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Availability and Consumption Status of CFC and Non-CFC Inhalers for Asthma and Chronic Obstructive Pulmonary Diseases in Thailand

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SUMMARY In response to the Montreal Protocol and the calls for global early-bird CFC phase-out before 2010, the demand and supply status of both CFC and non-CFC inhalers for prevention and treatment of asthma and COPD in Thailand were evaluated to determine how soon the country would be able to discontinue CFC MDIs with least impacts to both consumers and importers. Availability and supply of the inhalers were collected from registration and importation database of the Thai FDA. Demand and product cost were obtained from the local importers and from IMS, Thailand. Available inhaled products comprise of 39% CFC MDIs, 28% DPIs, 20% solutions for nebulizers and 13% HFA MDIs, respectively. All 31 brands of portable hand-held inhalers, comprising 16 CFC MDIs, 6 HFA MDIs and 9 DPIs, are imported, only solutions for nebulization are locally manufactured. Salbutamol is mostly prescribed MDI, its consumption is over 50% of all. The transition to non-CFC alternatives (HFA MDIs and DPIs) has become evidence since 2000. After being informed about the demand and supply of the inhalers, in 2005, Thai FDA has announced its CFC phase-out policy and encouraged importation of HFA alternatives by facilitating the registration and approval process. When the most prescribing CFC MDIs, salbutamol, is completely replaced with non-CFC form in 2006, Thailand would be able to reduce considerable amount of CFCs into our atmosphere.

Thailand has signed the Montreal Agreement on phase out of ozone depleting substances (mainly chlorofluorocarbons or CFCs) in production and consumption since July 7, 1989. During 1989-2004, the country has been able to reduce 92% of its importation and consumption of ozone-depleting substances. CFC metered-dose-inhalers (MDI) release approximately 28 tons a year or approximately 2% of the country's total consumption. Realizing the long-term consequences upon thinning atmospheric ozone, such as skin-cancer risk and disturbance of the global ecosystem if CFCs are still in use, the Government has actively responded the UN encouragement on discontinuing CFC consumption before 2010.

The inhaled route of administration of medication was a well established treatment modality recommended for the treatment of asthma and

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chronic obstructive pulmonary diseases (COPD) in international and Thai clinical practice guidelines.[1-4] The majority of such inhalant therapy are delivered by means of metered-dose inhalers (MDIs) which was first developed in the mid 1950's.[5]

The first propellant used in the MDIs was chlorofluorocarbons (CFCs), mainly CFC 12. CFC 11 and CFC 14 are also used in combination as pressure modifiers or as suspending or dissolving aids of the medication. This type of aerosol is called CFC-MDIs.[7]

Since 1974, CFCs have been known to be potentially harmful to the environment through depletion of atmospheric ozone layer in the stratosphere.[8] Reduction of the ozone thickness allows higher quantity of UV radiation reaching the earth surface and consequently cause vital effects to life on earth, such as increasing risk of skin cancer (squamous and basal cell carcinoma and melanoma) to human and animals. Acceleration of cataract, pterygium and retinal damage incidence, as well as variation of our ecosystem are among other consequences from the thinning ozone layer. Therefore, during the late 1980's great efforts made by the industry, including pharmaceutical companies, had been seriously searched and identified other non-ozone depleting substances which were suitable and safe to be used as alternatives. As a result, hydrofluoroalkanes (HFA) also known as hydrofluorocarbons (HFC), HFA 134a and HFA 227ea, are the only two propellants found today and widely accepted as the replacement of CFC propellants in the MDIs. This is called the non-CFC MDI.

The HFA preparations have low ozone depleting potential but still have another environmental effect known as global warming or green house effect. Moreover, some medications are not compatible with HFA propellants. To avoid compounding incompatibility, there is the need to develop other kinds of portable propellant-free inhalers, such as dry powder inhalers (DPIs).[9-11]

In 1987, an international agreement, termed Montreal Protocol on substances that deplete atmospheric ozone layer, was signed by 135 countries, then totaled to 175 countries including Thailand. The agreement called for the total phase-out of CFC production and use by the year 2000. But the use of CFC propellants in MDIs has been defined as "essential," hence, exempted from the deadline until 2009.[12] Due to the very high stability nature of the CFC compounds, it may take a hundred of years before the atmospheric ozone layer will return to its normal level. This means that people on earth will have to expose to the high level of UV radiation and take all the risk of skin cancer incidence for a hundred of years. Realizing the long-term environmental effect and health risk, the Government of Thailand through the Department of Industrial Works (DIW), the Allergy and Immunology Society of Thailand (AIST) and the Thai Food and Drug Administration (FDA) have been working together to ensure the phase-out harmonization of CFC MDI with adequate replacement of non-CFC MDI formulations with least difficulties to consumers before the deadline (year 2009) as recommended by the UN.

This study was therefore designed to investigate the present status of the availability and the consumption of CFC and its substitution of MDI products, including the estimated demand in the future. The results obtained from this study will be used as background information to formulate the National CFC Phase-Out Plan for MDI products in Thailand.

MATERIALS AND METHODS

Data of MDIs commercially available in Thailand were collected from three sources:

1. From the Division of Drug Control, Food and Drug Administration (FDA), Ministry of Public Health. All kinds of inhaled drugs used for asthma and COPD which were registered with the Thai FDA were investigated for the following data: the trade name, active ingredient(s), propellant (if any), producer and country of origin, the local importers and the registration date. The amounts of the products imported per year were available only from 1996-2003.

2. From the pharmaceutical companies which are local importers of inhaled drug formulations. In addition to the information as collected from the Thai FDA, the following data were requested from the importers themselves, i.e. the label price, the amount of sale per year dated back for five years (1999-

2003), if registered for more than 5 years, the proportion of sale compared between the sales in Bangkok and in the rural area.

3. From Index of Medical Specialties (IMS), Thailand. The amount of sale per year of each product including the proportion of sale between Bangkok and rural area during 1999-2003 and the launched date. The information from these three sources was analyzed and sorted according to the compositions of the products and classified by groups of medicines and types of propellant compositions as CFC, non-CFC or HFA MDIs, DPI and nebulized solutions. Variety of the reported package units of both active components and CFC contents were converted into the same unit before summation. The estimated quantity of CFC being released from CFC MDI consumption were calculated as the average weights of all CFC compounds contained in the products. Percentage of the demand and supply was calculated from the overall unit doses contained in a pack. The demand and supply information as obtained from the three sources were then graphically compared, analyzed and verified.

RESULTS

There is neither CFC nor MDI manufacturers in Thailand. All available MDIs, either original or generic products are totally imported from United Kingdom, Germany, Italy, Spain, Sweden, Finland, Australia and India. The MDIs registered with the Thai FDA for use in asthma and COPD are summarized according to categories: bronchodilators (also called acute relievers) and anti-inflammatory medication (also called controllers or preventers) and types of MDIs, as shown in Table 1. Inhaled bronchodilators are further subdivided into two classes, i.e., β-agonists and anticholinergics. Combination of β-agonists and anticholinergics is also available. The first CFC MDI registered for marketing in Thailand was ipratropium bromide in 1984. However, salbutamol MDIs, which came in two years later, has become the most widely available brandnames and the largest consumption of all. The first HFA MDI had come in 1992, the second one came in five years later. Presently, more and more HFA MDIs have been registered

The anti-inflammatory inhaled medication comprises of two groups- corticosteroids and cromoglycate-like drugs. The corticosteroids are: beclomethasone, budesonide, fluticasone and mometasone. The last one has only registered but not yet launched. Sodium cromoglycate is the only cromoglycate-like drugs available. Five brands are available as combinations of bronchodilator and anti-inflammatory drugs.

There are totally 47 brands of inhalers registered for treating asthma and COPD, 27 CFC MDIs, 7 HFA MDIs and 13 DPIs. However, 11 brands were later withdrawn from the market by the importers because of either marketing or safety and efficacy reasons. Moreover, the other 5 brands have not yet launched, so there are only 31 brands currently available in the market. These are 16 CFC MDIs, 6 HFA MDIs and 9 DPIs as shown in Table 2.

Even though the availability of CFC MDIs is almost three times that of HFA MDIs (as shown in Fig. 1), the trend is decreasing in numbers because original producers in developed countries will have to stop production of CFC MDIs by the year 2005. Capacities of puffs in a pack vary widely from 60 to 400 puffs, mostly 100-200 puffs. CFC contents in a puff ranged from 33 to 135 mg with the average of 85 mg. Importation of CFC MDIs in each therapeutic category during the past 8 years (1996-2003) was shown in Fig. 2 as the total numbers of puff.

The sale figures obtained from IMS (Thailand) were available as pack quantities during the past five years (1999-2003). The imported quantities of CFC MDIs were almost twice as much as the sale amounts. This might be due to some stockpiling

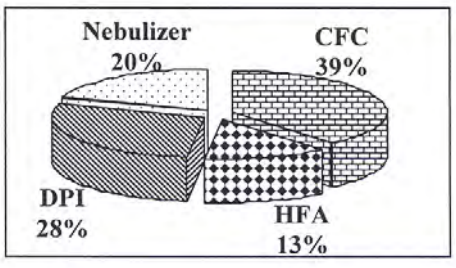

Fig. 1 Availability of CFC and non-CFC inhalers in Thailand (2003).

or some overdue sale reports. The total consumptions were therefore averaged from both sets of data during year 1999-2003, as shown in Fig. 3.

The estimated amounts of CFC released from MDIs each year during 1996-2003 are demonstrated in Fig. 4. It should be noted that the amount of CFC released in 2003 was lower than in 2002 even though the consumption of CFC MDI was about the same. This was due to more brands with lower CFC content were imported as the result of the global campaign on reduction of CFC consumption.

In response to the international agreements on combating the global environmental threat since 1987, the gradual replacement of CFC MDIs has oc-

Table 1 MDIs registered with the Thai FDA for use in asthma and COPD (data collected in 2004)

	Types of inhalers		
	CFC MDI	**HFA MDI**	**DPI**
I. Bronchodilators			
β agonists			
	Fenoterol HBr	**Fenoterol HBr**	**Formoterol fumarate**
	- Berotec®*	- Berotec®*	- Oxis® turbuhaler
	Hexoprenaline SO_4		
	- Ipradol®*		
	Orciprenaline SO_4		
	- Alupent®*		
	Procaterol		
	- Meptin Air®		
	Salbutamol SO_4	**Salbutamol**	**Salbutamol**
	- Asthalin®	- Airomir®	- Buventol® easyhaler
	- Buto Asma®		
	- Butovent®		
	- Respolin® inhaler/autohaler		
	- Servitamol®*		
	- Ventolin inhaler®*	- Ventolin® evohaler	- Ventodisk®*
	Salmeterol SO_4		**Salmeterol SO_4**
	- Serevent® inhaler - Serobid® inhaler**		- Serevent® accu-haler/rotadisk
	Terbutaline SO_4		**Terbutaline SO_4**
	- Bricanyl® inhaler		- Bricanyl® turbuhaler
Anticholinergics			
	Ipratropium bromide		**Tiotropium bromide**
	- Atrovent®		- Spiriva®
Combination of beta-agonist and anticholinergics			
	Ipratropium+Fenoterol HBr	**Ipratropium+Fenoterol HBr**	
	• Berodual®	• Berodual®	
	Ipratropium bromide +Salbutamol SO_4		
	• Combivent®		

Table 1 MDIs registered with the Thai FDA for use in asthma and COPD (continued)

	Types of inhalers		
	CFC MDI	**HFA MDI**	**DPI**
II. Antiinflammatory			
Inhaled steroids			
	Beclomethasone dipropionate	**Beclomethasone dipropionate**	**Beclomethasone dipropionate**
	- Becloforte®*	- Qvar®	- Beclomet® easyhaler
	- Becotide®*	- Clenil® inhaler / forte	- Becodisk®*
	Budesonide		**Budesonide**
	- Budecort®		- Pulmicort® turbuhaler
	- Inflammide®		
	- Pulmicort® inhaler		
	Fluticasone		
	- Flixotide® inhaler		
			Mometasone
			- Asmanex® twisthaler**
Cromoglycate-like			
	Sodium cromoglycate		
	- Intal 5® inhaler		
	Nedocromil sodium		
	- Tilade Mint®**		
III. Combination of reliever and preventer			
	Salbutamol+Beclomethasone		
	• Butosol®**		
	• Clenil Co®		
	• Ventide® inhaler*		
			Formoterol+Budesonide
			• Symbicort® turbuhaler
		Salmeterol+Fluticasone	**Salmeterol+Fluticasone**
		• Seretide® evohaler	• Seretide® accuhaler

*presently quit marketing
**not yet marketed

curred around the world including in Thailand. The first CFC-free inhaler (except Intal) launched in Thai market was DPI in 1990 while the first HFA MDI came in 1997. The average content of HFA in a puff of MDIs is 58 mg (40-75 mg range). Importation and consumption of HFA MDIs have been increasing since year 2000 as shown in Fig. 5.

Overall consumption of portable, hand-held inhalers for treating asthma and COPD are on the rise as shown in Fig. 6.

Consumption of MDIs increased to the maximum in the year 2001, then dropped a little when the country faced economic crisis. Even though all types of MDIs and DPIs are available throughout the country, approximately 80 percent of the total sale are consumed by Bangkokians which are 20 percent of the country population. This may be due to more air- pollution and higher incidence of asthma, especially in children, in the city areas. However, the overall increasing incidence indicates more needs for MDIs in the future since many

Table 2 Availability of portable inhalers for treatment of asthma and COPD in Thailand (2005)

Categories	Number of brands			
	CFC MDI	HFA MDI	DPI	Total
Bronchodilators				
- β-agonists	(13)→ 7	(3)→ 2	(6)→ 4	13
- Anti-cholinergics	1	-	1	2
- β-agonists +anti-cholinergics	2	1	-	3
Anti-inflammatory				
- Corticosteroids	(6)→ 4	2	(4)→ 2	8
- Cromoglycate-like	(2)→ 1	-	-	1
- Bronchodilator+anti-inflammatory	(3)→ 1	1	2	4
Total	(27)→ **16**	(7)→ **6**	(13)→ **9**	(47)→ **31**

Note: The numbers in parentheses are registered products.
The numbers really available in the market are not parenthesized.

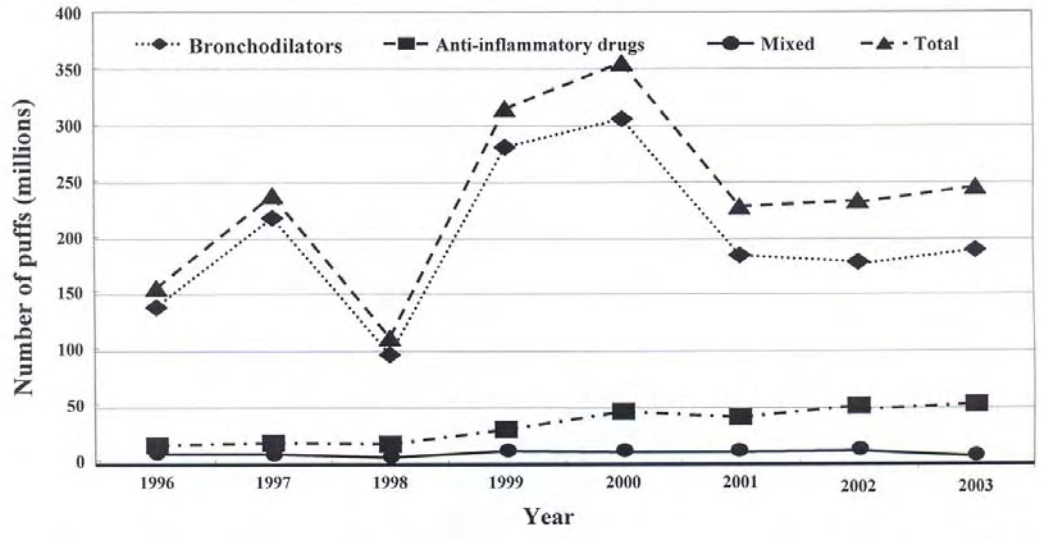

Fig. 2 Importation of CFC MDIs in Thailand during years 1996-2003.

patients who should be prescribed MDIs presently received only oral bronchodilators and/or oral steroids instead.

During the past five years, there has been some progressive transition from CFC MDIs to HFA and DPI. in Thailand as shown in Fig. 7. In 2001, importation of CFC MDIs reduced by over 37 percent while that of HFA MDIs increased tremendously (8.5 times) and significant increase of DPIs.

The transition to HFA MDIs has become more obvious this year when the Thai FDA has decided to cut down some inhalers which have appropriate substitutions by the end of 2005. The policy has received good collaboration from pharmaceutical companies by stocking their CFC MDIs for distribution in a year. Reduction of CFC MDI importation and increase of HFA MDIs are remarkably observed during the first half of 2005 as shown in Fig. 8.

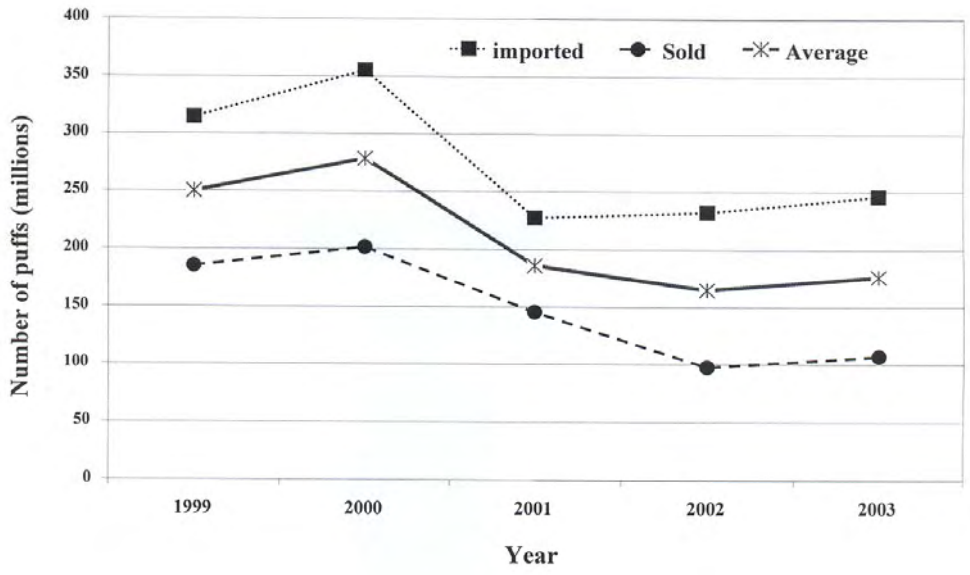

Fig. 3 Importation and sale of CFC MDIs (as unit puffs) during years 1999-2003.

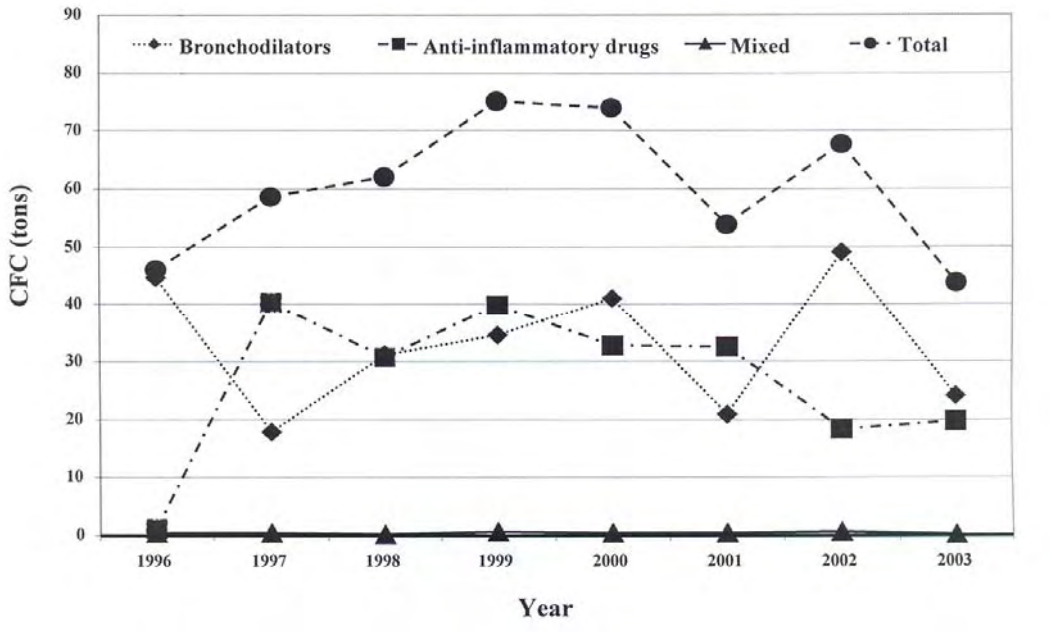

Fig. 4 Yearly estimated CFCs (tons) being released from MDIs during years 1996-2003.

DISCUSSION

Increasing prevalence of asthma and COPD are evidenced around the world. Western Europe seems to have the highest prevalence rates (children 13.0%, adults 8.4%) of asthma in the world. According to the population based surveys, there has been a 2-4% annual increase in asthma prevalence

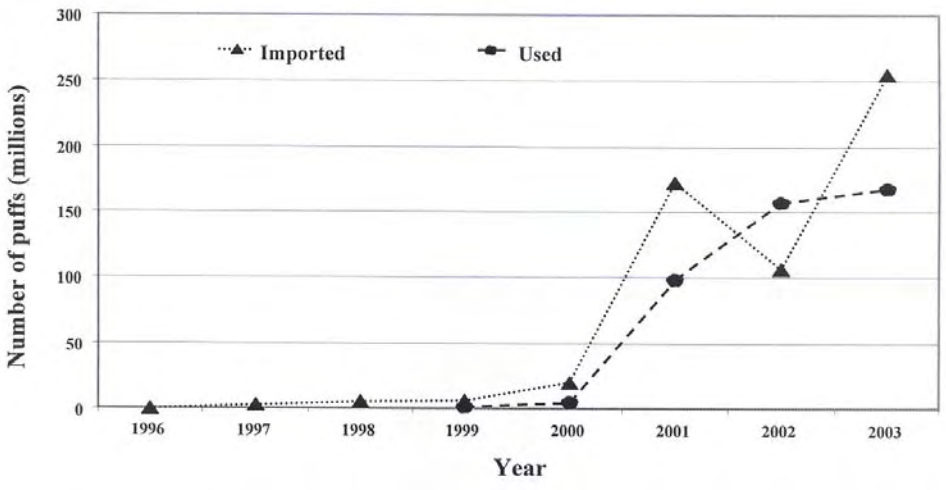

Fig. 5 Importation (1996-2003) and consumption (1996-2003) of HFA MDIs (puffs) are on the rise.

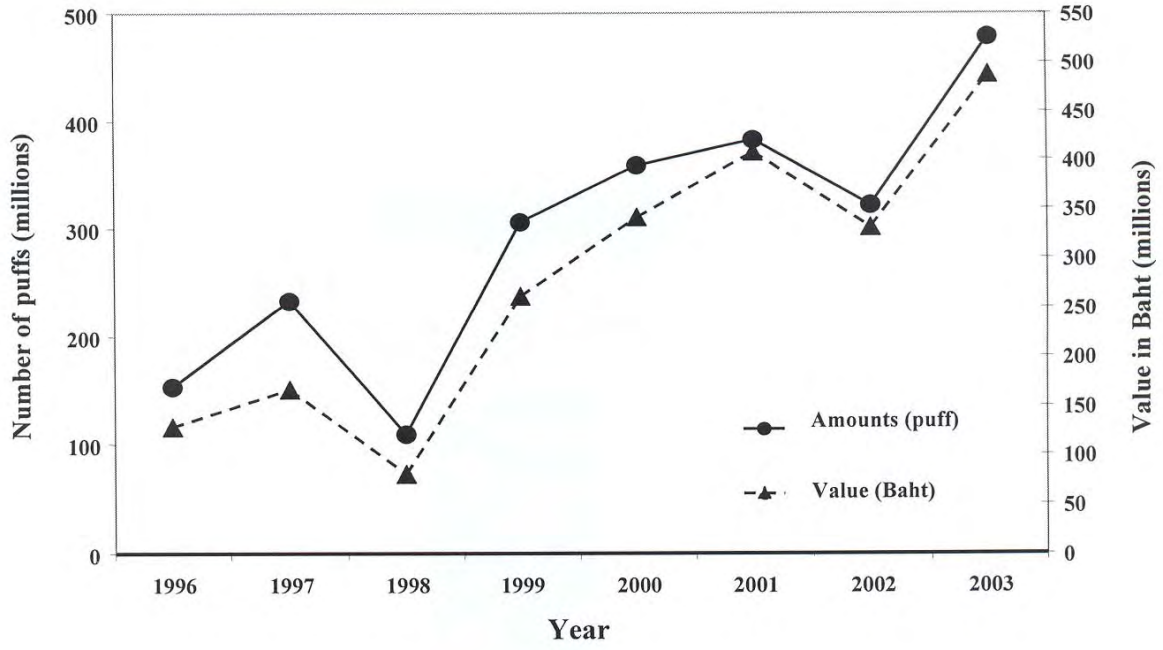

Fig. 6 Overall consumption (puff) of portable, hand-held, inhaled medicines for treating asthma and COPD in Thailand during 1996-2003, demonstrated along with its total value in Baht (millions).

rates in most European countries over the past 15 years.[14]

In Thailand, asthma prevalence in adults rose from 2.4% in 1975[15] to 4.8% in 1995[16] and to between 8.8% (diagnosed asthma) and 10% (wheeze during 12 months) in 1998.[17] In addition, the survey with 12,219 adults aged 20-44 years living in the inner area of 4 cities, Bangkok, Chiang Mai, Khonkaen and Songkla, during October 2000-April 2001 using the

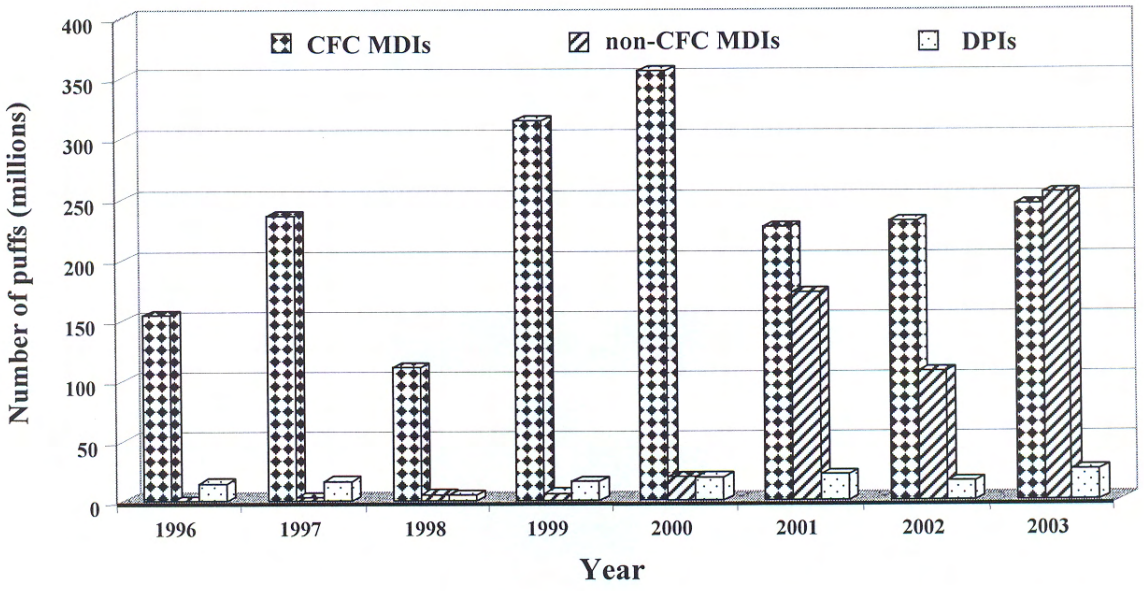

Fig. 7 Progressive transition from CFC MDIs to non-CFC MDIs and DPIs in Thailand during the past five years (1999-2003).

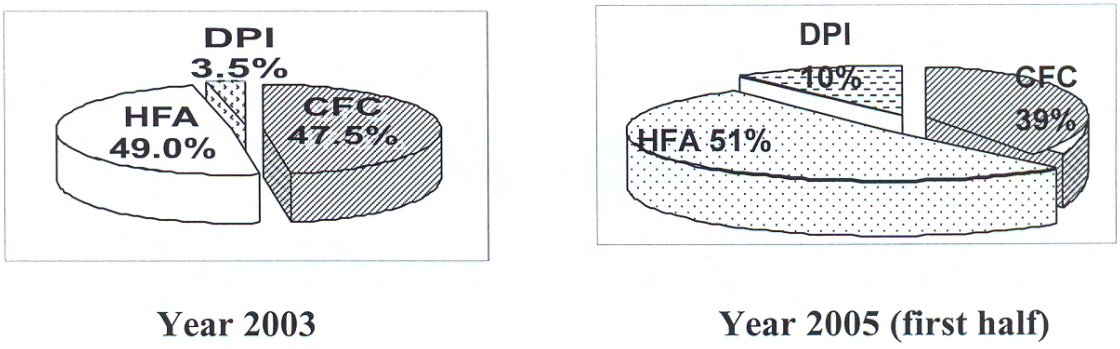

Fig. 8 Importation of inhaled products during the first half of 2005 indicated increasing market share of HFA MDIs and decreasing of CFC MDIs.

written ISAAC (International Study on Asthma and Allergy in Childhood) questionnaires and trained interviewers, indicated the national prevalence of 10.8% ever-wheeze, 6.8% current wheeze, and 4% ever-had an asthma diagnosis. Bangkok metropolitans have the highest prevalence of ever-wheeze and current-wheeze (13.6% and 9.4%, respectively).[18] On a phase I study in children, study using the ISAAC questionnaires and the validated international video questionnaires with two groups of Thai children (aged 6-7 and 13-14 years) living in Bangkok metropolitan area, the cumulative and period prevalence of wheezing were 18.3% and 12.7%, respectively. The period prevalence of wheezing increased 4 folds as compared to that in 1990 survey.[19]

The Asthma Society of Thailand (http://www.asthma.or.th) reported in the year 2000 three million Thai people (approximately 5% of the total population) were affected by asthma.

The World Health Organization (WHO) study on global burden of the diseases reported COPD as the sixth leading cause of death worldwide

in 1990. The rank is predicted to climb up to the third after ischemic heart and cerebrovascular diseases by the year 2020.[20,21]

The overall prevalence rate of COPD as estimated by its prevalence estimation model in 12 Asian and Pacific countries including Thailand was 6.3%. The model projected the prevalence of moderate to severe COPD in Thai patients aged 30 years and older to be 5%.[22]

A field study on 3,094 older persons aged 60 years and over residing in the urban community around Siriraj Hospital, showed 7.1% (95% CI = 6.2-8.0) COPD prevalence. The prevalence was over four times higher in males than in females and increased with age, 6% at 60-74 years old and up to 12.9% at over 75 years. Another survey was repeated after a year and the closest estimated incidence of COPD in the same group of the elderly, aged over 60 years old, was found to be 3.6% (95% CI = 2.8-4.4).[23]

It is essential to note that the use of MDIs for asthma control in Thailand is still suboptimal. A questionnaire survey, performed by Vichyanond *et al.*[24] in 2001, regarding prescribing practices for the management of childhood asthma, revealed the drug of choice for the treatment of acute asthma among 174 respondents be nebulized salbutamol or turbutaline (81.8%). The choice, however, does not match the availability of the inhaled products in the market where majority (80%) are CFC, HFA MDIs and DPIs. For the treatment of chronic asthma, oral bronchodilators were preferred by 88% while MDIs and DPIs preferred by only 7.7% and 6.0%, respectively.

Another survey of asthma control in four cities in Thailand (Bangkok, Chiang Mai, Khonkaen and Songkla) by Boonsawat *et al.*[25] also indicated only 36.0% of asthma adult patients used reliever medication whilst inhaled steroids was consumed by only 6.7%. These findings are not surprising since appropriate asthma therapy remains inadequate even in the United States.[26]

Nevertheless, increase understanding of the pathogenetic mechanisms underlying both asthma and COPD including the successful development of different kinds of conveniently portable MDIs, which can be easily and topically applied as either acute relievers or controllers, will tremendously increase physicians' prescribing preferences.

The overall projected consumption of portable hand-held inhalers for treating asthma and COPD in Thailand increases approximately 15% or 40 million puffs a year.

In conclusion, three forms of portable hand-held inhalers, i.e. CFC-MDIs, HFA MDIs and DPIs, are available in Thailand for treatment of asthma and COPD. Supply of inhaled products depends totally on imported products. Therefore, phase-out of CFC MDIs should not have impacts to local manufacturers. Some CFC transition has begun since 2001 through initiation of the importing companies. More and more replacement products have increasingly been available in the country. However, not all drugs have substitutions. For instance, ipratropium bromide and its combinations are available only as CFC formulation. Tiotropium bromide is available only as DPI, which is too expensive to be affordable by most patients. Besides, many drugs do not have generic alternatives. Another interesting point is that generic drugs, in general, have significantly lower price than their original brands. This is not the case for some generic MDIs because they are imported or different in device design.

The impacts of concern are those that may affect consumers, i.e. patients and prescribers, mainly on either perception of the changes and the treatment cost. Presently the prices of HFA MDIs, especially corticosteroids and combined products, are normally little higher ($\leq$ 1.2 times) than those of the CFC inhalers. Since prices of DPI products are much higher (over 2-3 times) than those of MDIs, substitution of CFC MDI with DPI may be difficult. Keeping these factors in minds when formulating the national CFC reduction plan on discontinuing consumption of CFC MDI before the year 2010, it is quite possible that Thailand can contribute to speeding up restoration of the global atmospheric ozone. After Thai FDA has been informed about the study results in December 2004, CFC MDI phase-out has become the agency's policy since then. The outcome is clearly demonstrated by the increasing import figures of HFA MDIs and the decreasing of CFCs during the first half of 2005.

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