

Use of inhalant medications with and without chlorofluorocarbon propellants in the United States, 1996-2000

Diane K. Wysowski, PhD, and Joslyn Swann, RPh, MPH Rockville, Md

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The ozone layer in the Earth's upper atmosphere protects the planet's life forms from the harmful effects of UV radiation from the sun. Some substances, including chlorofluorocarbon (CFC) propellants, deplete the ozone layer. On September 16, 1987, the United States signed an international agreement called the Montreal Protocol on Substances that Deplete the Ozone Layer and agreed to phase out production and importation of ozone-depleting substances, including CFCs.^{1,2} The Montreal Protocol was codified by Congress into US law as the Clean Air Act. Although the United States has generally banned the use of CFCs in consumer aerosols for decades, the Montreal Protocol allows the production or importation of CFCs for use in essential medical products. Most of the products considered essential are respiratory medications that use metered-dose inhalers for treatment of asthma and chronic obstructive pulmonary disease.

Metered-dose inhalers have been marketed in the United States since the mid-1960s. Aqueous intranasal corticosteroids delivered by means of CFC-free metered-dose pump sprays for the treatment of rhinitis became available in the 1980s. The first CFC-free metered-dose inhaler for the treatment of asthma was approved by the Food and Drug Administration (FDA) in 1996.

In this article we describe the progress the United States made from 1996 through 2000 in the approval and prescription of CFC-free inhalant medications.

METHODS

National data on the use of inhalant medications were derived from a pharmaceutical marketing research database purchased from IMS HEALTH, the National Prescription Audit Plus (NPA Plus, formerly called the National Prescription Audit). The NPA Plus provides national estimates of prescriptions dispensed by chain, inde-

Abbreviations used

CFC: Chlorofluorocarbon
FDA: Food and Drug Administration
NPA: National Prescription Audit

pendent, food-store, and mail-order pharmacies in the contiguous United States.³ For the year 2000, the number of dispensed prescriptions was obtained from a sample of 22,044 pharmacies and projected nationally. IMS HEALTH's pharmacy database consists of more than 34,000 reporting stores; prescription data are derived primarily from a panel of some 22,000 randomly selected stores. The pharmacies in the database account for 40% of pharmacy stores and represent 45% of prescription coverage, according to estimates of IMS HEALTH. The NPA Plus was used to obtain the annual number of dispensed prescriptions for each inhalant medication (including brand and generic names). Although the NPA Plus sampling methodologies have changed over time, the data have always been projected to obtain timely national prescription estimates.

Because of its size, national projection estimates from the NPA Plus are expected to be reliable and accurate. The database is widely subscribed to by pharmaceutical companies that can compare IMS HEALTH information with their own distribution and sales data. The NPA Plus data appear consistent with trends in prescriptions obtained from HMO databases,⁴ from state Medicaid files, and with clinical practice.⁵

Prescription data for inhalant drugs were organized by class and by CFC content (Table I). The classes include β -agonist bronchodilators, anticholinergic bronchodilators, nasal steroids, bronchial corticosteroids, bronchial nonsteroidals, and nasal nonsteroidals. We did not include data on inhaled nebulizer solutions. In general, the nasal formulations are prescribed for the treatment of rhinitis and sinusitis; the bronchial formulations are used for the treatment of asthma, chronic airway obstruction, emphysema, and bronchitis.

RESULTS

Inhalant medications organized by class and CFC content are presented in Table I. In the 5-year period from 1996 through 2000, the number of outpatient prescriptions dispensed for inhalant medications increased about 1.3-fold, from 79.4 million in 1996 to 101.4 million in 2000.³ This was largely accounted for by the increase in prescriptions of CFC-free medications that grew from 16.4 million in 1996 to 33.8 million in 2000, a 2-fold (206%) increase (Table II). Those that contained CFC propellants registered smaller growth, from 63.0 to 67.6 million dispensed prescriptions (Table II). Nasal steroids accounted for 80% of the increase in CFC-free prescriptions, β -agonists accounted for 13%, and bronchial steroids accounted for 4%.

From the Division of Drug Risk Evaluation, Office of Drug Safety, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville. The views expressed are those of the authors and do not necessarily represent the official position of the Food and Drug Administration.

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Reprint requests: Diane K. Wysowski, PhD, Division of Drug Risk Evaluation I, HFD-430, Food and Drug Administration, Parklawn Building, Room 15B-08, Rockville, MD 20857.

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Asthma, rhinitis,
other respiratory
diseases

TABLE I. Inhalant medications by class, generic and trade names, and CFC content, United States, 1996-2000

With CFCs	CFC free
β-Agonist bronchodilators	
Albuterol	Albuterol*
Ventolin inhaler	Ventolin Rotacaps (dry powder inhaler)
Proventil inhaler	Proventil HFA (metered-dose inhaler)
Salmeterol	Salmeterol†
Serevent inhaler	Serevent Diskus (dry powder inhaler)
Pirbuterol	
Maxair	
Metaproterenol	
Alupent	
Bitolterol	
Tornalate	
Epinephrine	
Primatene	
Bronkaid	
Terbutaline	
Brethaire	
Isoetharine	
Bronkometer	
Isoproterenol	
Medihaler-ISO	
Isuprel Misotmeter	
Duo-Medihaler	
Anticholinergic bronchodilators	
Ipratropium	—
Atrovent	
Combivent	
Bronchial steroids	
Fluticasone	Fluticasone
Flovent	Flovent Rotadisk (dry powder inhaler)
Triamcinolone	
Azmacort	
Beclomethasone	Beclomethasone
Vanceril	QVAR (metered-dose inhaler)
Beclovent	
Vanceril DS	
Flunisolide	Budenoside
Aerobid	Pulmicort Turbuhaler (dry powder inhaler)
Dexamethasone	
Dexacort	
Nasal steroids	
Beclomethasone	Beclomethasone
Vancenase	Vancenase AQ
Beconase	Vancenase AQ 84
Triamcinolone	Beconase AQ
Nasacort	Triamcinolone
	Nasacort AQ
	Trinasal spray
Budenoside	Budenoside
Rhinocort nasal inhaler	Rhinocort AQ
	Fluticasone
	Flonase
	Mometasone
	Nasonex
	Flunisolide
	Nasarel
	Nasalide
Dexamethasone	
Dexacort	
Bronchial nonsteroidal drugs	
Cromolyn	
Intal	
Tilade	
Nasal nonsteroidal drugs	
	Cromolyn
	Nasal crom (OTC)
	Ipratropium
	Atrovent nasal spray

*Ventolin HFA (albuterol sulfate HFA) metered-dose inhaler was approved by the FDA in April 2001.

†Foradil (formoterol) dry powder inhaler was approved by the FDA in February 2001.

TABLE II. Number of dispensed outpatient prescriptions (in millions) for inhalant medications by class and CFC content, United States, 1996-2000

	1996	1997	1998	1999	2000
β-Agonist bronchodilators					
With CFCs	34.8	35.1	35.4	37.2	36.8
CFC free	0.4	1.5	2.8	4.0	4.5
Anticholinergic bronchodilators					
With CFCs	6.1	6.6	7.6	8.4	8.8
CFC free	—	—	—	—	—
Bronchial steroids					
With CFCs	12.8	13.9	14.8	15.8	16.2
CFC free	—	0.001	0.3	0.8	1.3
Nasal steroids					
With CFCs	7.1	6.4	6.3	5.8	4.7
CFC free	14.4	16.7	20.4	24.2	27.2
Bronchial nonsteroidal drugs					
With CFCs	2.2	2.0	1.7	1.5	1.1
CFC free	—	—	—	—	—
Nasal nonsteroidal drugs					
With CFCs	—	—	—	—	—
CFC free	1.6	1.2	0.9	1.0	0.8
Total					
With CFCs	63.0	64.0	65.8	68.7	67.6
CFC free	16.4	19.4	24.4	30.0	33.8

Source: IMS HEALTH, NPA Plus; time period, 1996 through 2000, excluding the Long Term Care channel.

DISCUSSION

During the period from 1996 through 2000, the number of outpatient prescriptions dispensed for inhalant respiratory medications increased about 1.3-fold, whereas prescriptions for CFC-free inhalant medications increased 2-fold (206%). Nasal steroids accounted for 80% of the increase in CFC-free prescriptions, β-agonists accounted for 13%, and bronchial steroids accounted for 4%. Despite this increase, a large proportion of inhalant medications containing CFC propellants are still being prescribed.

In 1974, Molina and Rowland, who together with Crutzen received the 1995 Nobel Prize in Chemistry for their work in atmospheric chemistry, proposed that stratospheric ozone might be destroyed by industrially produced chlorine- and bromine-containing stable substances, such as CFCs commonly used in spray cans, refrigerators, and air conditioners.^{6,7} These inert substances are slowly decomposed in the stratosphere by high-energy UV radiation, and reactive chlorine and bromine are released. Although complicated by substantial daily, seasonal, and annual fluctuations (on the order of 20%), a gradual downward trend (on the order of 3%-6% per decade at midlatitudes) in the amount of stratospheric ozone has been measured in temperate and polar climate zones over the last 2 decades.⁶ However, unanticipated ozone holes caused by the generation of reactive chlorine on the surface of ice crystals in high-altitude polar clouds have developed seasonally,⁷⁻⁹ in which depletion of stratospheric ozone has been measured at greater than 50%.⁶ In October 1999, data from a Total

Ozone Mapping Spectrometer Earth Probe⁹ revealed depletion rates over the Antarctic that were “unprecedented” for that time of year. And between early January and mid-March 2000, scientists found that the concentration of ozone at an altitude of 60,000 feet over the Arctic declined by a “remarkable” 60%,¹⁰ a loss nearly as large as in the record-setting year 1997. The resultant increase in DNA-damaging UV radiation¹¹ is expected to deleteriously affect the planet’s life forms, including humans.⁷⁻⁹ In the austral spring of 1990 in the southern ocean waters near Antarctica, scientists documented alteration of the balance of spectrally dependent phytoplankton processes, including photoinhibition, photoreactivation, photoprotection, and photosynthesis.¹² Predicted human health effects associated with ozone depletion include increases in basal and squamous cell cancers, malignant melanomas, cataracts, and immunosuppression.⁷⁻⁹ In addition, there are other ecologic consequences,^{7-9,11,12} including a possible interaction with global warming.¹¹

Although CFCs in metered-dose inhalers constituted a small percentage of CFC use in the past, since 1996, their use in metered-dose inhalers for the treatment of asthma and chronic obstructive pulmonary disease is the only legal use of newly produced or imported CFCs in the United States. The FDA has not set a target date for the elimination of CFCs from metered-dose inhalers for the treatment of asthma and chronic obstructive pulmonary disease. Rather, the FDA will apply criteria, with public input, to determine whether the CFC metered-dose inhalers remain “essential” as CFC-free products are approved and used.¹ In a proposed rule published in the Federal Register in September 1999,¹ the FDA requested public comment on whether to eliminate the essential designation for nasal steroids. As of the writing of this report, the final regulation is still pending. Since 1996, it has not been legal to use newly imported or produced CFCs in nasal steroids. However, they have been produced with stockpiled CFCs. When the use of nasal

steroids containing CFCs is no longer considered essential, their marketing will no longer be allowed in the United States. Likewise, as CFC-free medications represented in other respiratory classes gain popularity, other classes would be expected to follow. In the meantime, physicians should be aware of CFC propellants in medications and encourage non-CFC inhalant use.

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REFERENCES

1. Proposed rule. Use of ozone-depleting substances; essential use determinations. Docket No. 97N-0023. In: Federal register. Rockville (MD): Food and Drug Administration; 1999 Sep 1.
2. Ozone Secretariat, United Nations Environment Programme. Synthesis of the reports of the Scientific, Environmental Effects, and Technology and Economic Assessment Panels of the Montreal Protocol-1999. Nairobi: The Secretariat; 1999. Available at: www.unep.org/ozone and www.unep.ch/ozone. Accessed 2001 Aug 17.
3. IMS HEALTH. National Prescription Audit Plus; time period includes 1996-2000, excluding the Long-Term Care channel. IMS Health; Plymouth Meeting, Pa.
4. Wysowski DK, Swann J, Vega A. Use of isotretinoin (Accutane) in the United States: rapid increase from 1992 through 2000. *J Am Acad Dermatol* 2002;46:505-9.
5. Wysowski DK, Golden L, Burke L. Use of menopausal estrogens and medroxyprogesterone in the United States, 1982-1992. *Obstet Gynecol* 1995;85:6-10.
6. De Grijl FR, van der Leun JC. Environment and health: 3. Ozone depletion and ultraviolet radiation. *CMAJ* 2000;163:851-5.
7. Tong S. the potential impact of global environmental change on population health. *Aust N Z Med* 2000;30:618-25.
8. Farman JC, Gardiner BG, Shanklin JD. Large losses of total ozone in Antarctica reveal seasonal ClOx and NOx interaction. *Nature* 1985;315:207-10.
9. Hole in ozone grows. *The Washington Post* 2000 Sep 11; Sect A:9.
10. Bad year for ozone over Arctic. *The Washington Post* 2000 Apr 10; Sect A:9.
11. McKenzie R, Connor B, Bodeker G. Increased summertime UV radiation in New Zealand in response to ozone loss. *Science* 1999;285:1709-11.
12. Smith RC, Prezelin BB, Baker KS, Bidigare RR, Boucher NP, Coley T, et al. Ozone depletion: ultraviolet radiation and phytoplankton biology in Antarctic waters. *Science* 1992;255:952-9.