La conversion à un propulseur au méthoxyméthane ou aux hydrocarbures est techniquement plus difficile que la conversion au HFC-134a, qui a des propriétés similaires à celles des CFC. Il faudra un investissement substantiel de la part de l'entreprise et, en certains cas, le déplacement du circuit de production, afin de respecter les exigences en matière de sécurité. La conversion au HFA-134a exigera des modifications mineures aux circuits de production existants, et sa mise en oeuvre sera donc moins chère et plus rapide. De plus, le HFC-134a est largement utilisé comme propulseur d'aérosol dans d'autres pays;

d) Bien que le méthoxyméthane et les hydrocarbures soient moins chers que le HFC-134a, les économies associées à leur utilisation seront petites en raison de la plus petite quantité de propulseur utilisé dans les aérosols pharmaceutiques comparativement à d'autres produits en aérosol;

e) Il n'existe aucune expérience à l'international pour la conversion des aérosols à base de CFC pour la médecine chinoise traditionnelle. Certaines entreprises avaient mentionné que, sur la base d'essais préliminaires, les HC n'étaient pas compatibles avec leurs produits en aérosol;

f) Le plan pour les aérosols pharmaceutiques propose donc la reconversion de toutes les entreprises au propulseur HFC-134a, à titre d'option la moins dispendieuse pour le maintien de la qualité du produit.

18. En ce qui a trait à la sélection du HFC-134a comme propulseur de remplacement, le Secrétariat prend note de ce qui suit :

a) Bien que le HFC-134a ait été sélectionné comme propulseur de remplacement pour les aérosols pharmaceutiques, la proposition indique que « actuellement, en raison du peu de données d'essai, les fabricants chinois de produits pharmaceutiques ne sont pas en mesure de décider quel est le meilleur produit de remplacement pour leurs produits en aérosol, et en particulier ceux qui fabriquent des produits en aérosol pour la médecine traditionnelle chinoise ». On indique aussi que « du financement est demandé afin de permettre à ces entreprises d'évaluer les produits de remplacement possibles. Le but du dépistage est de déterminer le meilleur produit de remplacement ou autre système de libération pour leurs produits pharmaceutiques en aérosol »;

b) Les spécialistes auxquels le Secrétariat a recours indiquent que tous les produits pharmaceutiques en aérosol pourraient être convertis à l'utilisation d'hydrocarbures comme propulseurs. Cette conclusion, qui a été contestée par la Banque mondiale, est basée sur la preuve documentée en matière d'utilisation du propulseur avec HC dans les produits pharmaceutiques en aérosol disponibles partout dans le monde pour la peau ou pour cavité,[1] et sur l'expérience du Secrétariat avec des projets de conversion des aérosols pharmaceutiques financés par le Fonds multilatéral dans au moins trois pays visés par l'Article 5, où

[1] Ces produits comptent entre autres le vasodilatateur au nitrate pour le soulagement rapide de l'*angor pectoris* (angine de poitrine) attribuable à une maladie de l'artère coronaire et pulvérisé sur ou sous la langue; les mousses topiques en aérosol avec acétate d'hydrocortisone et hydrochlorure de pramoxine pour usage anal; les corticostéroïdes topiques utilisés comme agents anti-inflammatoires et antiprurigineux; plusieurs aérosols antifongiques pour le traitement du *tinea pedis* (pied d'athlète), du *tinea cruris* (eczéma marginé), et du *tina corporis* attribuable à *T. rubrum*, *T. mentagrophytes* et *E. flocossum*, sauf dans les ongles et les cheveux; le valérate de bétaméthasone pour le traitement des dermatoses du cuir chevelu qui réagissent aux corticostéroïdes; le bandage liquide anesthésique en pulvérisation pour premiers soins; la formulation en aérosol contenant du dipropionate de béclométhasone; et la pulvérisation anesthésique topique contenant de la benzocaïne comme ingrédient actif).

plusieurs aérosols pharmaceutiques sont actuellement produits avec des hydrocarbures comme propulseurs;[2]

c) Les HC sont de meilleurs propulseurs que les CFC ou le HFC-134a, en raison surtout de leur faible poids moléculaire. Par exemple, les mêmes produits en aérosol qui utilisent 8 pour cent (en poids) de CFC n'utiliseraient que 4 pour cent de HC ou 9 pour cent de HFC-134a. Aussi, les produits pharmaceutiques en aérosol à l'eau ne peuvent être reformulés pour utiliser du HFC-134a comme propulseur, parce que la pression interne serait trop élevée dans le vaporisateur et que, en raison de sa densité (1,2 g/ml), le propulseur tombe au fond de la bombe et endommage ainsi le produit;

d) De plus, il n'existe aucune preuve probante pouvant suggérer que les médicaments de la médecine chinoise traditionnelle sont compatibles avec les CFC mais non avec les hydrocarbures comme propulseurs. Il n'a jamais été fait mention que les HC de catégorie aérosol ait fait l'objet de réactions chimiques avec les milliers d'ingrédients aérosols actuellement produits, y compris les médicaments de nature chimique, les herbes médicinales, les extraits de plantes marines, d'animaux ou de poissons, d'autres composés actifs du point de vue pharmaceutique, et les produits alimentaires en aérosol;

e) Sauf pour les inhalateurs à doseur, il est déjà interdit d'employer du HFC-134a comme propulseur dans la plupart des applications d'aérosols au Canada, dans plusieurs pays européens et aux États-Unis.[3]

Modifications apportées au circuit de production

19. Le coût d'investissement pour le remplacement des propulseurs à base de CFC dans 20 circuits de production (13 pour les aérosols pour la peau et 7 pour les aérosols pour cavité) est basé sur les hypothèses suivantes :

a) 63 750 $ US pour chaque circuit automatique de production de produits en aérosol pour la peau converti au HFC-134a comme propulseur;

b) 38 750 $ US pour chaque circuit semi-automatique de production de produits en aérosol pour cavité converti au HFC-134a comme propulseur;

c) 360 000 $ US pour chaque circuit de production, peu importe le type de produit

[2] Ces produits comprennent : un analgésique et un relaxant musculaire qui utilise du salicylate de méthyle et des produits chimiques connexes; un anesthésique local avec un produit chimique comme la lignocaïne; des produits pharmaceutiques pour le soulagement et la guérison des brûlures y compris les antiseptiques et les anesthésiques; le povidone-iode (antifongique et antiseptique à large spectre); un assainisseur d'air antiseptique contenant du BKC; un désodorisant corporel médicinal; et des pansements en aérosol qui contiennent du cétrimide; des fournitures dentaires contenant de la lidocaïne et d'autres produits chimiques pour arrêter le saignement; et une pulvérisation d'alcool à friction pour massage contenant de l'alcool isopropylique.

[3] Aux États-Unis, le HFC-134a est accepté comme propulseur dans des applications où l'on doit tenir compte de l'inflammabilité et qu'aucune autre solution en nature n'est disponible ou applicable.

en aérosol (peau ou cavité), converti aux HC. Ce coût comprend 190 000 $ US pour le remplacement du circuit de production existant.

20. Si l'on se base sur les hypothèses ci-dessus, le coût d'investissement total estimatif pour la conversion au HFC-134a comme propulseur est de 1 100 000 $ US, et de 7 200 000 $ US pour la conversion aux HC comme propulseur. Un montant supplémentaire estimatif de 3 509 474 $ US a été déterminé pour les coûts d'exécution associés à l'utilisation du HFC-134a comme propulseur sur une période de deux ans (si une période de quatre ans avait été envisagée, les coûts d'exécution auraient été d'environ 6,63 millions $ US).

21. Le Secrétariat prend note de ce qui suit :

a) L'analyse des coûts ne mentionne pas qu'il n'est pas nécessaire de remplacer la totalité du circuit de production lorsqu'on remplace les CFC par des HC comme propulseurs.[4] Les seules pièces d'équipement qui pourraient devoir être fournies sont un gazéifieur, des pompes, des capteurs de gaz, des sertisseuses, et des appareils de ventilation. Le coût total des équipements requis pour la conversion, y compris les coûts d'expédition, d'installation, de formation (au niveau de l'usine) et des imprévus (à 10 pour cent), a été évalué à 2 460 000 $ US;

b) Le remplacement de tout le circuit de production au coût de 190 000 $ US tel que le propose le projet exigerait un accroissement de la capacité de production de tous les circuits de production existants. Par exemple, le prix, aux États-Unis, d'un nouveau circuit de production des aérosols (40 bombes/min) comprenant une table de rotation avec deux produits de remplissage, une sertisseuse à vide, un chargeur de propulseur et un convoyeur, serait actuellement de 100 000 $ US. Cette machine pourrait produire 5 millions d'aérosols par an au cours d'une période de production normalisée de 2 080 heures par année;

c) La quantité annuelle de HC qui serait requise par cinq entreprises est minime (de 8 à 143 kg par an). Pour cinq autres entreprises, la quantité annuelle de HC pourrait être stockée dans deux ou trois cylindres d'une tonne (citernes mobiles horizontales d'environ 800 mm de diamètre et 2,4 m de longueur, contenant environ 375 kg de mélanges de HP et qui devront être remplies de nouveau une ou deux fois par an). Pour les six entreprises restantes, leur réservoir de CFC en vrac actuels pourraient être utilisés pour les HC.[5] Pour éviter d'augmenter la taille des réservoirs de CFC pour compenser pour la plus faible densité des HC, les réservoirs devraient être remplis plus fréquemment (tous les quatre mois au lieu de tous les six mois comme actuellement);

d) De plus, l'utilisation de propulseurs à base d'hydrocarbures permettrait une

[4] Il n'est pas nécessaire de remplacer l'agent de remplissage du produit, la sertisseuse ou le gazéificateur lorsqu'on passe des CFC aux HC comme propulseurs. Le remplacement du gazéifieur (et de la sertisseuse pour les productions importantes) pourrait être justifié si le but était de réduire les fuites de HC comme propulseur, de réduire le temps d'arrêt de la production, et d'améliorer la précision de l'injection.

[5] Les réservoirs de CFC-11 en vrac exigeraient d'être nettoyés au jet de sable et remplis avec du isobutane ou de l'azote, après quoi on pourrait sceller le trou de visite de réservoir et le remplir de HC.

économie d'exploitation de 710 000 $ US pour une période de deux ans, ou presque 1,3 million $ US si l'on envisage une période de quatre ans (cette analyse est basée sur le prix de 2,20 $ US/kg pour les CFC comme propulseur et de 1,56 $ US/kg pour les HC comme propulseur, et une réduction de 37,5 pour cent par poids de la quantité des HC comparativement aux CFC). Comparativement, l'utilisation du HFC-134a entraînerait des coûts d'exécution de 3 536 824 $ US pour une période de deux ans;

e) De plus, il y a en Chine deux usines dotées d'équipements d'hydrogénation et de purification qui permettent de produire des HC de catégorie aérosol.

22. Le Secrétariat a aussi pris note que, si le HFC-134a devait être sélectionné comme propulseur, il ne serait pas nécessaire de remplacer aucun équipement dans les circuits de production existants utilisant du CFC comme propulseur. Certains fournisseurs d'équipements suggèrent d'utiliser des types particuliers de joints de caoutchouc pour le gazéifieur, tel que le recommandent les producteurs de HFC-134a, mais ce coût d'investissement ne correspondrait pas au montant de 63 750 $ US demandé pour chaque circuit de production de produits en aérosols pour la peau et de 38 750 $ US pour chaque circuit de production de produits en aérosols pour cavité convertis au HFC-134a comme propulseur.

23. En réponse, la Banque mondiale a fait remarquer que :

a) Il y a plusieurs différences entre les types et les modèles d'équipements pour les circuits de production d'aérosols pharmaceutiques en Chine. Étant donné les avancées en matière de machines pour la fabrication de produits pharmaceutiques, il ne serait pas pratique d'acheter les équipements bas de gamme requis pour remplacer la combinaison actuelle de circuits de production automatiques et semi-automatiques, principalement parce que le principe du programme est de maintenir l'échelle initiale et le niveau initial de production sans accroître ou réduire la capacité de production;

b) Le coût des modifications devrait être basé sur les circuits de production, plutôt que sur la production de base, parce que la production dépend de la demande du marché et pourrait s'accroître plus tard. Les circuits de production existants peuvent produire de 500 à 5000 bombes aérosol par heure;

c) En ce qui a trait aux économies de coût représentées par la technologie HC, la quantité de HC utilisée pour chaque aérosol doit être déterminée en fonction des résultats de l'évaluation générale du produit de remplacement.

Problèmes en rapport avec l'assistance technique

24. Lors de l'examen des coûts unitaires proposés dans le plan pour les aérosols pharmaceutiques, le Secrétariat a pris note que :

a) Un montant de 1,1 million $ US a été demandé pour des activités d'assistance technique : ateliers, programmes de formation et de sensibilisation du public,

consultants, tournées d'études, et autres activités non précisées. Un montant supplémentaire de 6 212 250 $ US a été demandé pour les activités suivantes : 1 793 500 $ US pour des produits de remplacement pour examen; 3 318 750 $ US pour la préparation de dossiers techniques pour l'enregistrement; 750 000 $ US pour la validation de la production; et 350 000 $ US pour la formation du personnel. En bon nombre de cas, des montants seraient comptés deux fois parce que des activités similaires sont demandées plus d'une fois (évaluations toxicologiques et essais, études de la qualité, formation du personnel de vente);

b) Le financement demandé pour les produits de remplacement pour examen, pour la préparation des dossiers techniques et pour la validation de la production n'a pas tenu compte des quantités fabriquées de chaque produit. Par exemple, le coût total associé à ces éléments pour l'entreprise ayant une capacité de production de 100 bombes aérosol par an est de 312 500 $ US, tandis que le coût total pour une entreprise produisant plus de 5 millions de bombes par an est de 156 250 $ US. Si les deux entreprises ont fabriqué des aérosols similaires, le coût par bombe de ces éléments seulement serait de 3 125,00 $ US et 0,03 $ US, respectivement;

c) Seulement 21 types différents d'aérosols pharmaceutiques sont produits en Chine (certains produits sont fabriqués par plus d'une entreprise). Toutefois, du financement pour des produits de remplacement pour examen et pour la préparation des dossiers techniques est demandé pour 41 produits en aérosol. Cela constituerait un double comptage;

d) Les entreprises pharmaceutiques qui fabriquent le même type de produit pourraient partager les données de développement (données de formulation, données d'emballage, méthodologie de mélange du concentré, méthodes et résultats d'essai des médicaments, données sur la stabilité du produit), ce qui empêcherait la duplication et la perte de temps dans plusieurs secteurs de coût. Les données partagées pourraient alors servir à combler bon nombre d'exigences du formulaire d'enregistrement du produit;

e) Un chimiste supérieur possédant une grande expérience en développement de formulations d'aérosols pharmaceutiques pourrait développer des formulations quantitatives pour remplacer les CFC comme propulseurs dans tous les aérosols, y compris dans le plan pour les aérosols pharmaceutiques; la méthode de mélange du concentré; les données sur la stabilité limitées aux essais physiques des formules et la compatibilité des distributeurs (comme l'absence de corrosion des bombes aérosol ou le fonctionnement continu satisfaisant du distributeur de l'aérosol); les spécifications de la bombe et du distributeur; et les notes relatives à l'emballage;

f) De l'assistance technique peut être obtenue auprès du Spray and Aerosol Research Centre à Shanghaï, en Chine. Le directeur général du centre a présenté des centaines d'exposés lors de séminaires et de symposiums nationaux et

internationaux, et publié plusieurs livres en chinois et en anglais (Aerosol Technology, Aerosol Propellant Handbook; Aerosol Valve and Spray Pump Handbook; Design of Aerosols and its Formulation Technology).

25. En réponse aux questions ci-dessus, la Banque mondiale a indiqué que :

a) La formation dans le cadre du programme d'assistance technique comprend la protection de la couche d'ozone; les procédures de mise en oeuvre et les exigences du programme d'élimination des SAO soutenu par le Fonds; les directives pour l'achat, le financement, et l'établissement de rapports; les exigences en matière de vérification; et les politiques. Toutefois, la formation dispensée à chaque entreprise comprend la présentation de produits de remplacement ou de techniques de remplacement des circuits de production;

b) Seulement cinq produits sont fabriqués par plus d'une entreprise. Lorsqu'une application est produite par plusieurs entreprises, le procédé de production est souvent différent, et le dossier technique doit donc être traité séparément. En outre, des problèmes de protection du caractère confidentiel des données sur les entreprises peuvent survenir lors de la conversion, et le partage des données n'est donc pas envisagé;

c) Puisqu'une évaluation générale et des essais des produits de remplacement sont requis par la loi lors de leur enregistrement, les procédures nécessaires pour le programme de conversion aux CFC sont indépendantes du nombre d'aérosols fabriqués; et

d) En raison de la spécificité des médicaments, le coût des activités techniques mises en oeuvres pour répondre aux exigences juridiques est très élevé, et il n'y a aucune relation directe avec le niveau de production des aérosols pharmaceutiques ou la consommation de CFC.

Rationalisation industrielle et rapport coût-efficacité

26. Lors de l'examen du plan pour les aérosols pharmaceutiques, le Secrétariat a élaboré un tableau indicatif associant chaque coût unitaire proposé dans le plan à chacune des 17 entreprises admissibles (Tableau 4 joint). Dans cette analyse, la totalité des demandes d'assistance technique et les coûts d'exécution ont été divisés par la quantité totale de CFC à éliminer (465,355 tonnes PAO) et calculés au prorata entre les 17 entreprises admissibles au financement sur la base de leur consommation totale de CFC.

27. En se basant sur cette analyse, le Secrétariat est arrivé aux conclusions suivantes :

a) La consommation de CFC de cinq des entreprises est très petite (de 13 à 229 kg PAO par année). La consommation totale de CFC d'une des entreprises (273,3 tonnes PAO) représente 65,1 pour cent de la consommation totale admissible du secteur;

b) Le rapport coût-efficacité (CE) global du projet est de 27,23 $ US $ US/kg (sur la base des 17 entreprises admissibles), ce qui est plus de 6 fois le seuil de CE (4,40 $ US/kg) établi pour le secteur des aérosols par le Comité exécutif à sa 16e réunion;

c) L'entreprise la plus efficace au niveau coût-efficacité est le plus important producteur d'aérosols pharmaceutiques en Chine (usine n° 24), avec un CE de 12,15 $ US/kg. Du coût total demandé pour la reconversion de cette entreprise (3 321 869 $ US), le montant de 2 065 780 $ US représente les coûts d'exécution associés à l'utilisation du HFC-134a comme propulseur;

d) Les cinq entreprises « les moins efficaces au niveau du coût-efficacité » ont des valeurs de CE entre 1 152,03 $ US/kg et 40 279,05 $ US/kg;

e) Contrairement aux pratiques établies en matière de formulation de plusieurs des plans sectoriels d'élimination nationaux approuvés pour la Chine et tous les autres pays visés par l'Article 5, on n'a pas tenu compte de la rationalisation industrielle dans le plan pour les aérosols pharmaceutiques.

28. Le Secrétariat prend aussi note que les cinq projets d'aérosols pharmaceutiques qui ont été financés par le Fonds multilatéral avaient un CE égal ou inférieur au seuil de CE de 4,40 $ US/kg pour le secteur des aérosols.

29. En réponse à l'analyse du Secrétariat, la Banque mondiale a indiqué que :

a) Les petits niveaux de production de certaines des entreprises ne reflétaient pas l'importance du produit. La faible consommation de CFC lors de la fabrication de 12 aérosols pharmaceutiques était en rapport avec la demande du marché et la demande clinique, ainsi qu'avec la fréquence d'utilisation et le prix, ce qui faisait varier considérablement la quantité produite. De plus, les données présentées dans la proposition étaient basées sur la production réelle des entreprises, laquelle pourrait être augmentée lorsque les conditions prescriptives de la loi et la capacité de production auront été obtenues;

b) Le CE du projet est faible. Toutefois, comme ce secteur est nouveau, la Banque n'était pas d'accord que le seuil de 4,40 $ US/kg pourrait s'appliquer au secteur général des aérosols, en particulier parce que des éléments de coût non pertinents au secteur général des aérosols sont nécessaires pour les aérosols pharmaceutiques. Le Comité exécutif n'a pas encore discuté, ni décidé, de politiques et de lignes directrices pour le secteur des aérosols pharmaceutiques;

c) La consommation de CFC par unité dans les aérosols pharmaceutiques est de beaucoup inférieure à celle du secteur général des aérosols (10 à 20 pour cent de ce qui est contenu dans les aérosols du secteur général). Donc, le coût de conversion des aérosols pharmaceutiques par kilogramme de CFC éliminé serait beaucoup plus élevé pour les aérosols du secteur général;

d) Bien que les tests de remplacement pour l'évaluation générale et les essais pour l'enregistrement sont les points clés visant à assurer l'élimination des CFC, ils se situent plutôt dans la portée des activités techniques. En soustrayant ces deux coûts et le coût de l'utilisation d'un substitut (à 5 593 869 $ US), la valeur CE globale est de 6,45 $ US à 6,71 $ US/kg;

e) Sauf pour une entreprise, les 20 entreprises restantes utilisent seulement un circuit de production pour fabriquer plusieurs produits. Les produits d'une entreprise sont, dans la plupart des cas, différents de ceux des autres entreprises. En outre, des problèmes en rapport avec la protection du caractère confidentiel des données sur les entreprises et les droits de propriété surviendraient lors de la reconversion, et la rationalisation industrielle n'est dont pas envisagée dans le secteur pharmaceutique.

Niveau de financement proposé

30. Selon les calculs du Secrétariat, le coût d'investissement total pour la reconversion au HC comme propulseur de toutes les entreprises admissibles serait de 2 460 000 $ US; les économies (calculées pour une période de deux ans au lieu de la période de quatre ans utilisée pour tous les projets d'aérosols) serait de 710 000 $ US (comparativement à 5 340 501 $ US pour l'utilisation du HFC-134a comme propulseur), avec un surcoût net de 1 750 000 $ US pour une valeur CE de 4,17 $ US/kg. Le Secrétariat recommande toutefois d'appliquer le seuil CE du secteur des aérosols à la consommation admissible de CFC, plus un autre 20 pour cent pour les activités d'assistance technique de la totalité du secteur des aérosols pharmaceutiques (sauf le sous-secteur des inhalateurs à doseur). Ainsi, le niveau de financement serait de 2 221 500 $ US. Ce montant ne comprend pas les coûts associés à l'évaluation générale, à l'enregistrement des médicaments et aux dossiers techniques pour lesquels la Banque mondiale demande 5 862 250 $ US; le Secrétariat ne peut indiquer le niveau de financement pour ces coûts, parce que des coûts similaires n'ont pas été demandés dans aucun des projets pharmaceutiques approuvés par le Comité exécutif.

31. La Banque mondiale a répondu que, bien que le projet ne soit pas aussi efficace quant aux coûts que le Secrétariat le souhaiterait, tous les coûts sont des surcoûts et donc admissibles, et ils devraient être considérés comme tels. Elle a réitéré que le secteur des aérosols pharmaceutiques comprend des éléments qui ne sont pas pertinents au secteur général des aérosols, et que le CE pour ce secteur ne devrait donc pas être appliqué. Enfin, la date de cessation de 1995 ne devrait pas être appliquée, du fait que la technologie n'était pas disponible en Chine à ce moment.

RECOMMANDATION

32. Le Comité exécutif peut souhaiter tenir compte du plan pour les aérosols pharmaceutiques à la lumière des observations ci-dessus.

Tableau 4

Analyse par le Secrétariat du Fonds du coût du plan pour les aérosols pharmaceutiques présentée pour toutes les entreprises admissibles

Nom de l'entreprise	CFC admissibles	TAS	Évaluation	Dossier	Mod. usine	Validation	Formation	Coût d'exécution	Imprévus	Coût total	CE
1. Wuxi Shanhe Group No. 1 Pharmaceutical Co., Ltd	823	2 158	87 500	150 000	127 500	75 000	35 000	6 220	48 338	531 715	646,07
5. Guiyang Dechangxiang Pharmaceutical Co., Ltd	13	34	43 750	93 750	38 750	37 500	17 500	98	23 138	254 521	19 578,51
7. Beijing Tongrentang Technologie Développement Co.	14	37	131 250	262 500	63 750	37 500	17 500	106	51 264	563 907	40 279,05
9. Fujian Nanshaolin Pharmaceutical Co., Ltd	10 684	28 010	87 500	150 000	63 750	37 500	17 500	80 747	46 501	511 508	47,88
11. Penglai Nuokang Pharmaceutical Co., Ltd	3 491	9 152	43 750	75 000	63 750	37 500	17 500	26 384	27 304	300 340	86,03
13. Hubei Nanyang Pharmaceutical Co., Ltd	34 575	90 646	43 750	52 500	63 750	37 500	17 500	261 310	56 696	623 651	18,04
14. Shenyang Jingcheng Pharmaceutical Co., Ltd	28 859	75 659	43 750	37 500	63 750	37 500	17 500	218 105	49 376	543 140	18,82
16. Pharmaceutical Factory of Hunan Bencao pharmacy Co. Ltd	1 300	3 408	43 750	75 000	63 750	37 500	17 500	9 825	25 073	275 807	212,16
18. Shandong Jewim Pharmaceutical Co., Ltd BlueBox	12 080	31 670	131 250	262 500	63 750	37 500	17 500	91 297	63 547	699 015	57,87
19. Suizhou Pharmaceutical Co. Ltd of Wuhan Jianmin Group	13	34	87 500	150 000	63 750	37 500	17 500	98	35 638	392 021	30 155,43
20. Guizhou Antai Pharmaceutical Co., Ltd	20 827	54 602	87 500	150 000	63 750	37 500	17 500	157 405	56 826	625 083	30,01
21. Guizhou Xinyi Pharmaceutical Co.	229	600	43 750	75 000	63 750	37 500	17 500	1 731	23 983	263 814	1 152,03
23. Xinjiang Biochemistry Pharmaceutical Co., Ltd	2 592	6 795	43 750	93 750	38 750	37 500	17 500	19 590	25 764	283 399	109,34
24. Yunnan Baiyao Group Corporation	273 333	716 602	43 750	75 000	63 750	37 500	17 500	2 065 780	301 988	3 321 869	12,15
27. Zhanjiang Xintongde Pharmaceutical Co., Ltd	29 397	77 071	306 250	562 500	63 750	37 500	17 500	222 175	128 675	1 415 420	48,15
29. Guizhou Hongyu Pharmaceutical Co., Ltd	1 231	3 227	87 500	168 750	63 750	37 500	17 500	9 304	38 753	426 284	346,29
32. Shanghai Yishengyuan Pharmaceutical Co., Ltd	112	294	87 500	150 000	63 750	37 500	17 500	846	35 739	393 129	3 510,08
	419 573	1 100 000	1 443 750	2 583 750	1 097 500	675 000	315 000	3 171 020	1 038 602	11 424 623	27,23

Sector Plan for Phaseout of CFCs Consumption in China Pharmaceutical Aerosol Sector

State Environmental Protection Administration

State Food and Drug Administration

and

National Institute for the Control of Pharmaceutical and Biological Products

January 20, 2007

TABLE OF CONTENTS

Summary

This sector plan aims to assist China to phase out CFCs consumption in its pharmaceutical aerosol sector excluding MDIs applications. The funding request targets the consumption of 485.089 ODP MT CFCs. The sector plan was prepared on the basis of a detailed analysis of eligible aerosol applications in China. It proposes conversion to non-ODS substitute aerosol where mature substitutes are available. Before new non-CFCs production starts, manufacturers are allowed to use stockpiled CFCs to maintain production to meet clinical demand. The sector plan will be implemented through two biennial programs starting in 2007. The sector plan includes policy actions to ensure that the phase-out proceeds on schedule. An action plan indicating annual CFC phase-out targets is included in the proposal and the first biennial program for 2007-2008 is submitted along with this sector plan.

Pharmaceutical Aerosol Manufacturers:	**39**
Eligible Manufacturers:	**32**
Applications by Eligible Manufacturers:	**24** Skin Aerosol Applications **16** Cavity Aerosol Applications
CFCs Baseline Consumption(Average of 2003-2005):	**485.089 ODP MT**
ow. CFCs Consumption Requested for MLF Grant:	**464.355 ODP MT**
Project Duration:	**4 years**
Project Incremental Cost:	**US$12.303 million**
Requested MLF Funding:	**US$ 12.303 million**
IA Support Cost	**US$ 922,725**
Total cost to the MLF	**US$ 13.226 million**
Cost Effectiveness:	**US$ 25.36/kg ODP**
National Coordinating Agency:	**SFDA and SEPA**

PROJECT COVER SHEET – MULTI-YEAR PROJECTS

COUNTRY: China, Peoples Republic of

PROJECT TITLE	**BILATERAL/IMPLEMENTING AGENCY**
Phaseout of CFC consumption in the Pharmaceutical Aerosol Sector	WORLD BANK

NATIONAL CO-ORDINATING AGENCY: STATE ENVIRONMENT PRTOCTION ADMINISTRATION

LATEST REPORTED CONSUMPTION DATA FOR ODS ADDRESSED IN PROJECT

A: ARTICLE-7 DATA (ODP TONNES, 2005, SUBMITTED SEPT 2006

Annex A, Group 1 productions (CFCs)		Annex A, Group 1 consumption (CFCs)	

B: COUNTRY PROGRAMME SECTORAL DATA (ODP TONNES, 2006 AS OF SEPT 2006

ODS	Pharmaceitical aerosol	ODS			
CFC-11	112.723				
CFC-12	372.366				

CFC consumption remaining eligible for funding (ODP tonnes)	Not Applicable

CURRENT YEAR BUSINESS PLAN: Total funding $10 million: total phase-out ODP tonnes.

PROJECT DATA		2006	2007	2008	2009	2010	Total
CFC (ODP tonnes)	Montreal Protocol Production Limits	4,471.5	4,471.5	4,471.5	4,471.5	Tbd	
	Montreal Protocol Consumption Limits	8,385.57	8,385.57	8,385.57	8,385.57	Tbd	
	Max CFC consumption (Note 2: CFC-11 and CFC-12)	485.1	485.1	0	0	0	485.1
	Stockpiled CFC used during a transitional period from Aug. 2007	-	Note 1	Note 1	Note 1	Note 1	
TOTAL ODS CONSUMPTION TO BE PHASED OUT		485.1	485.1	0	0	0	485.1
Total ODS consumption to be phased-in (HCFCs)		NA	NA	NA	NA	NA	NA
Project Funding for P.R. China : (US $ in thousands)			8,793,520	0	3,509,474	0	12,302,994
Funding for lead agency [*WB*], (US $ in thousands):			8,793,520	0	3,509,474	0	12,302,994
Total project funding			8,793,520	0	3,509,474	0	**12,302,994**
Support costs (US $ (US $ in thousands):))			659,514	0	263,211	0	922,725
Support cost for lead agency WB (US $ in thousands):]			659,514	0	263,211	0	922,725
Total support costs			659,514	0	263,211	0	**922,725**
TOTAL COST TO MULTILATERAL FUND (US $)			**9,453,034**	**0**	**3,772,685**	**0**	**13,225,719**

Project cost effectiveness (US $/kg)

Note 1: CFC from stockpile established before July 2007 may be used based on special permission from SFDA

Note 2: 112.723 ODP tons of CFC-11 and 372.366 ODP tons of CFC-12

FUNDING REQUEST: FOR THE BI-ENNIAL PROGRAM FOR 2007-2008 US$ 12,680,000 and support cost of US$ 951,000

Prepared by: SEPA and SFDA **Date: January 2007**

Reviewed by: World Bank **Date: January 2007**

CHAPTER 1 Introduction

1. Background

1. The Government of China ratified the Montreal Protocol on Substances that Deplete the Ozone Layer in 1991 and finalized China Country Program for Ozone Depleting Substances Phase-out in January 1993. This Country Program was submitted to the 9th Executive Committee (ExCom) of the Multilateral Fund of the Montreal Protocol in March 1993 and was updated by China in November 1999. From 1997 to 2006, several phase-out sector plans have been developed and implemented, reaffirming China's commitment to meeting its obligations for phase-out of ODS consumption with the support of MLF.

2. Funding of US$ 135,000 was approved at the 43rd ExCom meeting in July 2004 to prepare *the Sector Plan for Phase-out of CFCs Consumption in China Pharmaceutical Aerosol Sector (non-MDIs)*. As the leading agency for the implementation of Montreal Protocol, the State Environmental Protection Administration of China (SEPA), in cooperation with the State Food and Drug Administration (SFDA), selected National Institute for the Control of Pharmaceutical and Biological Products (NICPBP) to prepare this sector plan.

2. Objectives

3. The main objectives of this sector plan include the following:

   a Identify all CFCs-based pharmaceutical aerosol manufacturers, their aerosol applications and CFCs consumption;

   b Design a technical scheme for phaseout of CFCs consumption in China pharmaceutical aerosol sector based on available non-ODS substitutes;

   c Develop a CFCs Phaseout Action Plan to meet the requirement of *China Accelerated Phase-out Plan(APP);*

   d Request MLF funding consistent with the MLF policies and guidelines to phase out CFCs in the sector[1];

   e Develop new CFCs phase-out policies for pharmaceutical aerosol sector; and

   f Develop a monitoring and management system to ensure successful implementation of the CFC phase-out in the pharmaceutical aerosol sector and rational utilization of MLF funds.

[1] As substitute technology was not available in 1990s, it is proposed that the cutting off date should be July 1, 1999 after which Article 5 Parties had the obligation to freeze CFCs production and consumption (see paragraph 45).

CHAPTER 2 Sector Profile

1. Background

4. China pharmaceutical aerosol industry started fairly late. In 1964, Shanghai Institute of Pharmaceutical Industry, in cooperation with Shanghai Sine Pharmaceutics Factory, Wuxi First Pharmaceutics Factory and Chongqing Seventh Pharmaceutics Factory, developed and produced Pingchuan (Anti-asthmatic), the first aerosol product in China. The period from 1964 to the 1980s saw comparatively slow development of China pharmaceutical aerosol sector due to the bottleneck of development of containers, valves and metered-dosed charging equipment. However, after those problems were solved, great progress has been achieved in the sector.

2. Sector Survey

5. NICPBP was selected to carry out the sector survey and to prepare the sector plan for China pharmaceutical aerosol sector. The survey covered both non-MDIs and MDIs pharmaceutical aerosol manufacturers. To collect data, an investigation questionnaire was jointly prepared by SFDA, SEPA and NICPBP.

6. In June 2004, SFDA sent the questionnaire to pharmaceutical aerosol manufacturers in China. By November 2004, SFDA had received feedback from 57 enterprises.

7. In August 2004, SEPA, NICPBP and SFDA verified three aerosol manufacturers by site visit, namely, S&P Pharmaceutical Industry Co. Ltd., Xinjiang Biochemical Pharmaceutical Co. and Xinjiang Pharmaceutical Factory.

8. In September 2005, SFDA and NICPBP visited 40 pharmaceutical aerosol manufacturers to collect data.

9. In March 2006, SFDA requested again that its provincial Food and Drug Administration Bureaus confirm the list of aerosol manufacturers and their aerosol products.

10. In April 2006, pharmaceutical manufacturers were invited to attend a meeting in Beijing to learn the CFCs phaseout for the sector. At the meeting, they confirmed their data of aerosol products. The meeting also provided information on the process for phasing out CFC and the requirements for new registrations of aerosol products.

11. In April 2006, NICPBP visited eight pharmaceutical manufacturers. Therefore, total 51 manufacturers have been investigated by site visit. For the other 11 manufacturers without aerosol production, NICPBP had collected by sending questionnaires their relevant information including product approval numbers. So total 62 pharmaceutical aerosol manufacturers were investigated. It is confirmed by NICPBP that the survey covered all the CFCs-based non-MDIs pharmaceutical aerosol manufacturers.

12. The sector survey indicates that Chinese pharmaceutical aerosol manufacturers only have conceptual ideas on the CFCs substitutes and conversion technology.

3. Sector Profile

13. The *UNEP 2002 Report of the Aerosol S, Sterilants, Miscellaneous Uses and Carbon Tetrachloride Technical Options Committee 2002 Assessment* clearly states that "the reformulation of medical aerosol products (other than MDIs) and industrial/technical aerosols may require technical and financial assistance. In the case of medical aerosols, approval by national health and drug authorities will be required, after pharmacological and toxicity tests and clinical trials."

14. In evaluating the cost effectiveness of projects in the pharmaceutical sector, a) the amount of CFC used per can is much smaller than for general aerosol products, hence the CFC consumption for the same amount of cans produced would be significant smaller than for general aerosol and cost effectiveness in terms of USD/kg ODP would be significant higher and b) cost of registration and certification does not apply to general aerosol products. In reviewing the pharmaceutical aerosol in orther countries, it was found that HFC-134a indeed is used as propellant.

15. To ensure any changes to the medicinal products do not give rise to public health concerns, re-registration of medicine is required in many countries. When these changes are taken place, such as changes of specifications of excipident, or change to different excipident, or change to different type of drugs, respective requirement and procedures of re-registrations are specified by medicinal administrations of many countries.

16. Pharmaceutical aerosol product comprises the propellant compatible with the drug, a container capable of withstanding vapor pressure of propellant and a valve system. Propellants used in China pharmaceutical aerosol sector are mainly CFCs including CFC-11 and CFC-12. CFC-11 is used as a dispersant while CFC-12 as a propellant. Containers are made of glass, aluminum, stainless steel and plastic, but glass and aluminum containers are more often seen. Valves are often made of plastic, rubber, aluminum and stainless steel. Valves have to be inert with formulations in the canisters.

17. Pharmaceutical aerosols can be grouped by dispersing system into three types, namely, solution type, suspension type and emulsion type. China pharmaceutical aerosols can also be divided by medical usage into three groups – i) aerosol absorbed through skin (Skin Aerosol hereinafter), which is also called as external-use aerosol in China. ii) aerosol absorbed through cavity and mucosa, e.g. oral, nasal and vaginal cavity (Cavity Aerosol hereinafter) and iii) aerosol inhaled through respiratory tract (MDIs). The first two groups are referred to as non-MDIs aerosols, which are addressed in this sector plan. China will submit another sector plan for MDIs sector separately at a later stage. Table 2-1 is the survey summary of the non-MDIs sector.

Table 2-1 Summary of China Pharmaceutical Aerosol Sector

	Eligible for MLF Grant*	Not Eligible for MLF Grant	Total
CFCs Baseline Consumption (MT)	464.355	20.733	485.089
Number of Manufacturers	32	7	39
Number of Production Lines	35	6	41
Number of Production Lines with	22	5	27

Baseline Consumption			
Number of Skin Aerosol Applications	24	3	-
Number of Cavity Aerosol Applications	16	4	-
Number of Skin Aerosol Products	42	3	45
Number of Cavity Aerosol Products	21	4	25

* Aerosol manufacturers with production lines established before cutting-off date (July 1, 1999).

3.1 Aerosol Applications

18. **Skin Aerosol Applications.** Skin Aerosols are used for wound surface protection, cleaning, sterilization, topical anesthesia and homeostasis etc. They are requested to have no stimulation effect. The surface coverage (thin film) provided by those aerosols should have good permeability. SFDA has issued 51 drug production approval numbers (i.e. drug specifications), relating to 25 applications (see table 2-3). Out of the 25 applications, 10 are chemicals applications which are as same as those in foreign countries; 15 are Traditional Chinese Medicine (TCM) Applications, of which 12 are proprietary applications owned by Chinese manufacturers. There are total 30 manufacturers with registration numbers for Skin Aerosol products.

19. **Cavity Aerosol Applications.** SFDA has issued 24 registration approval numbers for Cavity Aerosols, relating to 19 applications (see Table 2-3), among which 8 are chemicals applications and 11 TCM applications. There are four nasal aerosol applications, mainly peptides and protein drugs, which exert general action, obviate gastrointestinal and hepatic first-pass action and improve bioavailability. There are two vaginal aerosol applications, mainly with tropical therapy for virginities and with contraception purpose. There are 13 oral aerosol applications, mainly with local action for the treatment of pharyngitis. Total 18 pharmaceutical manufacturers have registration numbers for cavity aerosol products.

Table 2-2 Information on Pharmaceutical Applications

Application ID	Application Name	Approval Number	TCM*/ Chemical Application	Effective Elements	Function and Indications
A01	Baofukang Foam	GUOYAOZHUNZI. Z10980092	TCM, proprietary product.	Oleum curcumae wenchowensis,Borneol	Bactericidal effect to Candida albicans and bacteriostatic action to Bacillus coli.
A02	Ice Cape Jasmine Distress Aerosol	GUOYAOZHUNZI. Z20025399	TCM, proprietary product.	Rhubarb,Cape Jasmine Fruit,Zhongjiefeng,Nux Vomica,Rehmannia Root-facient,Rosewood,tuber onion	Depriving the heat, activating blood circulation, odynolysis. Be used for low-grade empyrosis, soft tissue injury with blood stasis, boss, and soreness.

Application ID	Application Name	Approval Number	TCM*/ Chemical Application	Effective Elements	Function and Indications
				root,Borneol,Peach Seed,Chinese pine node,Camphor,et al	
A05	Cangxin Aerosol/ Xanthiun and Magnolia Flower Aerosol	GUOYAOZHUNZI. Z20027431	TCM	Siberian Cocklebur Fruit,Biond Magnolia Flower,pedicellus melo,et al	Be used for allergic coryza, acute coryza and chronic coryza.
A06	Fluconazol Aerosol	GUOYAOZHUNZI. H20010549	Pharmaceutical chemicals	Fluconazol	
A07	Fudekang Foam	GUOYAOZHUNZI. Z52020422	TCM, proprietary product.	Matrine	Clearing away heat and wetness, antibiosis. Be used for chronic cervicitis, cervical erosion, and coleitis.
A08	Compound Salicylic Acid and Clortrimazol Aerosol	GUOYAOZHUNZI. H52020529	Pharmaceutical chemicals,	Salicylic Acid,Clotrimazole,Phenol,Camphor,betula oil et al	Anti-eumycete, relieving itching, des-tinea.Be used for onychomycosis,neurodermatitis,the athlete's foot.
A10	Compound Chlorobutanol Aerosol	GUOYAOZHUNZI. H50021909, H32026527	Pharmaceutical chemicals	Chlorobutanol, Benzocaine, Chlorhexidine acetate	Preservation, hypothermy, sterilization. Be used for empyrosis.Chlorobutanol is used to antisepticize andrelieve pain □ Benzocaine is used to obstruct sensory nerve; Chlorhexidine acetate is used to sterilize.
A11	Compound Methyle Salicylater and Diphenhydramine Aerosol	GUOYAOZHUNZI. H44022736	Pharmaceutical chemicals	Methyle Salicylater and Diphenhydramine	Anti-bacterial and Pain relief
A13	Compound Cape Jasmine Aerosol	GUOYAOZHUNZI. Z20025744	TCM, proprietary product.	Lightyellow Sophora Root,Cape Jasmine Fruit,Arnebia Root,Garden Burnet Root,Pricklyash peel,Borneol,Rhubarb,Golden Thread,et al	Clearing away heat and toxic materials, haemostasis, detumescence, odynolysis.Be uesed for incised wound, furuncle.

Application ID	Application Name	Approval Number	TCM*/ Chemical Application	Effective Elements	Function and Indications
A14	Compound Arnebia Root Aerosol □Arnebia Root Oil Aerosol□	GUOYAOZHUNZI. Z20044383	TCM	Arnebia Root,et al	Clearing heat-evil, odynolysis. Be used for low-grade empyrosis.
A16	Haobai Damp Impairement Aerosol	GUOYAOZHUNZI. Z20027459 Z20027460	TCM	Shortstalk monkshood root,Dahurian Angelica Root,Paniculate swallowwort Root,Menthol,Extractum Belladonnae Liquidum,Tinospora Root,Zedoray Rhizome,et al	Activating blood circulation, odynolysis, dispelling wind-evil and wetness-evil. Be used for imperfecta, contusion, beriberoid disease, lumbodorsal pain.
A17	Hongyao Aerosol	GUOYAOZHUNZI. Z21021527	TCM, proprietary product.	Sanchi,Safflower ,Szechwan Lovage Rhizome,Chinese Angelica,Dahurian Angelica Root ,Himalayan Teasel Root,Ground Beetle	Many active constitutent,such as RADIX NOTOGINSENG Amoxcillin,Sanchi Glycoside,were found in Sanchi.RADIX NOTOGINSENG Amoxcillin has the effective of haemostasis and promoting blood flow at mean time,which wae said two-ways regulation,and dilating micrangium,anticogulation,improving microcirculation and oxygen delivery capacity.Sanchi Glycoside has the effective of antiinflammatory and enhancing immunologic function.
A19	Compound Lithospermi Aerosol	GUOYAOZHUNZI. Z20044009	TCM	Chinese Angelica,Szechwan Lovage Rhizome,Safflower,Clore,Fresh Ginger,Camphor,Turpentine Oil,et al	Activating blood circulation to dissipate blood stasis,detumescence,odynolysis.Be used for acute soft tissue injury
A21	Kuanxiong Aerosol	GUOYAOZHUNZI. Z11020961	TCM		Regulating vital energy and odynolysis. Be used for anesis of angina.

Application ID	Application Name	Approval Number	TCM*/ Chemical Application	Effective Elements	Function and Indications
A22	Dolicaine and Chlorhexidine Aerosol	GUOYAOZHUNZI. H35021400 H44024772	Pharmaceutical chemicals,	Lidocaine,Chlorhexidine acetate,Benzalkonii bromidum	Be used for incised wound, abrasion, soft tissue injury□the effectiveness is odynolysis, relieving itching, dephlogisticate.The effectiveness of lidocaine is local anesthesia and odynolysis; The effectiveness of chlorhexidine acetate and benzalkonii bromidum is dephlogisticate and disinfection.
A23	Dolicaine and Chlorhexidine Aerosol	GUOYAOZHUNZI. H20043850 H37023231 H37023255 H32026054 H44024771	Pharmaceutical chemicals,	Lidocaine,Chlorhexidine acetate,Benzalkonii bromidum	Be used for incised wound, abrasion, soft tissue injury, the effectiveness is odynolysis, relieving itching, dephlogisticate. The effectiveness of lidocaine is local anesthesia and odynolysis; The effectiveness of chlorhexidine acetate and benzalkonii bromidum is dephlogisticate and disinfection.
A24	Lidocaine Aerosol	GUOYAOZHUNZI. H10920107,	Pharmaceutical chemicals	Lidocaine hydrochloride	Local anesthetic.Be used for splanchnoscopy.Lidocaine hydrochloride belongs to trichostachine.After absorption, there would be periaqueductal gray stimulation and depressant effect to systema nervosum centrale.When the blood drug level is low□there will be analgesic effect and lethargy.
A25	Molsidomine Aerosol	GUOYAOZHUNZI. H23022579 H11022311 H23022943 H31022548	Pharmaceutical chemicals	Molsidomine	anti-anginal drug
A26	Qiweiqingyan Aerosol	GUOYAOZHUNZI. Z10980067	TCM, proprietary product.	Muscone,Vietnamese Sophora Root,Dwarf Lilyturf Tuber,Figwort Root,Blackberrylily Rhizome,Toad Venom,Borneol	Clearing heat-evil of lung and chylostomach, detumescence. Be used for Hoarseness, sore throat, diphtheria.

Application ID	Application Name	Approval Number	TCM*/ Chemical Application	Effective Elements	Function and Indications
A27	Ruxiang Rheumatism Aerosol	GUOYAOZHUNZI. Z20027458	TCM	Methyl Salicylate,Ole Menthal,Myrrh,Frankincense,Ocimum Oil,Cassia Bark Oil,Dragon's blood,Muscone,Eucalyptus oil,et al	Activating blood circulation to dissipate blood stasis, detumescence, odynolysis. Be used for rheumatalgia, arthralgia,lumbodynia.
A28	Shangle Aerosol	GUOYAOZHUNZI. Z10910038	TCM, proprietary product.	Szechwan Lovage Rhizome,Chinese Angelica,Danshen Root,Dahurian Angelica Root,Amur Cork-tree,et al	Activating blood circulation, dredging the meridian passage, detumescence.Be used for soft tissue injury, with manifestations of engorgement and stagnated blood
A29	Huoxinagquton g Aerosol	GUOYAOZHUNZI. Z20043551 Z42021342	TCM	Musk,Sanchi, Safflower, Dragon's blood,Rehmannia Root,Doubleteeth Pubesscent Angelica Root ,Camphor,Borneol,Menthol,et al	Activating blood circulation to dissipate blood stasis,dredging the meridian passage, detumescence, odynolysis
A30	Shiyang Aerosol	GUOYAOZHUNZI. Z10910039	TCM, proprietary product.	Golden Thread,Amur Cork-tree, Chinese Angelica, et al	Depriving the heat and wetness, detoxicating and relieving itching. Be used for acute eczema, with erythema, effusion, pruritus.
A32	Diclofenac Sodium Aerosol	GUOYAOZHUNZI. H19991425 H19991426	Pharmaceutical chemicals	Diclofenac Sodium	Be used for acute luxatio, contund and yosalgia.Also can be used for arthralgia.
A33	Methyl Salicylate Aerosol	GUOYAOZHUNZI. H35021187	Pharmaceutical chemicals	Methyl Salicylate	detumescence, odynolysis.Be used for acute soft tissue injury such as luxatio and myosalgia.
A34	Suxiaojiuxin Aerosol	GUOYAOZHUNZI. Z11020374	TCM, proprietary product.	Tree peony Bark,Szechwan Lovage Rhizome,Borneol	Depriving the heat, activating blood circulation, odynolysis.Be used for angina, with feverish dysphoria.
A35	Suxiaozhitong Aerosol	GUOYAOZHUNZI. Z11020364	TCM, proprietary product.	Dragon's blood,Safflower,Camphor, Frankincense(stir-frying with vinegar),Borneol,Musk	Detumescence, odynolysis, activating blood circulation to dissipate blood stasis, dephlogisticate, dredging the meridian passage. Be used for sprain, contusion, luxatio imperfecta,fracture, et al.

Application ID	Application Name	Approval Number	TCM*/ Chemical Application	Effective Elements	Function and Indications
A36	Wanjinxiang Aerosol	GUOYAOZHUNZI. Z20026302	TCM, proprietary product.	smartweed Herba,pungent litse fruit,Blume conspicua Hayata oil	Deintoxication, relieving itching, detumescence. Be uesed for baraquet, calefy, cephalalgia, flare of Sting
A38	Nitroglycerin Aerosol	GUOYAOZHUNZI. H20003570 H37021173 H44024858	Pharmaceutical chemicals	Nitroglycerin	Emergency medical treatment drug for angina.
A39	Isosorbide Dinitrate Aerosol	GUOYAOZHUNZI. H37022650	Pharmaceutical chemicals, proprietary product.	Isosorbide Dinitrate	Emergency medical treatment drug for angina.
A40	Econazole nitrate Aerosol	GUOYAOZHUNZI. H20043832 H44024735	Pharmaceutical chemicals	Econazole nitrate	Antimycotic drug. Bacteriostatic action to Dermatophyte, mould, Blastocystis, such as Candida albicans.
A41	Yansukang Aerosol (Rapid Recovery of throat)	GUOYAOZHUNZI. Z10960052	TCM,	Artificial bezoar,Pearl,Realgar,Toad Venom,Borneol,Musk,et al	Clearing heat-evil, detumescence, odynolysis. Be used for pharyngalgia, diphtheria, pneumonia. Anti-inflammatory effect, bacteriostatic action and analgesic effect.
A45	Yunnan Baiyao Aerosol □50g,100g□	GUOYAOZHUNZI. Z53021102 Z53021106 Z53021107 Z53021105 Z53021103 Z53021104	TCM, proprietary product.	Yunnan white powder	Activating blood circulation to dissipate blood stasis, detumescence, odynolysis.

Table 2-3 China Pharmaceutical Aerosol Applications

Application ID	Application Name	CFCs Baseline (kg)	Number of Manufacturers	Manufacturer Name(#ID)
1) Skin Aerosol Application (total 25 applications)				
A02	Ice Cape Jasmine Distress Aerosol	19,053	1	Guizhou Antai Pharmaceutical Co., Ltd (#20)
A08	Compound Salicylic Acid and Clortrimazol Aerosol	1,773	1	Guizhou Antai Pharmaceutical Co., Ltd (#20)
A09	Compound ethyl chloride aerosol	0	1	Guangzhou Baiyunshan Hejigong Pharmaceutical Co., Ltd (#03)
A10	Compound Chlorobutanol Aerosol	717	2	Wuxi Shanhe Group No.1 Pharmaceutical Co., Ltd. (#01); Chongqing Kerui Pharmaceutical Co., ltd. (#25)
A11	Compound Methyl Salicylate and Diphenhydramine Aerosol	0	2	Zhanjiang Xintongde Pharmaceutical Co., Ltd. (#27), Nantong Zhongbao Pharmaceutical Co., Ltd.(#37)
A13	Compound Cape jasmine Aerosol	229	1	Guizhou Xinyi Pharmaceutical Corporation (#21)
A14	Compound lithospermi aerosol	6	1	Suizhou Pharmaceutical Co. Ltd of Wuhan Jianmin Group (#19)
A16	Haobai Damp Impairment Aerosol	1,412	2	Hunan Bencao Pharmaceutical Co., Ltd. (#16); Shanghai Yishengyuan Pharmaceutical Co., Ltd. (#32)
A17	Hongyao Aerosol	57,717	1	Shenyang Jingcheng Pharmaceutical Co., Ltd. (#14)
A19	Keshangtong Aerosol	7	1	Suizhou Pharmaceutical Co. Ltd of Wuhan Jianmin Group (#19)
A22	Dolicaine chlorhexidine aerosol	833	2	South shaolin Pharmaceutical Co., Ltd in Fujian. (#09); Zhanjiang Xintongde Pharmaceutical Co., Ltd. (#27)

Application ID	Application Name	CFCs Baseline (kg)	Number of Manufacturers	Manufacturer Name(#ID)
A23	Dolicaine chlorhexidine aerosol	35,616	10	Wuxi Shanhe Group No.1 Pharmaceutical Co., Ltd. (#01); Guangdong Baiyunshan Hejigong Pharmaceutical Co., Ltd. (#03); Guangdong Baiyunshan Externally Applied Agent Factory (#04); Penglai Nuokang Pharmaceutical Co., Ltd. (#11); Shandong Jingwei Pharmaceutical Co., Ltd. (#18); Hangzhou Sino-US huadong Pharmaceutical Co., Ltd. (#22); Zhanjiang Xingtongde Pharmaceutical Co., Ltd. (#27); Heilongjiang Tianlong Pharmaceutical Co., Ltd. (#28); Nantong Zhongbao Pharmaceutical Co., Ltd. (#37); Anshan No.1 Pharmaceutical Factory (#39);
A24	Lidocaine aerosol	0	1	Sine Pharmaceutical Factory of Shanghai Pharmaceutical Group Co., Ltd. (#08)
A25	Molsidomine Aerosol	0	6	Beijing Haiderun Pharmaceutical Co., Ltd. (#02); Beijing Double-Crane Modern Pharmaceutical Technology Co., Ltd. (#06); Sine Pharmaceutical Factory of Shanghai Pharmaceutical Group Co., Ltd. (#08); Harbin Hengcang Pharmaceutical Co., Ltd. (#15); Heilongjiang Tianlong Pharmaceutical Co., Ltd. (#28), Harbin Guangji Pharmaceutical Factory. (#36);
A27	Ruxiang Rheumatism Aerosol	0	1	Zhanjiang Xingtongde Pharmaceutical Co., Ltd. (#27)
A28	Shangle Aerosol	0	1	Beijing Haiderun Pharmaceutical Co., Ltd. (#02)
A29	Huoxianqutong Aerosol	49,530	3	Hubei Nanyang Pharmaceutical Co., Ltd. (#13), Heilongjiang Tianlong Pharmaceutical Co., Ltd. (#28), Hubei Lishizhen Medical Group Co., Ltd. (#34)

Application ID	Application Name	CFCs Baseline (kg)	Number of Manufacturers	Manufacturer Name(#ID)
A30	Shiyang Aerosol	0	1	Beijing Haiderun Pharmaceutical Co., Ltd. (#02)
A32	Diclofenac Sodium Aerosol	5,583	1	Zhanjiang Xingtongde Pharmaceutical Co., Ltd. (#27)
A33	Methyl Salicylate aerosol	9,851	1	Fujian Nanshaolin Pharmaceutical Co., Ltd. (#09)
A35	Sunshangsuxiaozhitong Aerosol	0	1	Beijing Tongrentang Technology Development Corporation. (#07)
A36	Wanjinxiang Aerosol	38	1	Guizhou Hongyu Pharmaceutical Co., Ltd. (#29)
A37	Xiangbingqutong Aerosol	13	1	S & P Pharmaceutical Industry Co., Ltd.(#30)
A42	Lidocaine Hydrochloride Aerosol	0	1	Shanghai Fuxingzhaohui Pharmaceutical Co., Ltd. (#10)
A45	Yunnan Baiyao Aerosol	273,334	1	Yunnan Baiyao Group Corporation. (#24);
	Subtotal	**455,712**		
2) Cavity Aerosols Application (total 19 applications)				
A01	Bao Fu Kang foam	1,193	1	Guizhou Hongyu Pharmaceutical Co., Ltd.(#29)
A03	Beclometasone Tubinaire (Beconase)	20,390	1	Glaxo SmithKline (Tianjin) Pharmaceutical Co., Ltd.(#12)
A04	Beclometasone Aerosol	0	1	Guangzhou Dongkang Pharmaceutical Co., Ltd.(#31)
A05	Xanthiun and Magnolia flower Aerosol	2,592	1	Xinjiang Biochemistry Pharmaceutical Co., Ltd.(#23)
A06	Fluconazol Aerosol	0	1	Sine Pharmaceutical Factory of Shanghai Pharmaceutical Group Co., Ltd.(#08)
A07	Fudekang foam	13	1	Guiyang Dechangxiang Pharmaceutical Co., Ltd.(#05)
A12	Compound Chlorobutanol Aerosol	0	1	Chongqing Kerui Pharmaceutical Co., ltd.(#25)
A15	Isoconeazole Nitrate Aerosol	0	1	Heilongjiang Tianlong Pharmaceutical Co., Ltd. (#28)
A18	Jinlan aerosol	0	1	Anshan No.1 Pharmaceutical Factory. (#39)
A20	Stomatitis spraying agent	48	1	Shannxi Fengwuchendayaotang Pharmaceutical Factory Co., Ltd. (#35)
A21	Huanxiong Aerosol	0	2	Beijing Tongrentang Technology Development Corporation. (07); Anshan No.1 Pharmaceutical Factory. (#39)
A26	Qiweiqingyan Aerosol	293	1	Shandong Bencao Pharmaceutical Co., Ltd. (#17)

Application ID	Application Name	CFCs Baseline (kg)	Number of Manufacturers	Manufacturer Name(#ID)
A31	Shuanghuanglian Aerosol	145	1	Sanjing Pharmaceutical Co., Ltd of Harbin Pharmaceutical Group. (#33)
A34	Suxiaojiuxin Aerosol	14	1	Beijing Tongrentang Technology Development Corporation.(#07)
A38	Nitroglycerin Aerosol	528	4	Shandong Jewim Pharmaceutical Co., Ltd. (#18); Zhanjiang Xintongde Pharmaceutical Co., Ltd. (#27); Xian Lisheng Pharmaceutical Co., Ltd.(#38); Shandong Bencao Pharmaceutical Co., Ltd.(#17)
A39	Isosorbide Dinitrate Aerosol	3	1	Shandong Jewim Pharmaceutical Co., Ltd.(#18)
A40	econazole nitrate aerosol	3,780	3	Guangzhou Baiyunshan Hejigong Pharmaceutical Co., Ltd.(#03), Zhanjiang Xingtongde Pharmaceutical Co., Ltd. (#27); Heilongjiang Tianlong Pharmaceutical Co., Ltd. (#28)
A41	Rapid recovery of throat aerosol	380	1	Huayi Pharmaceutical Co., Ltd. (#26)
A44	Yinhuangpingchuan Aerosol	0	1	Anshan No.1 Pharmaceutical Factory (#39)
	Subtotal	**29,377**		
	Total	**485,089**		

Table 2-3 Overviews of Pharmaceutical Aerosol Manufacturers

Enterprise ID	Name of Enterprise	Chinese Share (%)	Lines	Date of Line.	Cap. (can/hour)	CFCs Baseline (kg)	Baseline CFCs for SA[1] (kg)	Baseline CFCs for CA[1] (kg)	Total Prodt. Quantity[2] (can)	SA Prodt. Quantity (can)	CA Prodt. Quantity (can)	SA App. ID	CA App. ID
01	Wuxi Shanhe Group No.1 Pharmaceutical Co., Ltd	100%	2	1965	2000	823	823	0	26,667	26,667	0	A10, A23	-
02	Beijing Haiderun Pharmaceutical Co., Ltd	100%	2	1978	-	0	0	0	0	0	0	A25, A28, A30	-
03	Guangzhou Baiyunshan Hejigong Pharmaceutical Co., Ltd	100%	1	1983	-	0	0	0	0	0	0	A09 A23	A40
04	Externally Applied Agent Factory of Guangzhou Baiyunshan Pharmaceutical Co., Ltd	100%	1	1959	-	0	0	0	0	0	0	A23	-
05	Guiyang Dechangxiang Pharmaceutical Co., Ltd	100%	1	1979	600	13	0	13	100	0	100	-	A07
06	Beijing Double-Crane Modern Pharmaceutical Technology Co., Ltd	100%	1	1980	-	0	0	0	0	0	0	A25	-
07	Beijing Tongrentang Technology Development Corporation	100%	1	1981	1800-3600	14	0	14	1,267	0	1,267	A35	A21,A34
08	Xinyi Pharmaceutical General Factory of Shanghai Pharmaceutical Group Co., Ltd	100%	1	1969	0	0	0	0	0	0	0	A24,A25	A06
09	Fujian Nanshaolin Pharmaceutical Co., Ltd	100%	1	1985	3000	10,684	10,684	0	48,571	48,571	0	A22, A33	-
10	Shanghai Fuxingzhaohui	100%	1	1988	-	0	0	0	0	0	0	A42	-

Enterprise ID	Name of Enterprise	Chinese Share (%)	Lines	Date of Line.	Cap. (can/hour)	CFCs Baseline (kg)	Baseline CFCs for SA[1] (kg)	Baseline CFCs for CA[1] (kg)	Total Prodt. Quantity[2] (can)	SA Prodt. Quantity (can)	CA Prodt. Quantity (can)	SA App. ID	CA App. ID
	Pharmaceutical Co., Ltd												
11	Penglai Nuokang Pharmaceutical Co., Ltd	100%	1	1986	2000	3,491	3,491	0	100,600	100,600	0	A23	-
13	Hubei Nanyang Pharmaceutical Co., Ltd	70%	1	1991	1000	49,393	49,393	0	1,171,333	1,171,333	0	A29	-
14	Shenyang Jingcheng Pharmaceutical Co., Ltd	50%	1	1992	2000	57,717	57,717	0	968,533	968,533	0	A17	-
15	Harbin Hengcang Pharmaceutical Co., Ltd	100%	1	1992	-	0	0	0	0	0	0	A25	-
16	Pharmaceutical Factory of Hunan Bencao pharmacy Co., Ltd	100%	1	1993	800-1000	1,300	1,300	0	58,333	58,333	0	A16	-
17	Shandong Bencao Pharmaceutical Co., Ltd	100%	1	1997	1500	428	0	428	56,720	0	56,720	-	A26,A38
18	Shandong Jewim Pharmaceutical Co., Ltd BlueBox	100%	1	1993	500-600	12,080	11,685	395	318,281	276,314	41,967	A23	A38,A39
19	Suizhou Pharmaceutical Co. Ltd of Wuhan Jianmin Group	100%	1	1993	2000	13	13	0	700	700	0	A14, A19	-
20	Guizhou Antai Pharmaceutical Co., Ltd	100%	1	1983	500-600	20,827	20,827	0	580,000	580,000	0	A02, A08	-
21	Guizhou Xinyi Pharmaceutical Corporation	100%	1	1993	500-600	229	229	0	8,333	8,333	0	A13	-
22	Hangzhou Sino-US Huadong Pharmaceutical Co., Ltd	75%	1	1993	-	0	0	0	0	0	0	A23	-

Enterprise ID	Name of Enterprise	Chinese Share (%)	Lines	Date of Line.	Cap. (can/hour)	CFCs Baseline (kg)	Baseline CFCs for SA[1] (kg)	Baseline CFCs for CA[1] (kg)	Total Prodt. Quantity[2] (can)	SA Prodt. Quantity (can)	CA Prodt. Quantity (can)	SA App. ID	CA App. ID
23	Xinjiang Biochemistry Pharmaceutical Co., Ltd	100%	1	1994	2500	2,592	0	2592	50,000	0	50,000	-	A05
24	Yunnan Baiyao Group Corporation	100%	1	1995	5000	273,333	273,333	0	5,306,667	5,306,667	0	A45	
25	Chongqing Kerui Pharmaceutical Co., ltd	100%	1	1975	-	0	0	0	0	0	0	A10	A12
26	Huayi Pharmaceutical Co., Ltd	100%	1	1996	500	380	0	380	70,000	0	70,000	-	A41
27	Zhanjiang Xintongde Pharmaceutical Co., Ltd	100%	1	1987	3600	29,397	25,917	3,480	1,240,000	1,036,667	203,333	A11, A22, A23,A27, A32,	A38, A40
28	Heilongjiang Tianlong Pharmaceutical Co., Ltd	100%	2	1996	1500-2000	300	0	300	33,333	0	33,333	A23, A25, A29	A15,A40
29	Guizhou Hongyu Pharmaceutical Co., Ltd	100%	1	1998	1500	1,230	38	1,193	76,933	2,800	74,133	A36	A01
31	Guangzhou Dongkang Pharmaceutical Co., Ltd.	100%	1	1987	-	0	0	0	0	0	0	-	A04
32	Shanghai Yishengyuan Pharmaceutical Co., Ltd	100%	1	1983	600-800	112	112	0	4,845	4,845	0	A16	-
37	Nantong Zhongbao Pharmaceutical Co., Ltd	100%	1	1990	-	0	0	0	0	0	0	A11, A23	-
39	Anshan No.1 Pharmaceutical Factory	100%	1	1990	-	0	0	0	0	0	0	A23	A18, A21, A44
30	Sanpu Pharmaceutical Co., Ltd	100%	0	2002	-	13	13	0	1,700	1,700	0	A37	-
33	Sanjing Pharmaceutical Co., Ltd of	100%	1	2003	1200	145	0	145	15,210	0	15,210	-	A31

Enterprise ID	Name of Enterprise	Chinese Share (%)	Lines	Date of Line.	Cap. (can/hour)	CFCs Baseline (kg)	Baseline CFCs for SA[1] (kg)	Baseline CFCs for CA[1] (kg)	Total Prodt. Quantity[2] (can)	SA Prodt. Quantity (can)	CA Prodt. Quantity (can)	SA App. ID	CA App. ID
	Harbin Pharmaceutical Group												
34	Hubei Lishizhen Medical Group Co., Ltd	100%	1	2004	100	137	137	0	86,667	86,667	0	A29	-
35	Shannxi Fengwuchendayaotang Pharmaceutical Factory Co., Ltd	100%	1	2003	1800	48	0	48	6,000	0	6,000	-	A20
36	Harbin Guangji Pharmaceutical Factory	100%	1	NA	-	0	0	0	0	0	0	A25	-
38	Xian Lisheng Pharmaceutical Co., Ltd	100%	1	NA	-	0	0	0	0	0	0	-	A38
12	Glaxo SmithKline (Tianjin) Pharmaceutical Co., Ltd	0%	1	1991	1300-2000	20,390	0	20,390	1,216,000	0	1,216,000	-	A03
	Total		41			485,089	455,712	29,377	11,446,793	9,678,730	1,768,063		
	Eligible for MLF Fund		**35**			**464,355**	**455,561**	**8,794**	**10,121,216**	**9,590,363**	**530,853**		
	Not Eligible for MLF Fund		6			20,733	150	20,583	1,325,577	88,367	1,237,210		

1: SA: Skin Aerosol, CA: Cavity Aerosol; 2: Production quantity of baseline year.(average of 2003-2005).

3.2. CFCs Historical Consumption and Forecast for Future CFCs Consumption.

3.2.1. CFCs Consumption for Skin Aerosol

20. Table 2-4 shows the annual CFCs consumption data from 1996 to 2005 for Skin Aerosol. Baseline consumption is based on the average CFCs consumption of 2003 to 2005.

Table 2-4 CFCs Consumption for Skin Aerosol (1996-2005)

Year	CFC-11 Consumption (kg)	CFC-12 Consumption (kg)	Total (kg)
1996	30,519	117,596	148,116
1997	32,274	145,891	178,166
1998	33,834	133,219	167,054
1999	31,884	148,851	180,736
2000	43,007	165,436	208,443
2001	90,215	236,591	326,807
2002	124,551	296,296	420,847
2003	127,041	342,803	469,844
2004	97,120	347,122	444,242
2005	97,940	355,109	453,049
Baseline Level Average of 03-05	107,367	348,345	455,712

Chart 2-1 Annual CFC-11 Consumption for Skin Aerosol (1996-2005)

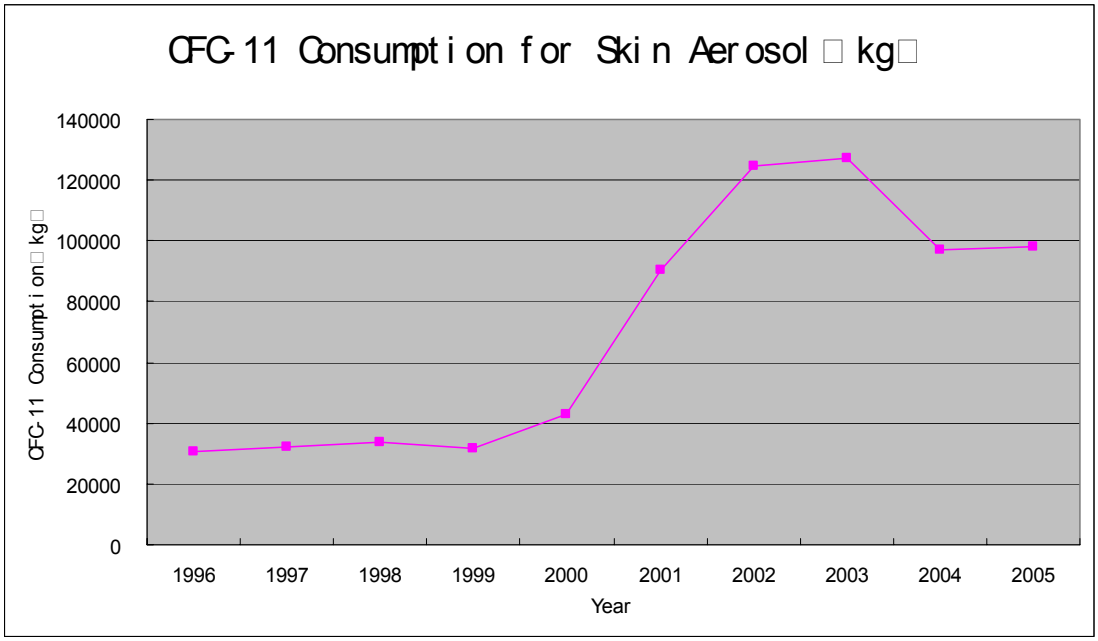


Chart 2-2 Annual CFC-12 Consumption for Skin Aerosol (1996-2005)

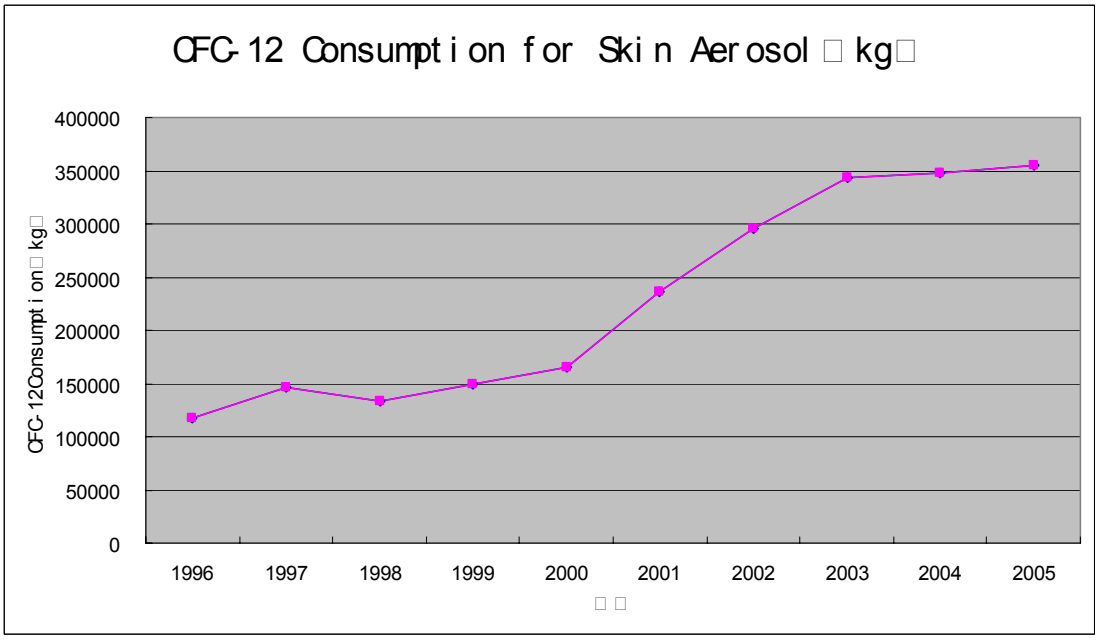
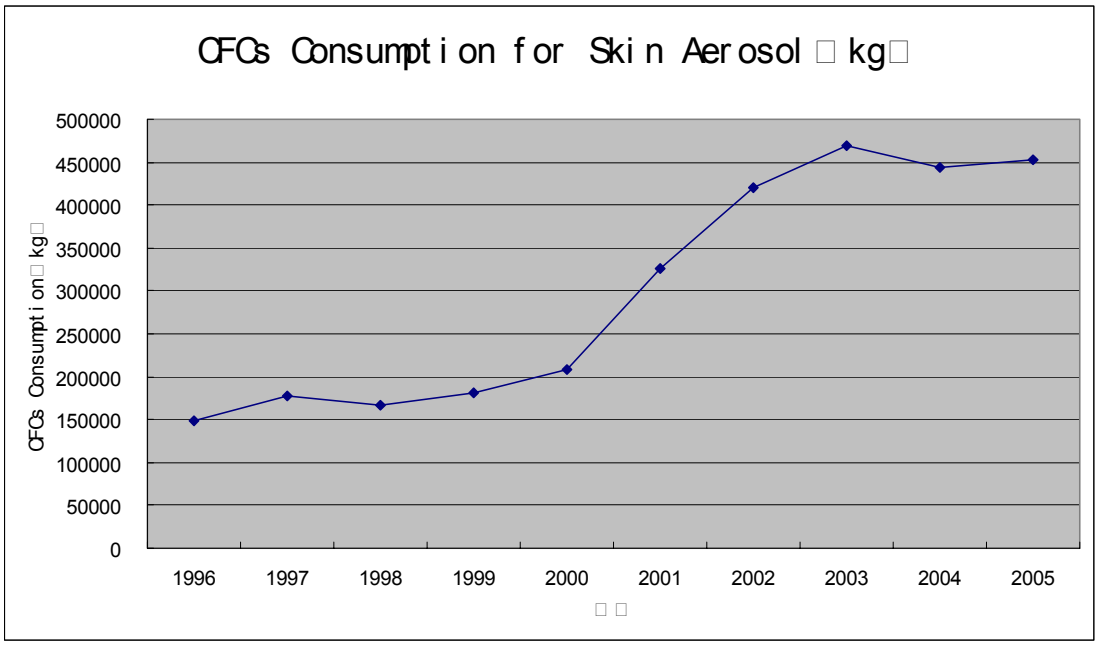


Chart 2-3 Aggregated Annual CFCs Consumption for Skin Aerosol (1996-2005)



3.2.2. CFCs Consumption for Cavity Aerosol

21. Table 2-5 shows annual CFCs consumption for Cavity Aerosol from 1996 to 2005. Baseline Consumption is based on the average CFCs consumption of 2003- 2005.

Table 2-5 CFCs Consumption for Cavity Skin Aerosol (1996-2005)

Year	CFC-11 Consumption (kg)	CFC-12 Consumption (kg)	Total (kg)
1996	1,137	2,924	4,061
1997	550	1,445	1,995
1998	1,614	6,125	7,739
1999	2,285	9,926	12,211
2000	2,058	9,881	11,939
2001	2,909	13,210	16,119
2002	1,867	10,425	12,292
2003	3,826	20,437	24,263
2004	8,228	32,471	40,699
2005	4,015	19,155	23,170
Baseline Level (average of 03-05)	**5,356**	**24,021**	**29,377**

Chart 2-4 CFC-11 Consumption for Cavity Aerosol (1996-2005)

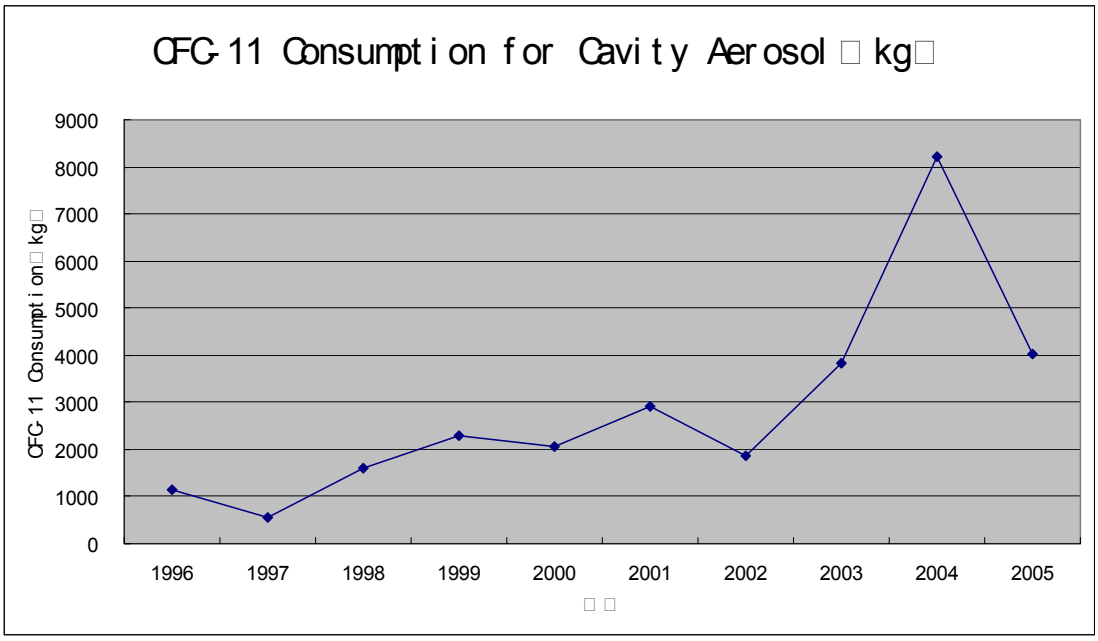


Chart 2-5 CFC-12 Consumption for Cavity Aerosol (1996-2005)

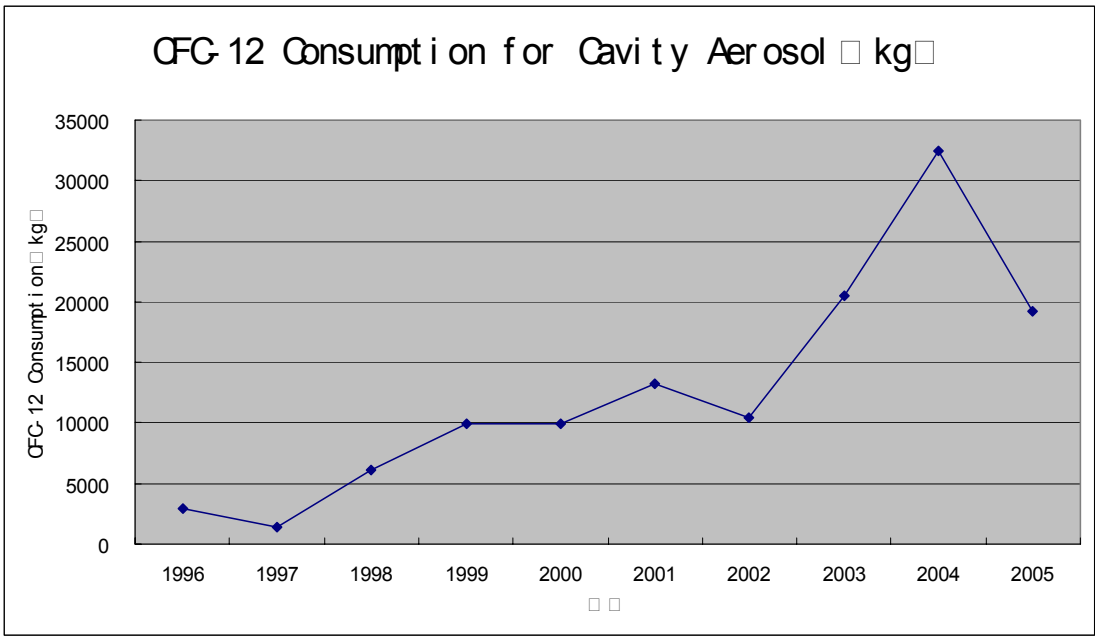
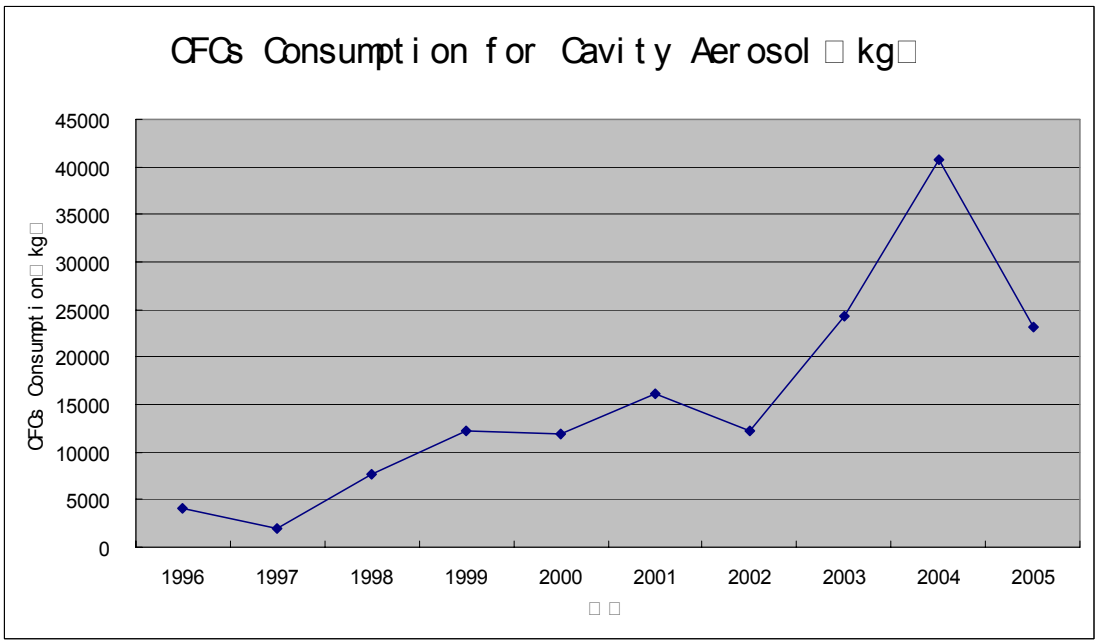


Chart 2-6 Aggregated Annual CFCs Consumption for Cavity Aerosol (1996-2005)



3.2.3. Forecast for CFCs Demand.

a) CFCs Demand Prediction for Skin Aerosol

22. CFCs consumption for Skin Aerosol increased from 1996 to 2005. Predicted by the tendency linear equation below, CFCs consumption for Skin Aerosol would reach at 700 tons in 2010.

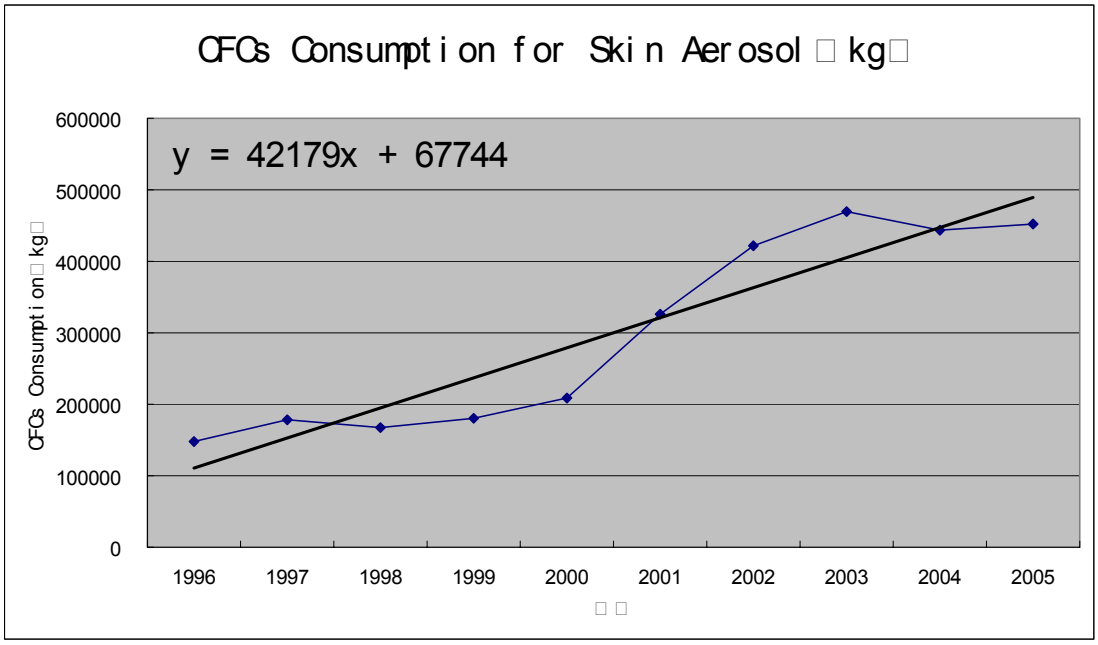
Y=42179X+67744

Where

X: The certain year minus 1995

Y: Annual CFCs consumption at a certain year;

Chart 2-7 Tendency Linear Equation for CFCs Demand Prediction for Skin Aerosol



b) CFCs Demand Prediction for Cavity Aerosol

23. CFCs consumption for Cavity Aerosol increased from 1996 to 2005. Predicted by the tendency linearity equation below, CFCs consumption for Cavity Aerosol would be about 37 tons in 2010.

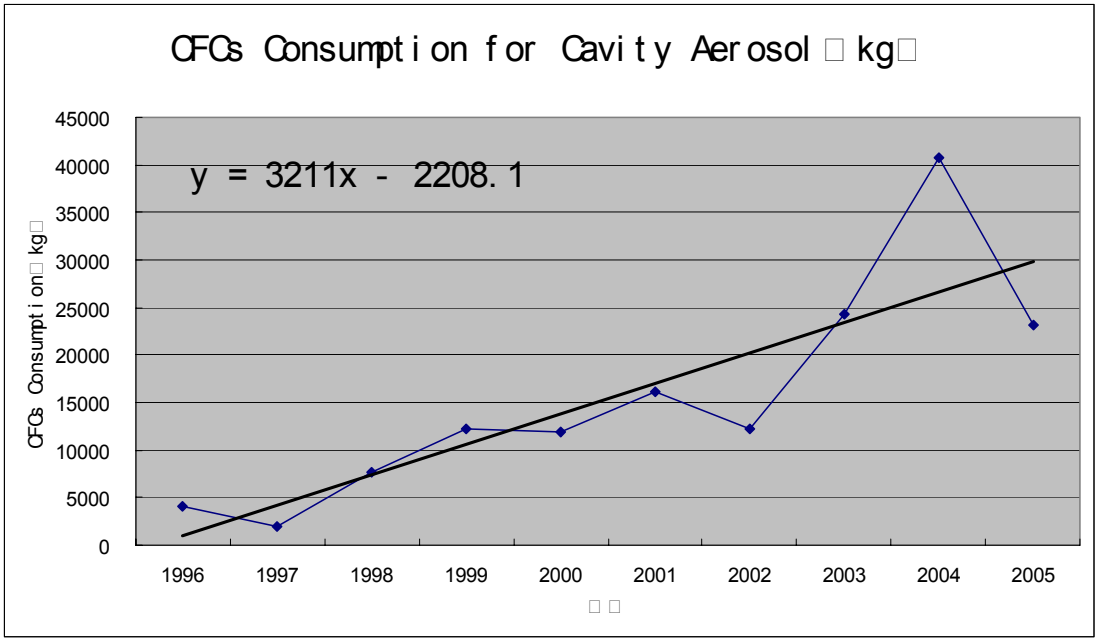
Y=3211X-2208.1

Where

X: The certain year minus 1995

Y: Annual CFCs consumption at a certain year;

Chart 2-8 Tendency Linear Equation for CFCs Demand Prediction for Cavity Aerosol



CHAPTER 3 Sector Polices

24. **Existing Policies** CFCs are used as excipients for pharmaceutical aerosol products. Replacement of CFCs with non-CFCs excipients or with different dosage form is subject to Chinese relevant laws, regulations and policies which mainly include the following:

1. Drug Administration Law of the People's Republic of China (effective since December 1, 2001)

25. This Law is enacted to strengthen drug administration, to ensure drug quality and safety for human beings, to protect the health of people and their legitimate rights and interests in the use of drugs. Article 2 of this law stipulates that all institutions and individuals engaged in research, production, distribution, use, or drug administration in the People's Republic of China shall abide by this Law. Some clauses related to the pharmaceutical aerosol sector plan include, but not limited to:

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

27. **Control over Drugs**. Article 29 stats 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 regulatory 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 administrative 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 regulatory department under the State Council.

28. Article 31 states that "A drug manufacturer may produce the drug only after an approval number is granted to it."

2. Provisions on Drug Registration issued by SFDA (No. 17, effective since May 1, 2005)

29. Article 8 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, add new indication shall be treated as a new drug application."

30. "Application for a drug already with national standards means application for production of a drug for which SFDA has already issued formal standards. Supplemental application means an application for the change, addition, or cancellation of any item or contents in the existing registration approval of a new drug, drug already with national standards, or import drug."

3. Notice of Stopping Using Chlorofluorocarbons (CFCs) as Excipients for Pharmaceutical Aerosol

issued by SFDA on June 22, 2006. In order to cooperate with China Accelerated Phaseout Plan - to stop CFCs production by June 30, 2007 - SFDA issued the following policy. As per this notice,

31. (i) China is to stop using CFCs as excipients for external-use aerosol production since July 1, 2007. CFCs-based external-use aerosols products in storage are allowed to be circulated and used until the expiration of their validity periods. China is to stop using CFCs as excipients for MDIs aerosol production since January 1, 2010. CFCs-based MDIs aerosols products in storage are allowed to be circulated and used until the expiration of their validity periods. SFDA will introduce special provisions for the transitional period from July 2007 to December 2009(see Chapter 5).

32. (ii) China is to stop importing CFCs-based external-use aerosols since July 1, 2007. CFCs-based external use aerosol products imported before this date are allowed to be circulated and used until the expiration of their validity periods. China is to stop importing CFCs-based MDIs aerosol since January 1, 2010. CFCs-based MDIs aerosol products imported before this date are allowed to be circulated and used until the expiration of their validity periods.

33. (iii) China is to stop approval of registration for external-use aerosols with CFCs as excipients from July 1, 2007 (including application for the imported CFC-based external use aerosol products). China is to stop approval of registration for MDIs aerosol products with CFCs as excipients (including application for the imported CFC-based MDIs aerosol products) since January 1, 2010.

34. (iv) Should any pharmaceutical manufacturer change excipients or dosage form of aerosols, it shall submit such applications in accordance with Provisions on Drug Registration.

CHAPTER 4 Technical Analysis

35. As CFCs propellants are degrading the ozone layer, researchers are studying on CFCs-free pharmaceutical aerosol. There are mainly two approaches to replace CFCs: i) to identify CFCs substitutes; ii) to use alternative delivery system, such as compressed-air spray, ultrasonic spray, two-phase system, self-pressurized system and dry powder inhaler. Presently, there are four commonly used CFCs substitutes: Hydrofluoroalkane (tetrafluoroethane HFA 134a and heptafluoropropane HFA 227), Dimethyl ether (DME), Hydrocarbon (isobutane) and compressed gas (e.g carbon dioxide). Substitute propellants being used in foreign countries comprise tetrafluoroethane HFA-134a, heptafluoropropane HFA-227 and DME.

1. Potential Substitutes

1) Hydrofluroalkane

36. Compared with CFCs, Hydrofluoroalkane has similar properties, poorer chemical stability and less polarity. Table 4-1 indicates the physical and chemical properties of Hydrofluoroalkane and its impact on the atmosphere in comparison to CFCs.

Table 4-1 Properties of Hydrofluoroalkane and CFCs

Item	Trichlorofluoromethane (CFC-11)	Dichlorodifluoromethane (CFC-12)	Dichlorotetrafluoroethane (CFC-114)	Tetrafluoroethane (HFA-134a)	Heptafluoroethane (HFA-227)
Molecular Formula	$CFCl_3$	CF_2Cl_2	CF_2ClCF_2Cl	CF_3CFH_2	F_3CHFCF_3
Vapor Pressure (Psig/20□)	-1.8	67.6	11.9	4.71	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	0.7	0	0
GWP*	1	3	3.9	0.22	0.7
Atmospheric Life Cycle (year)	75	111	7200	15.5	33

*Ozone Depleting Potential/ Global Warming Potential relative to CFC-11

2). Dimethyl Ether (DME)

37. Table 4-2 shows the properties of DME (CH3OCH3). DME is flammable and has low acute and

chronic toxicity. It is mainly used as CFCs substitute for external-use aerosols. One of DME's advantages is that it can be dissolved homogeneously with water at a certain proportion.

Table 4-2 Properties of DME

Molecular formula	CH_3OCH_3
Molecular weight	46.07
Boiling point	-24.9□
Vapor pressure	6kg/cm^2
Density	0.66g/ml
Water solubility	35.5%
Flammability Limits in Air, Vol %	3.4~26.7%
Damage on ozone layer	-

3). Hydrocarbon

38. Table 4-3 lists the physical properties of Hydrocarbon (mainly including isobutane, propane, and n-butane). Despite with good stability and low density, Hydrocarbon is toxic, inflammable and explosive, thus entailing high safety standard for production. Hydrocarbon is commonly blended with Hydrofluoroalkane as propellant.

Table 4-3 Physical Properties of Hydrocarbon

Chemical Name	Formula	Molecular Weight	Flashing Point (□)	Boiling Point (□)	Vapor Pressure (gauge pressure, kPa, 21.1□)	Liquid Density [21.1□ (g/cm^2)]	Flammability Limit in Air [% (ml/ml)]	
							Min.	Max.
Propane	CH3(CH2)CH3	44.1	-104.4	-42.1	744.8	0.50	2.2	9.5
Isobutane	CH(CH3)3	58.1	-32.8	-11.7	214.3	0.56	1.8	8.4
N-butane	CH3(CH2)2CH3	58.1	-73.9	-0.5	116.4	0.58	1.9	3.5

4). Compressed Gas.

39. Table 4-4 lists the physical properties of compressed gas (mainly including carbon dioxide, nitrogen and nitrogen monoxide). In comparison with DME and HFA, Compressed Gas is more chemically stable and inflammable but has lower boiling point after liquefaction and higher vapor pressure at normal atmospheric temperature, thus requiring that packaging containers should withstand higher pressure (e.g. small steel cylinder as the packaging container). If un-liquefied compressed gas is filled

in the container, pressure within the container falls rapidly and continuous injection cannot be maintained. Presently, compressed gas is basically not used for aerosol products, but for spray products.

Table 4-4 Physical Properties of Compressed Gas

Chemical name	Molecular Formula	Molecular Weight	Boiling Point (□)	Vapor Pressure (gauge pressure, kPa, 21.1□)	Inflammability
Carbon dioxide	CO_2	44.0	-78.3[1]	5767	No
Nitrogen monoxide	N_2O	44.0	-88.3	4961	No
Nitrogen	N_2	28.0	-195.6	3287[2]	No

1: Sublimation; 2: Critical temperature: -147.2□

40. During past few years, Boeheringer, Fisons, 3M, Glaxo and Riker have obtained relevant formulation patents which cover propellant system including components, co-solvent, hydrocarbon surfactant and fluoro-surfactant. It is reported that a few issues have to be solved for Hydrofluoroalkane being employed as propellants for pharmaceutical aerosol sector.

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

    ii) **Surfactant Selection.** Surfactant is to disperse medicament particles and lubricate the valve. As Hydrofluoroalkane has smaller 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 co-solvent which can dissolve surfactant.

    iii) **Drug Characteristics.** Some medicaments easily form solvate in 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 the suspended aerosol.

    iv) **Valve Selection.** As Hydrofluoroalkane is less chemically stable than CFCs, valve components (e.g airproof rubber and its additive should be compatible with propellants. 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.

v) **Alternative Actuator.** In case medicament can not be formulated into suspended aerosol, it is generally made into solution aerosol. In general, solution aerosol has poorer atomization effect. Decreasing vapor pressure of the canister results in bigger atomized particles sizes. Though increasing the pressure can reduce the particle sizes, 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.

2. Preliminary Analysis

Table 4-5 Comparison of CFCs Substitutes

	Advantage	Disadvantage	Remarks
DME	- Very soluble in water. - In aqueous solutions, the propellant is hydrolytically stable over a wide pH range. - Zero ODP.	- Acute and chronic toxicity. - May cause anesthetic effects. May irritate eyes, skin, and mucous membranes. - Flammable.	- DME is a flammable chemical. If using it as the CFCs substitute, Chinese pharmaceutical manufacturers have to renovate their workshops substantially or may have to relocate to other places. The incremental cost is likely to be astronomical.
Hydrocarbon	- Low cost of Hydrocarbon; - Zero ODP; - Negligible greenhouse effect; - Excellent solvent. - Low GWP.	- Highly flammable; - Aftertaste; - Unknown toxicity following inhalation; - Low level density. - Potential reaction and interaction with TCM. - High conversion cost.	- Hydrocarbon is a flammable chemical. If using it as the CFCs substitute, Chinese pharmaceutical manufacturers have to renovate their workshops substantially or may have to relocate to other places. The incremental cost is likely to be astronomical.
HFA	- Low inhalation toxicity; - High chemical stability; - High purity; - Zero ODP;	- Poor solvents; - GWP lower than CFC's; - High cost of HFA. - Low conversion cost.	- HFA is known to be used by foreign manufacturers as CFCs substitutes.

Compressed Gas	- Low inhalation toxicity; - High chemical stability ; - High purity; - Inexpensive; - Zero ODP.	- Require use of a non-volatile co-solvent; - Produce course droplet spray; - Pressure falls during use;	- Use of compressed gas propellant is typically restricted to applications where spray characteristics are not critical;

3. Conclusion

41. Based on the above technical analysis, it is tentatively concluded that

    a. Ideal CFCs substitutes should possess properties such as similar physical properties, insignificant damage to the atmosphere, similar toxicity, good thermodynamic property, non-inflammability and economical feasibility.

    b. Based on international literature, HFC-134a, HFA-227, DME, hydrocarbons (isobutane) and compressed gas are all potential substitutes for CFCs in pharmaceutical aerosol products. To choose the suitable substitute, Chinese pharmaceutical aerosol manufacturers have to take into account a number of factors including drug efficacy, compatibility between the substitute and drug substance, price of the substitute, different requirmenets for re-registration, safety standards, and incremental cost associated with the conversion. The manufacturers will choose a substitute that maintaine the effectiveness of their products and meet health and safety requirements at least cost. Investigation shows that majority of Chinese manufacturers are likely to use the HFA as CFCs substitute. The Sector Plan proposal is accordingly based on HFC-134a as the least cost option maintaining the product quality.

    c. The properties of DME and Hydrocarbon are not similar to those of CFCs. Exploring the conversion to DME or Hydrocarbon is technically more difficult, though the two chemicals are cheaper than HFA. Especially for Traditional Chinese Medicine Applications, there is no international experience for Chinese manufacturers. Some TCM enterprises reported that based on preliminary test, hyrdocaron is not compatible with their aerosol products.

    d. In comparison with DME and Hydrocarbon, the properties of HFA are similar to those of CFCs. Besides, international experience shows that HFA is the substitute being widely used in foreign countries.

    e. Conversion to DME or Hydrocarbon will require substantial investment in workshops modification and in some cases relocation to meet safety requirements. Due to the smaller amount of propellant used in pharmaceutical aerosols compared to general aerosol, there would not be the savings per unit from using the less costly hydrocarbon and DME. Converting to HFA-134a will require minor modification on existing equipment and associated facilities, is less costly and can be done quicker.

f. Compressed gas is often used for spray products but not for aerosol products.

CHAPTER 5 Phaseout Strategy

1. Principle.

42. The phaseout of CFCs in China pharmaceutical aerosol sector should not impose any significant negative impact on the clinic demand for aerosol products. In other words, the principle of the strategy is to phase out CFCs rather than the pharmaceutical aerosol products.

2. Two priority Issues.

43. **a. Substitute Selection**. Out of 44 aerosol applications, Chinese manufacturers have 26 Traditional Chinese Medicinal Aerosols, for which no experience can be borrowed from the abroad. Thus selection of suitable substitutes for those TCM aerosols will be challenging. Based on international experience, HFA-134a, HFA-227, DME, hydrocarbon (isobutane) and compressed gas (carbon dioxide) are deemed as potential CFCs substitutes. However, each CFCs substitute has different chemical and physical properties. Each aerosol application is different in terms of production process and formulation. Therefore, selection of suitable CFCs substitute or conversion technology (such as alternative delivery system) is the key issue for CFCs phase-out in China pharmaceutical aerosol sector. The pharmaceutical aerosol manufacturers will have to screen CFCs substitutes or conversion technology first, then determine conversion plan which covers new formulations and production process.

44. **b. Preparation for Technical Dossier for Registration**. In accordance with relevant laws and regulations, replacement of CFCs with alternative excipients is subject to the approval of the government agencies. Manufacturers have to prepare technical dossier stipulated by the regulations so as to have their CFCs-free products registered at SFDA. The preparation for registration should be immediately initiated after the completion of the substitute selection

3. New Policies Proposed.

45. **a. Policies over Transition Period (July 1, 2007~December 31, 2009).** China will stop using CFCs as excipients for external-use aerosols since July 1, 2007. Given the limited timeframe, pharmaceutical aerosol manufacturers have to use CFCs in storage before they can obtain from SFDA the approval numbers for their new products. However, using of CFC in storage would be under stringent supervision of the government. SFDA will make transitional arrangement within the framework of Country Program. 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. SEPA plans to establish a license system to control CFCs consumption for those aerosol manufacturers.

46. **b. Supervision after 2010.** After 2010, SFDA will monitor non-CFCs aerosol products so as to guarantee its safety and efficacy of clinical application.

4. Phaseout Schedule.

47. China plans to implement the CFCs phaseout for pharmaceutical aerosol sector in three stages.

    a. The first stage is to develop sector policies and to screen substitutes (January-December, 2007);

    b. the second stage is to complete registration for new aerosol products (January 2007-June 2009);

    c. In parallel, the third stage is to start new production after the completion of facility modification, production validation and staff training (July, 2007-December 2009).

CHAPTER 6 Cost Analysis

1. Basis for Cost Calculation

48. **Cutting-off Date.** The cutting-off date of July 25, 1995 should not be applied to the pharmaceutical sector as substitute aerosol technology in 1990s was not available. It is proposed that the cutting off date should be July 1, 1999 after which Article 5 Parties had the obligation to freeze CFCs production and consumption. China will not request MLF fund for seven manufacturers with production lines established after the cutting-off date. Those enterprises have to use their own funding to phase out CFCs consumption.

49. **Eligible Incremental Cost.** Cost calculation covers Technical Assistance (TA), preparation for technical dossier for registration of new aerosol products, modification on the existing facilities, production validation, staff training and two years (and not four years as used as default until the ExCom establishes guidelines for new sectors and sub-sectors)) of Incremental Operation Cost. For eligible manufacturers with baseline consumption, both Incremental Capital(IC) and Incremental Operation Cost (IOC) are considered as eligible Incremental Cost. A few eligible manufacturers have not been in production for years. However, as long as they have aerosol product approval numbers issued by SFDA, they have legal rights to resume production depending on the market demand. Therefore, for those manufacturers without the baseline consumption, only cost for substitute screening and cost for preparation for technical dossier for registration purpose are considered as eligible incremental cost.

50. **Reasons to Use HFC-134a for Cost Calculation.** Cost analysis is based on the sector survey and the literature review on international experience. It is estimated that from technical perspective, majority of Chinese pharmaceutical aerosol manufacturers may use HFA (e.g. HFA-134a, HFA-227) as CFCs substitute after screening a variety of substitutes. Besides, conversion to HFA is more financially feasible in China because in case of conversion to DME or Hydrocarbon, Chinese manufacturers have to renovate their workshops substantially or relocate to other places to meet safety standards. As CFCs has high chemical stability, it is not mandatory that the existing workshops meet national anti-explosive standards or safety standards. If converted to hydrocarbon and DME production, the existing facilities and the workshops would have to be replaced to meet the area hazard classification as per Chinese regulations. Storage vessels, pipe system and valves would have to be installed according to Chinese safety regulations, which might not in all cases be possible without relocation of workshops. As the filling takes place in special enclosed clean rooms, use of hydrocarbon as propellant would require changes to the ventilation system and enclosure as well. Consequently, the conversion cost to Hydrocarbon or DME would be very prohibitive.

51. In Chinese market, HFA-227 is slightly more expensive than HFA-134a. Besides, only limited experience on the conversion to HFA-134a is available when the sector plan is under preparation.

Therefore, the Incremental Cost calculation is based on the conversion to HFA-134a. In case any Chinese pharmaceutical aerosol manufacturer selects other substitutes (e.g. DME, Hydrocarbon or others) in the future, it is the manufacturer which has to raise sufficient counterpart funding for the renovation or the relocation of its workshops.

52. After the 50th ExCom meeting, a review of China Pharmaceutical Aerosol enterprises with zero/small CFCs baseline has been undertaken. Based on the review, China will not request funding for the following eleven enterprises which had neither pharmaceutical aerosol production in 2006 nor plans to resume such production in 2007.

Table 6-1 Enterprises without Funding Request

Enterprise ID	Name of Enterprise	CFCs Baseline (kg)	Skin Aerosol Application ID	Cavity Aerosols Application ID
28	Heilongjiang Tianlong Pharmaceutical Co., Ltd	300	A23, A25, A29	A15,A40
03	Guangzhou Baiyunshan Hejigong Pharmaceutical Co., Ltd	0	A09 A23	A40
04	Externally Applied Agent Factory of Guangzhou Baiyunshan Pharmaceutical Co., Ltd	0	A23	
06	Beijing Double-Crane Modern Pharmaceutical Technology Co., Ltd	0	A25	
10	Shanghai Fuxingzhaohui Pharmaceutical Co., Ltd	0	A42	
15	Harbin Hengcang Pharmaceutical Co., Ltd	0	A25	
22	Hangzhou Sino-US Huadong Pharmaceutical Co., Ltd	0	A23	
25	Chongqing Kerui Pharmaceutical Co., ltd	0	A10	A12
31	Guangzhou Dongkang Pharmaceutical Co., Ltd.	0		A04
37	Nantong Zhongbao Pharmaceutical Co., Ltd	0	A11, A23	
39	Anshan No.1 Pharmaceutical Plant	0	A23	A18, A21, A44
	Total	**300**		

2. Technical Assistance (TA)

53. In order to implement the sector plan smoothly, it is necessary to undertake TA activities 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 for government agencies such as local Food and Drug Administration Bureaus and Environmental Protection Bureaus on the implementation of the phaseout policies;

c. Public awareness promotion including training activities;

d. Recruitment of individual consultants to provide technical support for phaseout activities. Recruitment of consultant firms to provide technical support such as review test data and appraise feasibility study reports etc.;

e. Development of a MIS system.

f. Auditing for CFCs consumption annually for pharmaceutical aerosol manufacturers

g. Study tours to learn international experience.

h. Other TAs as necessary.

3. Incremental Cost for Manufacturers.

3.1. Substitute Screening

54. Presently, due to lack of testing data, Chinese pharmaceutical manufacturers are not able to decide which substitute is the best one for their aerosol products, particularly for those producing Traditional Chinese Medicine aerosol products. MLF Funding is requested to allow those enterprises to screen potential substitutes as mentioned in Chapter 4. The objective of the screening is to identify the best substitute or alternative delivery system for their pharmaceutical aerosol products. Due to business confidentiality and potential property rights which may arise from the conversion, manufacturers should screen substitutes by themselves. In case some manufacturers do not have such capacity, they may have to engage qualified institutions to do the screening. After the screening, manufacturers should submit feasibility study reports for the conversion to non-CFCs production, which consists of screening on formulations and production processes, preliminary evaluation on drug quality and stability, pharmacology comparison test, preliminary evaluation on toxicology and preliminary analysis on the manufacturing equipment. Those study reports will furnish technical basis to develop phase-out policies and to make arrangement for the transitional period. These reports may also provide technical reference for those non-eligible manufacturers so as to facilitate CFCs phase-out in the whole sector.

55. If suitable CFCs alternatives can not be identified for an application, it would be necessary to use alternative delivery system, such as compressed air spray, ultrasonic spray, two-phase system, self-pressurized system and dry powder inhaler. Such alternative delivery system would have to follow the same screening procedures as that for aerosol products.

56. In case some manufacturers are not able at all to identify suitable substitute or alternative delivery system, their study reports may also be used as technical basis for exemption applications for essential

use after January 1, 2010.

57. The cost for each item of the tests is shown in table 6-2. There are 41 aerosol products, so the total cost adds up to USD 1,793,750.

Table 6-2 Cost for Screening Substitutes

Item	Activity	Cost (USD)
Screening for Formulations and Production Process	Test for Formulation and Production Process	12,500
Evaluation on Quality and Stability	Evaluation on Quality-related Factors	6,250
	Preliminary Stability Test	6,250
Pharmacodynamics Comparative Test		6,250
Preliminary Toxicology Evaluation		6,250
Pre-analysis on Major Equipment		6,250
Subtotal		43,750
Number of Products		41
Total Cost (US$)		**1,793,750**

3.2. Preparation of Technical Dossier for CFCs-Free Aerosol Registration Application

58. As any change in excipients or delivery system may have consequence for the safety and efficacy, *China Drug Administration Law* and *Provisions of Drug Registration* require that pharmaceutical aerosol manufacturers apply for new registration. For the registration purpose, manufacturers have to prepare technical dossier in accordance with relevant national regulations, Table 6-3 lists the dossier for application for change of excipients already with National Standards; Table 6-4 lists the dossier for Drug Registration Application with New Excipients; Table 6-5 lists the dossier for Drug Registration Application for Change in Dosage Form.

Table 6-3 Dossier for Application for Change of Excipients with National Standards

No.	Document Name
1	photocopy of drug approval certificate and appendix
2	supporting 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	Sample of drug

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

Table 6-4 Dossier for Drug Registration Application with New Excipients

No	Document Name
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 pharmacodynamics 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

Table 6-5 Dossier for Drug Registration Application for Change in Dosage Form.

No.	Document Name
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 documents & 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

59. Cost for preparation for the technical dossier will depend on applications, selected propellants and production process. It can not be accurately calculated at the currant stage. Therefore, Table 6-6 is the best estimation based on the past experience. Six key items are included for the estimation, though there are other items not included. Compared with the Skin Aerosol, cost for dossier preparation for Cavity Aerosol is more costly because the requirement for the latter is more stringent.

60. In accordance with relevant regulations, each manufacturer has to make registration for their aerosol products based on its formulation and production process, though some products may also be produced by multiple manufacturers. Therefore, enterprises have to make registration application for total 28 Skin Aerosol products and 13 Cavity Aerosol products.

Table 6-6 Cost for Preparation for Technical Dossier for Registration

No.	Name of the data	Cost for Skin Aerosol Product (USD$)	Cost for Cavity Aerosol Product (USD$)
1	Study on Pharmacy	6,250	6,250
2	Study on Production Process	12,500	12,500
3	Study on Quality	6,250	6,250
4	Pharmacological Study	18,750	25,000
5	Toxicological Study	18,750	25,000
6	Special Safety Test	125,00	18,750
	Subtotal	75,000	93,750
	Number of Products	28	13
	Subtotal	**2,100,000**	**1,218,750**
	Total	**3,318,750**	

3.3. Modification on Existing Facilities

61. The requested incremental cost for modification on existing facilities is based on the assumption that these manufacturers will convert to a non-flammable propellant such as HFA-134a. As HFC-134a is not compatible with hermetic materials of the existing facilities, it is needed to modify or replace existing pumps, pipes, hermetic components for pipes, valves and filling&charging equipment and associated instruments.

62. Based on the sector survey, existing production lines can be divided into two groups, one is automatic (Type A), while the other is semi-automatic (Type B). Modification cost is showed in Table 6-7.

Table 6-7 Modification Cost for Existing Facilities

Items	**Type A**	**Type B**
	(USD)	**(USD)**
1.1 Storage Vessel for Propellant	15,000	15,000
1.2 Pipes and Hermetic Components(for pipes, valves, filling& charging equipment)	10,000	10,000

1.3 Pumps	12,500	12,500
1.4 Detecting Leakage Equipment	25,000	N.A
1. 5 Labor Cost	1,250	1,250
Total Cost for One Line with Baseline Consumption	63,750	38,750
Number of Lines with Baseline Consumption	13	7
Subtotal	828,750	271,250
Total	**1,100,000**	

63. In the case of conversion to Hydrocarbon, estimated modification cost based on initial assessment for enterprises would be as follows:

Table 6-8 Modification Cost for One Production Line Converted to Hydrocarbon*

Item	Cost (USD)
1.1. Replacement of Existing Filing Line	150,000
1.2 Piping and Valves	40,000
1.3. Hydrocarbon Storage Tank	30,000
1.4. Replacement of Electrical Installation and Grounding of Filling Line:	20,000
1.5. Aerosol Lid Control	5,000
1.6. Clean Room Modification and Ventilation System:	20,000
1.7. Gas Detection System:	15,000
1.8. Fireproof Facility	30,000
1.9. Installation	20,000
1.10: Safety Certification:	30,000
Subtotal	**360,000**
Number of Lines with Baseline Consumption	20
Total	**7,200,000**

* Cost for workshop relocation is not taken into accounted.

3.4. Production Validation

64. *Provisions on Quality Management for Pharmaceutical Production* (SFDA #9, effective August 1, 1998) was issued by SFDA in 1998. Article 57 stipulates that validation for pharmaceutical production shall consist of validation for workshop, validation for installation of facilities and equipment, validation for facility operation and performance and validation for products. Article 58 states that re-validation shall be carried out in case of change of main quality related factors such as production process, quality control method, main excipients and production facility,

65. In accordance with *Guidance of Validation for 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, new production technology and new product application may be introduced. Therefore, it is necessary to carry out prospective validation before commercial production. The purpose of prospective validation is to evaluate and confirm the reproducibility and reliability of production process. Concurrent validation is to obtain data from the actual process operation, so as to prove that it fulfills the expected requirements. Retrospective validation is to collect statistics data and make trend analysis after normal production for a certain period of time, thus discovering the worst conditions for the process operation and indicating the risk of potential malfunction. Revalidation includes compulsive validation, alterant validation and regular validation.

A. Validation for Changing Excipient (Alternative Propellant)

66. Changing of excipients has to conduct prospective validation, concurrent validation, retrospective validation and revalidation. The validation include 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

a) Validation for Workshop, Public Utility System and Computer System

67. Validation of workshop is to confirm that 1) reconstructed workshops shall be in compliance with design standards; 2) the flow of people and materials shall be reasonable;3) workshop cleanliness shall be up to the level of 300,000. Validation of public utilities consists of six items, namely, heating, ventilation, air conditioning, discharging system, cooling system and propellant supply system. 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.

b) Validation for Production Equipment

68. 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.

c) Validation for Production Process

(i) Validation items for dispensing preparation includes: temperature of liquid product in compound vessels, particle sizes and homogenization of the drug liquid.

(ii) Validation of cleaning effect of containers: various impurities placed into the container shall be totally removed after cleaning.

(iii) 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.

(iv) Validation items for weighting equipment include weighing accuracy and elimination of under-weighed and over-weighed samples.

(v) Validation items for the product inspection time 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.

(vi) Validation item for spray inspection include the performance of spray and elimination of samples that don't spray or don't spray constantly.

(vii) Against product quality standard, validation items for metered aerosols comprise appearance, active ingredient per actuation, times of actuation per canister, shot weight per actuation, spray distribution, microbes, etc. Validation for non-metered aerosol includes appearance, spray speed, shot weight per actuation 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.

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

d) Validation for Personnel and Other Relevant Items

69. Validation for personnel consists of establishment of filing system for each person engaged in aerosol production, including records for training, health and safety and personnel performance, etc. Validation for other relevant items includes document record, instrument calibration, preventative maintenance, production areas, and area for changing clothes, and waste cleansing and sterilization.

B. Validation for Change in Dosage Form

70. 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, which are part of production process validation. 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. Validation items for non-metered aerosol includes appearance, spray speed, shot weight per actuation 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.

71. Validation is needed for 20 production lines befor commercial production. Cost for production validation is detailed in Table 6-9.

Table 6-9 Cost for Production Validation

No.	Validation	Contents	Cost (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.	18,750
3	Others	Workshop; Public Utilities; Computer System; Others	6,250
		Subtotal for One Production Line	37,500
		Number of Production Lines with Baseline Consumption	20
		Total	**750,000**

3.5. Staff Training

72. Due to the introduction of new substitute, 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 sales.

Table 6-10 Staff Training Cost

	Production Staff	**Sales Staff**
Number of Trainees	20	40
Unit Cost (US$/person)	125	375
Subtotal (US$)	2500	15,000
Subtotal for One Production Lines(US$)	17,500	
Number of Production Lines with Baseline Consumption	20	
Total	**350,000**	

3.6. Incremental Operating Cost

73. The calculation is based on the data collected from manufacturers during the survey undertaken by NICPBP, SFDA and SEPA. Baseline production data is shown in Table 2-3. Calculation of IOC is based on the ExCom guidelines and using Incremental Operating Cost for a period of two years.

74. For the new production, the propellant, valve and canister etc. have to be changed. Table 6-11 shows the prices of CFCs and HFA-134a in 2005, which is consistent with the baseline year.

Table 6-11 Price of Propellant

	Baseline Consumption (MT)	Price (USD/MT)
CFC-11	112.723	1,643
CFC-12	365.964	2,366
CFCs Weighted Price		2,196
HFC-134a Price		7,380

75. The total production quantity of baseline year is 10,121,216 pieces of aerosol products, of which 9,590,363 are of skin aerosols. The average CFCs consumption for skin aerosol products is 47.50 gram/canister, while that for cavity aerosol is 16.57gram/canister. Literature reviews indicates that on average, HFA aerosols uses 30% less propellant than CFCs aerosols. Therefore, it is assumed that after conversion, the average HFA-134a consumption for skin aerosol products is 33.25 gram/canister, while that for cavity aerosol is 11.60 gram/canister. Calculation for Incremental Operation Cost is shown in Table 6-12.

76. Due to the price difference of HFA-134a and CFCs, it is proposed that those manufacturers be financed with two years of Incremental Operation Cost only (USD 3,536,824) (and not four year as per the general rules until the Excom decides). The IOC will be allocated to eligible pharmaceutical aerosol manufacturers based on their baseline year production.

3.7. Contingency

77. Contingency is calculated as 10% of the TA and total Incremental Capital(IC).

3.8. Deduction Due to Foreign Share

78. Out of 32 eligible manufacturers, there are three joint ventures (#13, #14, and #22) with foreign shares (i.e. British Virgin Islands and USA). Funding for these enterprises is prorated according to Chinese share. Total USD 460,230 will be deducted (see Annex I).

Table 6-12 Incremental Operation Cost

I. IOC for Skin Aerosol							
Items	Before Conversion (CFCs as propellant)		After Conversion (HFA-134a as propellant)		IOC for One Piece of Aerosol	Skin Aerosol Production Quantity	IOC for Skin Aerosol
		Unit Cost (US$/can)		Unit Cost (US$/can)			
1. Propellant		0.10433		0.24523	0.14090		
Price(USD/g)	*0.00220*		*0.00738*				
Average Propellant Consumption(g/can)	*47.50*		*33.25*				
2. Canister		0.16875		0.19125	0.02250		
3 Valve		0.04813		0.05188	0.00375		
Subtotal		**0.32120**		**0.48835**	**0.16715**	**9,590,363**	**1,603,058**
II. IOC for Cavity Aerosol							
Items	Before Conversion (CFCs as propellant)		After Conversion (HFA-134a as propellant)		IOC for One Piece of Aerosol	Cavity Aerosol Production Quantity	IOC for Cavity Aerosol
		Unit Cost (US$/can)		Unit Cost (US$/can)			
1. Propellant		0.03638		0.08552	0.04914		
Price(USD/g)	*0.00220*		*0.00738*				
Average Propellant Consumption(g/can)	*16.57*		*11.60*				
2. Canister		0.16875		0.19125	0.02250		
3 Valve		0.12250		0.47500	0.35250		
Subtotal		**0.32763**		**0.75177**	**0.42414**	**530,853**	**225,156**
III. Total IOC for one year							**1,828,214**

IOC (discount @7%)		**Cumulative**
IOC for one year	1,828,214	1,828,214
IOC for 2nd year	1,708,611	**3,536,824**[2]
ICO for 3rd year	1,596,833	5,133,657
IOC for 4th year	1,492,367	6,626,024

[2] IOC for two years is reduced to USD3,509,474 after the fund request for Heilongjiang Tianlong(Plant #28) is withdrawn.

Summary: Incremental Cost

No.	Components	Cost (USD)	
A	**Technical Assistance**	**1,100,000**	
B	**Incremental Capital Cost (Manufacturer Conversion Cost**	**7,312,500**	
B.1	Screening Substitutes		1,793,500
B.2	Cost for Preparation for Technical Dossier for Registration Application		3,318,750
B.3	Modification on Existing Facilities		1,100,000
B.4	Validation		750,000
B.5	Staff Training		350,000
C	**IOC of Two Years (discount rate@7%)**	**3,509,474**	
D	**Contingency (10% of A+B)**	**841,250**	
	Subtotal (A+B+C+D)		12,763,224
E	**Deduction Due to Foreign Share**	**- 460,223**	
	Total(A+B+C+D+E)	**12,302,994**	
	Total Requested Funding	**12,302,994**	

Chapter 7 Operation Mechanism

79. This Chapter explains the procedures for establishing funding arrangements and operating mechanisms for project management, coordination, supervision and evaluation as well as the responsibilities of various institutions involved in implementation of this Sector Plan.

1. Umbrella Grant Agreement

80. China and the World Bank have signed an Umbrella Grant Agreement in December 1997. The Agreement sets forth the terms and conditions under which grant resources approved by the ExCom in sector approaches in China would be carried out. This Agreement includes provisions that allow the Bank to disburse funds to China based on performance indicators, and will also be extended to the pharmaceutical aerosol sector.

2. Funding Arrangements

81. MLF Approval: it is anticipated that funds for this Sector Plan would be approved in two steps:

    a The Government, through the World Bank, will request that the ExCom consider this overall sector plan and agree to fund the phase-out with tranches, provided that China meets agreed annual phase-out targets for the previous year. At the same time, the Government will also apply for approval of the First Biennial Program, presently proposed to cover activities in the calendar years from 2007 to 2008, which will be submitted to the ExCom as a separate document.

    b From 2007 onwards, another Biennial Programs will be submitted to the last ExCom meeting of 2008, setting out the annual targets and funding requests. The amount of annual funding request would be consistent with the funding amounts indicated in the overall sector plan. The ExCom would be asked to release funds at the levels agreed to in the sector plan based on achievement of previous phase-out targets, so that the next Biennial Program could start in the following January. In general, approval of funds would be based on achievement of agreed ODS phase-out targets.

82. In case China fails to reach the phase-out targets for a given year, i.e., if CFCs consumption for pharmaceutical Aerosol Sector exceeds the agreed targets or the phase-out amount contracted is less than that required to meet the target, the Bank and China would agree on remedial actions before applying for the next funding. The remedial actions proposed would be to bring the program back on track in the coming year, and would be further subject to ExCom approval. Other conditions as stated in the Umbrella Grant Agreement would also apply.

83. The Biennial Program would contain the following sections:

    a Sector phase-out schedule, including phase-out activities, manufacturers involved, phase-out

approaches adopted and the phase-out timetable arranged;

b Status of all activities of previous year(s) and any agreed remedial actions if necessary, for the current year;

c Objectives of Biennial Program – phase-out targets and funding requirements for activities in the following year;

d Description of activities in the Biennial Program, including phase-out activities for the manufacturers involved, any new policies to be taken up, and technical assistance activities;

e Performance indicators of the Biennial program.

84. The World Bank would approve the technical assistance consistent with the Biennial Program, based on agreed Terms of reference for each TA (including the funding level of TA) in that year's Biennial Program.

3. Disbursement Mechanism

85. MLF disbursement to the World Bank: Upon approval of the Biennial Program by the ExCom, the Multilateral Fund will transfer the funding to the World Bank account.

86. World Bank disbursement to China: There would be four disbursements into the ODS Phase-out Account at SEPA for each Biennial Program. The Government would be allowed to request these four disbursements at any time during the year, provided that the disbursement conditions have been met. In any particular year, disbursement to China will start only when the Bank receives grants for that Biennial Program from the MLF. Disbursement conditions and amounts to be disbursed are as follows:

a ***First disbursement*** – funds for technical assistance and DIA's agency fees. ***Condition:*** Approval of the Biennial Program by the ExCom and release of funding to the World Bank.

b ***Second disbursement*** – 50% of funds allocated for manufacturer activities and 50% of China's management fees.

Conditions:

I) 30% of all contracts covering target phase-out amount of the current year's Biennial Program have been signed by government with manufacturers;

II) Progress report on this sector plan implementation is satisfactory to the Bank; and

III) Any other conditions as specified in the current Biennial Program.

c ***Third disbursement*** – 30% of funds allocated to manufacturer activities and 30% of China's management fees.

Conditions*:*

I) 100% of all contracts covering target phase-out amount and TA contracts of the current year's

Biennial Program have been signed;

II) The government reports the actual consumption does not exceed the consumption target set for the previous year (not applicable to the first implementation program);

III) A Progress report should be provided to the Bank, which is satisfactory to the Bank;

IV) the Biennial Program implementation should be considered satisfactory to the Bank; and

V) Any other conditions as specified in the current Biennial Program.

d ***Fourth disbursement*** – 20% of funds allocated to manufacturer activities and 20% of China's management fees.

Conditions:

I) Performance audit of the previous year's Biennial Program is acceptable to the Bank;

II) Progress report on sector plan implementation is satisfactory to the Bank; and

III) Any other conditions as specified in the current Biennial Program.

87. In the event that any phase-out target is not met, the Bank will suspend further disbursements to China. Disbursements will resume only after China and the Bank agree on and carry out remedial actions.

88. The grant funds will be allocated to manufacturers in consistence with the MLF funding approved for the sector. Manufacturers would sign ODS reduction contracts with SEPA.

89. The contracts will stipulate, among others, (a) Date and amount of ODS phase-out in applications; (b) the disposal equipment list, if any; (c) and agreed disposal dates.

4. Management and Coordination

90. The Government would be responsible for implementing this Sector Plan. PMO will manage and coordinate execution of each Biennial Program. In addition, SFDA and SEPA will select a qualified firm as a Domestic Implementing Agency (DIA) to help manage day-to-day activities at manufacturer level. The World Bank will supervise overall implementation of this Sector Plan, replenish the ODS IV project account, report implementation progress to the ExCom and submit future funding requests to the ExCom.

A) State Food and Drug Administration

91. State Food and Drug Administration (SFDA) will play an important role in the preparation and execution of the yearly program. Responsibilities of SFDA include the following

(i) To establish CFCs phase-out policies for pharmaceutical aerosol sector;

(ii) To organize local FDAs to impalement phase-out policies and undertake irregular spot check to the pharmaceutical aerosol manufacturers

(iii) To supervise CFCs consumption of pharmaceutical aerosol manufacturers;

(iv) To ensure adequate clinical supply of pharmaceutical aerosol products.

B) Foreign Economic Cooperation Office (FECO)

92. FECO is a management department to implement the environmental protection projects financed by the organizations of the United Nations and international or regional financial organizations. It hosts the project management office (PMO) for ODS projects. Responsibilities of FECO include the following:

a To supervise PMO activities,

b The financial division of FECO manages the ODS IV phase-out special account,

I) prepare and submit withdrawal applications to WB for advance deposit;

II) review the application of disbursement from beneficiaries according to the manufacturer contracts and TA contracts and make disbursement,

III) keep financial records and account details,

IV) Provide financial information on the ODS IV account to the audit agency and assist the work of the audit agency.

c On behalf of SEPA, sign the ODS phase-out contracts, including manufacturer contracts and TA project contracts;

d On behalf of SEPA, handover the ownership of all the equipment purchased under the ODS project to the manufacturers after the project commissioning.

C) *Project Management Office (PMO)*

93. PMO is the National Ozone Unit (NOU) of China with full responsibility to implement the international and national policies and regulations, and manage the information concerning the ozone layer protection. It is also in charge of the project selection, development and submission to the Multilateral Fund. Once the ExCom approves project, the PMO will coordinate, manage and monitor its implementation. PMO consists of the staff from Pollution Control Department, International Cooperation Department of SEPA and FECO. It is responsible for the routine management of all the activities of ODS phase-out consistent with the MP and reports to the Leading Group on key issues. PMO is set up in the FECO of SEPA. Its responsibilities are as follows:

a. To coordinate with related line ministries, industrial departments and related industrial association to jointly prepare the sector plans for completely phasing out ODS in a given sector, including the implementation mechanism and the policies in favor of ODS phase-out to ensure healthy development of industries;

b. To select the domestic implementing agents (DIA) and endorse procurement agents selected;

c. To organize and implement sector plans strictly in accordance with the agreement signed between the Chinese Government and the ExCom;

I) review of the Biennial Programs prepared by the special working groups (SWG) and submit the Biennial Programs to the ExCom through the World Bank for approval,

II) review of the work plans prepared by the SWGs,

III) approval of project documents prepared and submitted by SWGs,

IV) review of progress reports submitted by SWGs,

V) helping SWGs to solve problems encountered during project implementation,

VI) Coordinating SWGs on ODS data reporting, policy formulation, training, and information exchange.

d. To supervise SWGs' activities and provide with necessary working conditions,

e. To communicate and reach an agreement with the World Bank on the important issues during the implementation of projects,

f. To cooperate with audit agency to carry out audit,

g. To assist the World Bank and the ExCom in necessary project evaluation.

h. To be responsible for implementation of Technical Assistant Projects (TAs)

I) To define the demand on TA projects;

II) To review all of the TORs of TA projects written by the SWG;

III) To review the selection of consultants for TA projects;

IV) To authorize disbursement to all the technical assistant project;

V) To evaluate the results of technical assistant projects and determine if further improvement is necessary.

D) ***Local Environmental Protection Bureau(EPB) and Local Food and Drug Administration(FDAs)***

94. Local EPB and FDAs are bureaus with jurisdiction over the geographical areas where the project manufacturers are located. The responsibilities of local FDAs and EPBs are the following:

a. To implement the ODS phase-out policies in the region;

b. To assist to resolve the issues in the region during the implementing of the project with the request of the SFDA and SEPA;

c. To assist to verify the ODS consumption of the manufacturers, attend the project commissioning with the request of the SEPA and SFDA;

d. To supervise the disposal of the ODS equipment, if any;

e. To supervise the manufacturers to comply with ODS quota system;

f. To attend the training with the request of SFDA and SEPA.

E) ***Domestic Implementation Agent (DIA)***

95. A DIA will be competitively selected by PMO for the Sector Plan (SP) after it is approved. The DIA will assist PMO in managing the implementation of SPs and Biennial Programs. Staffs from DIA usually work with staff from PMO in the SWGs. Under the guidance of PMO, DIA will carry out the following activities:

a. Overall management --

I) Assist SWGs in project preparation and implementation;

II) Keep all project preparation and implementation documentation for audit by the audit agency during annual performance audit and for the annual verification by the Bank,

III) Input data into (monitoring and information system) MIS in a timely manner and generate various project progress reports; and

IV) Review project implementation status and report identified problems to SWGs.

b. During project Preparation --

I) Prepare work plan with SWGs for each Biennial Program;

II) Assist SWGs in publicizing the sector plan;

III) Assist SWGs in training manufacturers, local experts, and general contractor(s) if needed;

IV) Review project application submitted by manufacturers;

V) Assist SWGs to organize experts to help manufacturers in preparing project proposals and feasibility study,

VI) Assist SWGs to organize experts to help manufacturers in evaluating project proposals and feasibility study; Assist SWGs to organize experts to provide technical support to manufacturers during project implementation

VII) Supervise expert activities and verify its working load and cost, and report to the SWGs accordingly; and

VIII) Assist SWGs in project appraisal.

c. During project implementation --

I) Prepare ODS phase-out contracts and its annexes;

II) Review project implementation status and verify the progress report submitted by beneficiary manufacturers and general contractor through plant visits;

III) Review of payment applications submitted by beneficiary manufacturers, and submission of applications to sector team;

IV) Assist PMO to select the procurement agency and review the procurement organized by the procurement agency in conform with the agreed procedures;

V) Assume responsibility for supervising equipment destruction and maintain relevant data and information;

VI) Assist PMO in selecting general contractors for sub-projects, if needed, including:

- Advertise the procurement notices in specified newspaper;

- Organize local experts to prepare bidding document for general contractor and submit to PMO for approval;
- Invite bids, organize bid opening and bid evaluation;
- Prepare bid evaluation reports and submit to PMO for approval;
- Prepare contract for general contractor and sign the contract with the winning bidder together with FECO and manufacturers;

VII) Review payment requests from project beneficiaries and general contractors, and prepare disbursement requests to FECO;

VIII) maintain project documentation and coordinate sector teams to provide all information necessary for financial and performance audit, and assist audit agency whenever necessary,

IX) Organize necessary training for manufacturers,

X) Assist PMO in implementing TA projects.

d. Reporting

I) reporting on technical, financial, procurement, and management problems occurred during project implementation in a timely manner, and submission of reports to PMO with recommendations to solve problems;

II) compilation of progress reports on manufacturer activities;

III) preparation of project completion reports and commissioning report and,

IV) input of information into the MIS in a timely manner on the status of implementation of manufacturer projects.

96. The World Bank plays a major role in assisting developing countries to meet their obligations as Parties to the Montreal Protocol. The Bank partners with developing countries in its role as an implementing agency for the Multilateral Fund. The World Bank and China began their partnership on Montreal Protocol program in 1993 to help China meet its national phase-out obligations. The WB is responsible for a range of activities specified in the project document along the lines of the following:

a. assisting China in preparation of the Biennial Programs;
b. verifying for the Executive Committee that consumption of the substances have been eliminated in accordance with the targets;
c. providing a verification report to the Executive Committee bringing evidence that the targets have been met and associated annual activities have been completed as indicated in the Biennial Program;
d. ensuring that achievements in previous Biennial Program are reflected in future Biennial Programs and will serve as the progress report;
e. Reporting on the implementation status of all previous years' Biennial programs activities will be included in Biennial Program.
f. carrying out supervision missions;

g. helping China to set up an operating mechanism to allow effective and transparent implementation of the Biennial Program;

h. co-coordinating the activities of the co-coordinating Implementing Agencies, if any;

i. ensuring that disbursements made to China are based on the use of the indicators; and

j. Providing China with the necessary policy, management and technical support.

5. Monitoring and Evaluation

97. PMO is the core organization for monitoring the implementation of Biennial Programs with the responsibility for reporting to the World Bank. PMO will be responsible for tracking the implementation of policy measures and the technical assistance activities; submit progress reports to the Bank every quarter. PMO will also report on specific issues if requested.

98. DIA will oversee the progress of Biennial Programs, and submit written reports to PMO quarterly.

99. The implementation status of all activities in Biennial Programs will be reported to ExCom once a year during preparation of following year's Biennial Program, and at other times if specifically requested.

100. There are two means for monitoring and evaluating the implementation of ODS PA phase-out plan.

A) Verification

101. The Bank will conduct an independent verification annually to verify CFCs consumption and conversion activities. The Bank will supervise the implementation of Biennial Programs and will have access to any ongoing or completed manufacturers for spot checks of the records of projects, including random factory visits. The Bank will also carry out such additional verifications as are required by the ExCom.

B) Audit

102. There will be an annual financial audit of the ODS Phase-out Account at SEPA, conducted by an independent audit agency acceptable to the Bank, and a performance audit, also by an independent audit agency acceptable to the Bank.

Chapter 8 Action Plan

103. This Chapter presents the Action Plan and schedule for implementing CFCs phase-out for the pharmaceutical aerosol sector. This is a rolling plan where the impact of a Biennial Program can be spread over subsequent years. Every Biennial Program will provide detailed progress of all program activities of previous years, including policy implementation, manufacturer activities and technical assistance activities. The proposed Action Plan is summarized in table 8-1.

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

Line		Baseline (average of 03-05)	2007	2008	2009	2010
1	CFCs Consumption (newly produced CFCs)	485.089	485.089	0	0	0
2	CFCs from Stockpiled CFCs	0	0	1/	1/	1/
3	Total CFCs Consumption	485,089	485.089	0	0	0
Funding Request(US$)						
4	Enterprise-Level Activities[1]		7,693,520		3,509,474	
5	Technical Assistance Activities		1,100,000		0	
6	Support Cost		659,514		263,211	
7	Total MLF Cost		9,453,034		3,772,685	

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

1. Biennial Program

1). 2007-2008 Biennial Program: The following activities will be covered under this program:

a Substitute screening. To support manufacturers to identify substitutes for their aerosol products before the first half year of 2007.

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

c Modification of Existing Facilities, Validation and New Production.

d Workshops, trainings and public awareness promotion.

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

f Verification on CFCs consumption;

3). 2009-2010 Biennial Program: This will be submitted to the last ExCom meeting of 2008. It will consist of the following, but not limited to:

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

b Modification of Existing Facilities, Validation and New Production.

c Workshops, Trainings and public awareness promotion.

d Verification on CFCs consumptions, including final verification of all phase out targets under the sector plan.

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

2. Implementation Schedule

Stage	Activities
Start-up	To complete policy development and substitute screening
Registration Application	To complete registration for new aerosol products. Registration application for new aerosol, if possible, will be initiated in the first year.
Production	To complete modification on the existing facilities, validation for production process and training for staff.
Commissioning	To undertake project commissioning organized by SFDA and attended by SEPA, the World Bank and DIA. All the original record, report and related documents should be retained.

Table 8-2 Implementation Schedule

Year / Process	2007				2008				2009				2010			
	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q
Start-up	X	X	X	X												
Registration Application	X	X	X	X	X	X	X	X	X	X						
Production	X	X	X	X	X	X	X	X	X	X	X	X				
Acceptance													X	X	X	X

Annex I. Incremental Cost for Pharmaceutical Aerosol Manufacturers

Incremental Cost for Aerosol Producers (USD'000)

Enterp. ID	Enterprise Name	Chinese Share (%)	Line Type	CFCs Baseline (kg)	SA Prodt. Quantity (can)	CA Prodt. Quantity (can)	Incremental Capital					IOC	Subtotal	Adjusted Total
							Substitute Screening	Dossier Preparation	Modification	Validation	Training			
01	Wuxi Shanhe No.1	100%	A, B	823	26,667	0	88	150	102.5	75	35	8.62	459	459
02	Beijing Haiderun Pharmaceutical Co., Ltd	100%	-	0	0	0	131	225	0	0	0	0.00	356	356
03	Guangzhou Baiyunshan Hejigong	100%	-	0	0	0	0	0	0	0	0	0.00	0	0
04	Externally Applied Agent Factory of Guangzhou Baiyunshan	100%	-	0	0	0	0	0	0	0	0	0.00	0	0
05	Guiyang Dechangxiang Pharmaceutical Co., Ltd	100%	A	13	0	100	44	93.75	63.75	37.5	17.5	0.08	256	256
06	Beijing Double-Crane Modern Pharmaceutical Technology Co., Ltd	100%	-	0	0	0	0	0	0	0	0	0.00	0	0
07	Beijing Tongrentang	100%	B	14	0	1,267	131	262.5	38.75	37.5	17.5	1.04	489	489
08	Xinyi Pharmaceutical General Plant	100%	-	0	0	0	131	243.75	0	0	0	0.00	375	375
09	Fujian Nanshaolin	100%	A	10,684	48,571	0	88	150	63.75	37.5	17.5	15.71	372	372

Enterp. ID	Enterprise Name	Chinese Share (%)	Line Type	CFCs Baseline (kg)	SA Prodt. Quantity (can)	CA Prodt. Quantity (can)	Incremental Capital					IOC	Subtotal	Adjusted Total
							Substitute Screening	Dossier Preparation	Modification	Validation	Training			
	Pharmaceutical Co., Ltd													
10	Shanghai Fuxingzhaohui	100%	-	0	0	0	0	0	0	0	0	0.00	0	0
11	Penglai Nuokang Pharmaceutical Co., Ltd	100%	A	3,491	100,600	0	44	75	63.75	37.5	17.5	32.53	270	270
13	Hubei Nanyang Pharmaceutical Co., Ltd	70%	A	49,393	1,171,333	0	44	75	63.75	37.5	17.5	378.77	616	431
14	Shenyang Jingcheng Pharmaceutical Co., Ltd	50%	A	57,717	968,533	0	44	75	63.75	37.5	17.5	313.20	551	275
15	Harbin Hengcang Pharmaceutical Co., Ltd	100%	-	0	0	0	0	0	0	0	0	0.00	0	0
16	Pharmaceutical Plant of Hunan Bencao	100%	B	1,300	58,333	0	44	75	38.75	37.5	17.5	18.86	231	231
17	Shandong Bencao Pharmaceutical Co., Ltd	100%	B	428	0	56,720	88	187.5	38.75	37.5	17.5	46.54	415	415
18	Shandong Jewim Pharmaceutical Co.,	100%	A	12,080	276,314	41,967	131	262.5	63.75	37.5	17.5	123.79	636	636
19	Suizhou Pharmaceutical Co. Ltd.	100%	B	13	700	0	88	150	38.75	37.5	17.5	0.23	331	331
20	Guizhou Antai Pharmaceutical Co., Ltd	100%	A	20,827	580,000	0	88	150	63.75	37.5	17.5	187.56	544	544
21	Guizhou Xinyi	100%	A	229	8,333	0	44	75	63.75	37.5	17.5	2.69	240	240
22	Hangzhou Sino-US	75%	-	0	0	0	0	0	0	0	0	0.00	0	0

Enterp. ID	Enterprise Name	Chinese Share (%)	Line Type	CFCs Baseline (kg)	SA Prodt. Quantity (can)	CA Prodt. Quantity (can)	Incremental Capital					IOC	Subtotal	Adjusted Total
							Substitute Screening	Dossier Preparation	Modification	Validation	Training			
	Huadong													
23	Xinjiang Biochemistry Pharmaceutical Co., Ltd	100%	A	2,592	0	50,000	44	93.75	63.75	37.5	17.5	41.03	297	297
24	Yunnan Baiyao Group Corporation	100%	A	273,333	5,306,667	0	44	75	63.75	37.5	17.5	1716.02	1,954	1,954
25	Chongqing Kerui Pharmaceutical Co., ltd	100%	-	0	0	0	0	0	0	0	0	0.00	0	0
26	Huayi Pharmaceutical Co., Ltd	100%	B	380	0	70,000	44	93.75	38.75	37.5	17.5	57.44	289	289
27	Zhanjiang Xintongde Pharmaceutical Co., Ltd	100%	A	29,397	1,036,667	203,333	306	562.5	63.75	37.5	17.5	502.07	1,490	1,490
28	Heilongjiang Tianlong Pharmaceutical Co., Ltd	100%	A,B	300	0	33,333	0	0	0	0	0	0	0	0
29	Guizhou Hongyu Pharmaceutical Co., Ltd	100%	A	1,230	2,800	74,133	88	168.75	63.75	37.5	17.5	61.73	437	437
31	Guangzhou Dongkang Pharmaceutical Co.	100%	-	0	0	0	0	0	0	0	0	0.00	0	0
32	Shanghai Yishengyuan Pharmaceutical Co., Ltd	100%	B	112	4,845	0	44	75	38.75	37.5	17.5	1.57	214	214
37	Nantong Zhongbao Pharmaceutical Co., Ltd	100%	-	0	0	0	0	0	0	0	0	0.00	0	0
39	Anshan No.1	100%	-	0	0	0	0	0	0	0	0	0.00	0	0

Enterp. ID	Enterprise Name	Chinese Share (%)	Line Type	CFCs Baseline (kg)	SA Prodt. Quantity (can)	CA Prodt. Quantity (can)	Incremental Capital					IOC	Subtotal	Adjusted Total
							Substitute Screening	Dossier Preparation	Modification	Validation	Training			
	Pharmaceutical Plant													
30	Sanpu Pharmaceutical Co., Ltd	100%	-	13	1,700	0	0	0	0	0	0	0	0	0
33	Sanjing Pharmaceutical Co., Ltd of Harbin Pharmaceutical Group	100%	A	145	0	15,210	0	0	0	0	0	0	0	0
34	Hubei Lishizhen Medical Group Co., Ltd	100%	A	137	86,667	0	0	0	0	0	0	0	0	0
35	Shannxi Fengwuchendayaotang	100%	A	48	0	6,000	0	0	0	0	0	0	0	0
36	Harbin Guangji Pharmaceutical Factory	100%	-	0	0	0	0	0	0	0	0	0	0	0
38	Xian Lisheng Pharmaceutical Co., Ltd	100%	-	0	0	0	0	0	0	0	0	0	0	0
12	Glaxo SmithKline (Tianjin)	0%	A	20,390	0	1,216,000	0	0	0	0	0	0	0	0
	Eligible for MLF Fund						**1,794**	**3,319**	**1,100**	**750**	**350**	**3,509**	**10,822**	**10,362**
													Deduction	**-460**