Market Characterization of the U.S. Metered Dose Inhaler Industry

Prepared for:

Stratospheric Protection Division
Office of Air and Radiation
U.S. Environmental Protection Agency
Washington, D.C. 20460

Prepared by:

ICF
2550 S Clark St.
Suite 1200
Arlington, VA 22202

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1. Summary

Metered dose inhalers (MDIs) are handheld pressurized inhalation systems that deliver small, precisely measured therapeutic doses of medication directly to the airways of a patient. MDIs treat health conditions such as asthma and chronic obstructive pulmonary disease and are approved by the Food and Drug Administration (FDA). The pharmaceutical industry historically used chlorofluorocarbons (CFCs), specifically CFC-11, CFC-12, and CFC-114, as a propellant. The pharmaceutical industry introduced hydrofluorocarbon (HFC) (also known as hydrofluoroalkanes (HFA)) propellants for MDIs as replacements for CFCs in the mid-1990s, specifically HFC-134a in 1996 followed by HFC-227ea in 2006.[1]

By 2014, the CFC MDI market was fully replaced with HFC MDIs and not-in-kind (NIK) medical inhalers. In 2020, approximately 1,284 metric tons (MT) of HFC-134a and 207 MT of HFC-227ea propellant were contained in MDIs sold in the United States. The use of HFC MDIs in the United States is expected to continue as they may be more appropriate for certain patients than NIK medical inhalers, such as when the patient requires a reliever medication for exacerbations of asthma, patient preference, or other requirements (e.g., inhalation strength) (GSK 2019, MCTOC 2018, IPAC 1999). In 2025, approximately 1,373 MT of HFC-134a and 222 MT of HFC-227ea propellant is estimated to be sold in MDIs.

2. Introduction

MDIs treat health conditions such as asthma and chronic obstructive pulmonary disease (COPD), providing reliable and effective therapy, and are approved by the FDA (MCTOC 2018). They are handheld pressurized inhalation systems that deliver small, precisely measured therapeutic doses of medication directly to the airways of a patient.[2] According to the Centers for Disease Control and Prevention (CDC), in 2018 in the United States, 19.2 million adults and 5.5 million children had asthma while 12.8 million adults had some form of COPD (CDC 2018a, CDC 2018b).

The pharmaceutical industry historically used CFCs, specifically CFC-11, CFC-12, and CFC-114, as a propellant in MDIs. In response to the phaseout of CFCs under both the Clean Air Act and the *Montreal Protocol on Substances that Deplete the Ozone Layer* (Montreal Protocol), the pharmaceutical industry introduced HFC propellants for MDIs as replacements for CFCs in the mid-1990s, specifically HFC-134a in 1996 followed by HFC-227ea in 2006. Medication for asthma and COPD also shifted in part to not-in-kind (NIK) products in the form of dry powder inhalers (DPIs). The remainder of this report characterizes HFC use by the pharmaceutical

[1] In the pharmaceutical industry, HFC is also referred to as HFA and HFC-134a is occasionally referred to as norflurane.

[2] MDIs can be used to administer medicine orally or nasally. Only MDIs designed for oral use are considered in the scope of this market characterization.

industry for MDIs in the United States, including key market players and historical and current sales of HFC MDIs and other medical inhalers.

3. Market Characterization

This section provides an overview of MDI products and applications as well as the current market and key manufacturers.

3.1. Overview of MDI Products

MDI devices include a valve and actuator designed to facilitate a consistent delivery of a specific dose of a drug to the patient in particles of a specific size distribution delivered via a propellant. MDIs require gas propellants with vapor pressures that allow them to be liquefied at ambient temperatures at pressures between 40 and 70 psi inside the canister. Propellants used in MDIs for inhaled medications must be certified by the FDA as *current Good Manufacturing Practice* (cGMP) inhalation grade with high purity levels. Propellants for MDIs must meet cGMP requirements for the methods, facilities, and controls used in manufacturing, processing, and packaging to ensure the product is safe for use and that it has the ingredients and strength it claims to have (FDA 2020a).

MDI Products Available in 2020

- Albuterol Sulfate
- Beclomethasone Dipropionate
- Budesonide
- Ciclesonide
- Epinephrine
- Fluticasone Propionate
- Formoterol Fumarate
- Formoterol Fumarate Dihydrate
- Glycopyrrolate
- Ipratropium Bromide
- Levalbuterol Tartrate
- Mometasone Furoate
- Salmeterol Xinafoate

The first HFC MDI approved by the FDA was for albuterol sulfate utilizing HFC-134a propellant in 1996. As of 2020, the number of FDA-approved MDI products has expanded considerably (FDA 2020b). Current MDI products and their FDA approval dates are shown in Table 1. As of 2018, salbutamol (also known as albuterol) sulfate MDIs still represent approximately 60% of the overall MDI market in the United States (ICF 2020). Inhalation grade HFC-227ea and HFC-134a are both used in MDIs as a propellant.

3.2. Major Manufacturers

The United States manufactures MDIs and imports MDI products and/or medical grade HFC for MDI product manufacture from European Union (EU) member states, Asian countries, and Mexico. Manufacturers of HFC MDIs available in the United States are listed in Table 1 by product name, active ingredient, propellant type, and date of FDA approval.[3]

[3] Several manufacturers of MDIs also produce DPIs under the same product line. See Appendix A for a list of DPI manufacturers.

Table 1. Manufacturers of Currently Available HFC MDIs for use in the United States

Manufacturer[a]	MDI Product Name[a]	Active Ingredient[a]	FDA Approval Date[b]
HFC-227ea			
AstraZeneca	Symbicort®	Budesonide; Formoterol Fumarate Dihydrate	07/21/2006
Merck Sharp and Dohme	Asmanex® HFA	Mometasone Furoate	04/25/2014
Merck Sharp and Dohme	Dulera®	Mometasone Furoate; Formoterol Fumarate Dihydrate	06/22/2010
HFC-134a			
Sunovion Pharmaceuticals Inc	Xopenex®	Levalbuterol Tartrate	03/11/2005
AstraZeneca	Bevespi Aerosphere®	Formoterol Fumarate; Glycopyrrolate	04/25/2016
	Breztri Aerosphere®	Budesonide; Formoterol Fumarate; Glycopyrrolate	07/23/2020
Boehringer Ingelheim	Atrovent®	Ipratropium Bromide	11/17/2004
Covis Pharma B.V.	Alvesco®	Ciclesonide	01/10/2008
GlaxoSmithKline	Advair®	Fluticasone Propionate; Salmeterol Xinafoate	06/08/2006
	Flovent®	Fluticasone Propionate	05/14/2004
	Ventolin®	Albuterol Sulfate	04/19/2001
Kindeva Drug Delivery LP[e]	Proventil® HFA	Albuterol Sulfate	08/15/1996
Teva	ProAir®	Albuterol Sulfate	10/29/2004
Norton Waterford LTD	QVAR® Redihaler™	Beclomethasone Dipropionate	08/03/2017
Armstrong Pharmaceuticals Inc.	Primatene Mist	Epinephrine	11/07/2018
Cipla LTD	Generic Albuterol Sulfate Inhaler	Albuterol Sulfate	04/08/2020
Lupin Inc	Generic Albuterol Sulfate Inhaler	Albuterol Sulfate	08/24/2020
Perrigo Pharmaceuticals Co	Generic Albuterol Sulfate Inhaler	Albuterol Sulfate	02/24/2020
Unspecified			
Catalent Pharmaceuticals[c,d]	N/A	N/A	N/A

N/A: Not Applicable.

Note: The companies in this report may not represent an exhaustive list of all companies manufacturing within the United States. In addition, there are companies that acquire licensing to commercially distribute MDIs and/or authorizations to produce generic MDIs that are not listed in the table. For example, Sandoz, Inc. has recently acquired licensing of commercial distribution rights to Proventil® HFA and authorized generic of respiratory inhalation medicine Proventil® HFA (albuterol sulfate) Inhalation Aerosol (Sandoz 2021). However, it is not known whether such companies have begun production of generic MDIs. [a] FDA (2020c).

[b] FDA (2020b).

[c] Catalent Pharmaceuticals (2021b).

[d] Catalent Pharmaceuticals manufactures MDI products as a contractor to other pharmaceutical companies, which may include other MDI products listed in this table (Catalent Pharmaceuticals 2021b).

[e] Kindeva Drug Delivery LP manufactures MDI products, including Proventil® HFA and others that may be listed in this table, as a contractor to other pharmaceutical companies (Kindeva Drug Delivery LP 2021).

4. Subsector Background and HFC Use

4.1. Propellants in Medical Inhalers

Historically, the pharmaceutical industry relied on CFC propellants, including CFC-11, CFC-12, and CFC-114, which have significant ozone depletion potential (ODP) and have been phased out under the Clean Air Act and Montreal Protocol. MDI manufacturers began transitioning to non-ozone-depleting HFC propellants in the mid-1990s with the introduction of HFC-134a in 1996 followed by HFC-227ea in 2006 (ICF International 2016, EPA 2020).[4] HFCs were the preferred propellants as MDIs transitioned from CFCs because HFC propellants allowed for the same continuation of MDI therapy without the ozone depleting potential. By keeping the function of the therapy the same, there was no change to the way a patient interacted with the MDI (IPAC 1999).

Table 2 summarizes the environmental characteristics, including ODP and global warming potential (GWP), for current MDI propellants.

Table 2. Environmental Characteristics of Propellants in MDIs

Propellant	ODP[a]	GWP[a]
HFC-134a	0	1,430
HFC-227ea	0	3,220

Note: GWPs are aligned with the exchange values used in the AIM Act.
[a] Ozone Secretariat (1987).

HFC-227ea and HFC-134a have demonstrated similar properties to CFC propellants. HFC-227ea has a lower vapor pressure, so it has primarily been used in HFC-134a formulations to lower the pressure and provide improved drug substance solubility in certain formulations (Mexichem Fluor 2015). Advances in valve technology have made the use of HFC-227ea not technically necessary in HFC-134a formulations to reduce the pressure (Noakes n.d.).

The pharmaceutical industry also made significant shifts toward NIK inhalers such as DPIs and, more recently, soft mist inhalers (SMIs).[5,6] These NIK inhalers have no ODP and no GWP as they do not contain any propellant. DPIs deliver powdered medication that is propelled by the inhalation of the patient (MCTOC 2018).

[4] Under 21 CFR 2.125(e) the FDA determined which uses of ODS in metered-dose inhalers was essential. Through rulemakings FDA determined that the use of ODS in MDIs was not essential when at least one non-ODS product with the same active moiety was marketed with the same route of administration, for the same indication, and with approximately the same level of convenience of use as the ODS product containing that active moiety.
[5] The only manufacturer of FDA-approved SMIs is Boehringer Ingelheim (FDA 2020c).
[6] The lengthy development and regulatory timescales, the rarity of new technical advancements, as well as the higher costs for new SMIs compared to MDIs and DPIs make SMIs less relevant to the discussion of the current and near future pharmaceutical market and will therefore not be discussed further in this market characterization (MCTOC 2018).

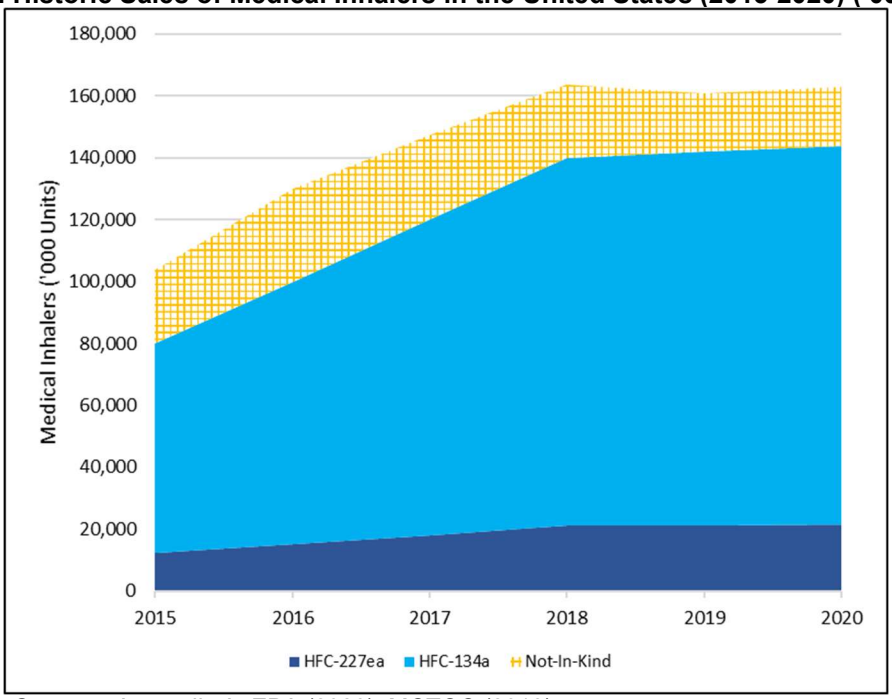
In 2020, approximately 75% of inhaler sales were HFC-134a MDIs and to a lesser degree HFC-227ea MDIs (13%).[7] Table 3. Historic HFC Propellant Sold in MDIs in the United States (2015-2020), Figure 1. Historic Sales of Medical Inhalers in the United States (2015-2020) ('000 Units), and Figure 2. HFC Propellant for MDIs Sold in the United States (2015-2020) (Million Metric Tons CO2 Equivalent (MMT CO2 Eq.)) show the historic unit sales and HFC propellant sold in medical inhalers in the United States from 2015 through 2020.

Table 3. Historic HFC Propellant Sold in MDIs in the United States (2015-2020)

	2015	2016	2017	2018	2019	2020
Amount of HFC Sold in MDIs (MT)						
HFC-134a	709	889	1,069	1,250	1,266	1,284
HFC-227ea	118	146	174	202	204	207
Total	**827**	**1,035**	**1,243**	**1,451**	**1,471**	**1,491**
Amount of HFC Sold in MDIs (MMT CO_2 Eq.)						
HFC-134a	1.01	1.27	1.53	1.79	1.81	1.84
HFC-227ea	0.38	0.47	0.56	0.65	0.66	0.67
Total	**1.39**	**1.74**	**2.09**	**2.44**	**2.47**	**2.50**

Note: Totals may not sum due to independent rounding.
Source: EPA (2020), NCEH (2021), CDC (2021).

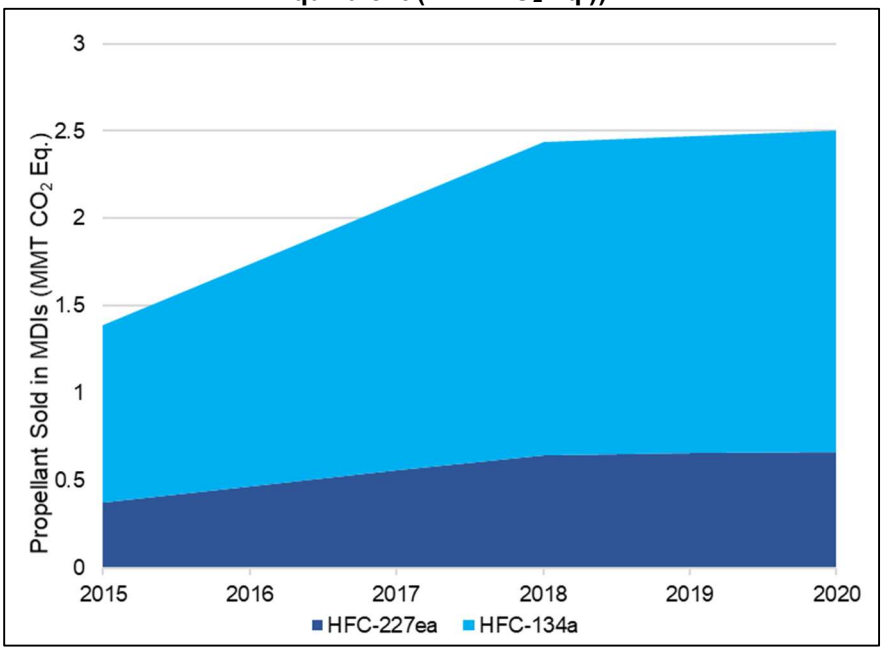
Figure 1. Historic Sales of Medical Inhalers in the United States (2015-2020) ('000 Units)



Sources: Appendix A, EPA (2020), MCTOC (2018).
Note: The 2015-2016 NIK estimates were derived from a DPI market share of 30% (MCTOC 2018). NIK estimates for 2017-2019 were determined in the DPI sales analysis detailed in Appendix A. The 2020 NIK estimate was determined by applying the growth rate of MDIs between 2019 and 2020 in EPA (2020).

[7] The remaining 12% of the market is NIK inhalers (DPIs) as determined by a separate analysis conducted to further investigate the size of the NIK inhaler market (see Appendix A).

Figure 2. HFC Propellant for MDIs Sold in the United States (2015-2020) (Million Metric Tons CO_2 Equivalent (MMT CO_2 Eq.))



Sources: EPA (2020), MCTOC (2018).

EPA is aware of research underway to investigate other propellants. The two most promising potential replacements for HFC-134a and HFC-227ea are HFO-1234ze(E) and HFC-152a. Both have most of the requisite physical properties to function as a propellant in MDIs with significantly lower GWPs than the current HFCs in use; however, neither propellant has significant use in pharmaceuticals today and will require extensive clinical research and FDA approval before they could replace the current HFCs (Pritchard 2020).

HFO-1234ze(E) is mainly used in refrigeration, technical aerosols, personal care products (e.g., hairspray, dry shampoo, hair mousse, and shaving gel) and some novelty aerosols (e.g., party string), and long-term human safety data would need to be collected before it could be considered for use in MDIs (Honeywell 2021, Pritchard 2020). A drug master file (DMF) has been submitted to the FDA for use by the pharmaceutical industry, allowing companies to file Investigational New Drug (IND) applications and initiate clinical trials (Honeywell 2021).

HFC-152a was considered as a possible replacement for CFCs in MDIs along with HFC-134a and HFC-227ea; however, its higher density and flammability would require numerous changes to manufacturing processes and the MDI design to ensure safe and effective use (Pritchard 2020). Koura, formerly Mexichem Fluor,[8] considers HFC-152a to be a likely replacement for

[8] Koura has been the largest supplier of medical grade HFC propellants globally and in the United States. Koura's global market share of HFC propellants for MDIs has been 75%.

other HFC propellants, because manufacturing sites can be adapted for the safe-handling of flammable materials (Koura 2021a). Propellant-only clinical trials for HFC-152a have been approved by the FDA and it is anticipated that program data from these trials will be supported by a DMF for the commercial use of medical-grade HFC-152a with the goal of introducing commercially available HFC-152a MDIs (Corr 2020).

NIK inhalers are not expected to completely replace HFC MDIs, as NIK inhalers have different mechanisms for the delivery of medication. MDI inhalers may be more appropriate for certain patients, such as when the patient requires a reliever medication for exacerbations of asthma, patient preference, or other requirements (e.g., patient inhalation strength) (GSK 2019, MCTOC 2018, IPAC 1999).

4.2. Current and Projected Sales of HFC MDIs

An estimated 144 million HFC MDIs (122 million HFC-134a MDIs and 22 million HFC-227ea MDIs) were sold in the United States in 2020, which accounts for both MDI products manufactured in the United States and MDIs imported from the EU and Asia. HFC MDI estimates were based on ICF (2020), an MDI sales analysis conducted as an update to EPA's Vintaging Model to inform the 2015 historical MDI use. The estimates in the sales analysis were derived from annual U.S. MDI sales in dollars, the estimated average manufacturers price (AMP) of MDIs, and the charge size of MDIs, differentiating between HFC-134a and HFC-227ea MDIs (ICF 2020).

Annual U.S. MDI sales were reported in annual reports from MDI manufacturing companies[9] (see Table 1). If sales data were unavailable for an MDI product,[10] Medicaid's State Drug Utilization Data (SDUD) of MDI product (in grams) reimbursed per year were used as a proxy[11] (ICF 2020). The AMP per unit was gathered from the National Average Drug Acquisition Costs (NADAC) metric that is reported annually by Medicaid and converted to AMP, utilizing the data from Levinson (2005) to account for difference between wholesale and retail cost as well as the pricing of generic versus proprietary inhalers.

The average charge size (i.e., propellant quantity) per unit was assumed to be equal to the net-fill weight of each cannister, because the active ingredients in MDI products typically make up less than 0.01% by weight of the total product.[12] The resulting average charge size for HFC-134a inhalers is 10.5 grams and 9.6 grams for HFC-227ea inhalers based on the volume sold

[9] In instances where a manufacturer did not delineate between MDI and DPI sales in the same product line, products were assumed to be MDIs.
[10] Alvesco®, Aerospan® (not included in Table 1 as it was discontinued in 2018), and Atrovent® were the only MDIs in the sales analysis for which Medicaid data was utilized.
[11] Information on the proportion of the U.S. MDI market that is met with Medicaid reimbursement products was not readily available, thus sales from this proxy data is likely underestimated (ICF 2020).
[12] This value was derived from a review of MDI product labels attained from the National Institutes of Health U.S. National Library of Medicine DailyMed database (NIH 2021).

per MDI unit at the year of peak MDI sales (i.e., 2011 and 2014 for HFC-134a and HFC-227ea, respectively) (ICF 2020, EPA 2020).

The resulting value for 2015 MDI units from sales analysis was assumed to grow linearly to reach the estimates of MDI units in MCTOC (2018).[13] Between 2015 and 2018, estimated HFC MDI sales increased by 75%, from 80 million units to 140 million units as shown in Figure 1. Historic Sales of Medical Inhalers in the United States (2015-2020) ('000 Units). The resulting amount of HFC propellant in MDIs sold in 2020 is 1,491 metric tons (MT) (i.e., 1,284 MT of HFC-134a and 207 MT of HFC-227ea) (EPA 2020, MCTOC 2018). HFCs in MDIs in the United States accounts for 0.5% of total estimated HFC use in 2020 (EPA 2020).

NIK inhalers are not expected to completely replace HFC MDIs; therefore, EPA (2020) assumes that the HFC MDI market retains its size post-2018, with a growth rate of approximately 1% per year through 2025 in alignment with expected population growth from 2020-2025 (U.S. Census 2017). An analysis examining the growth of prevalence (i.e., the percentage of the population with a certain medical condition) of COPD and asthma was also conducted. For both asthma and COPD, prevalence was determined to be constant based on available data (2001-2019 for asthma, and 2011-2018 for COPD) (NCEH 2021, CDC 2021). However, the growth rate of populations with asthma and COPD both grew by an average of about 1.3% annually (1.31% for asthma and 1.33% for COPD). To be conservative, projected HFC use in the MDI industry was calculated using an annual growth rate of 1.35% because it is more suitable than using population growth as a proxy growth rate.ok

HFC propellant sold in MDIs is estimated to grow to approximately 1,595 MT in 2025 (i.e., 1,373 MT of HFC-134a and 222 MT of HFC-227ea). EPA (2020) does not currently model transitions from HFC-134a and HFC-227ea to HFC-152a in MDIs; however, the replacement of current HFC propellants by HFC-152a within the next 15 to 20 years is possible (Koura 2021a). The projected amount of HFC propellant in MDIs sold from 2020 through 2025 can be found in Table 4, Figure 3, and Figure 4.

Table 4. Projected HFC Propellant Sold in MDIs in the United States (2020-2025)

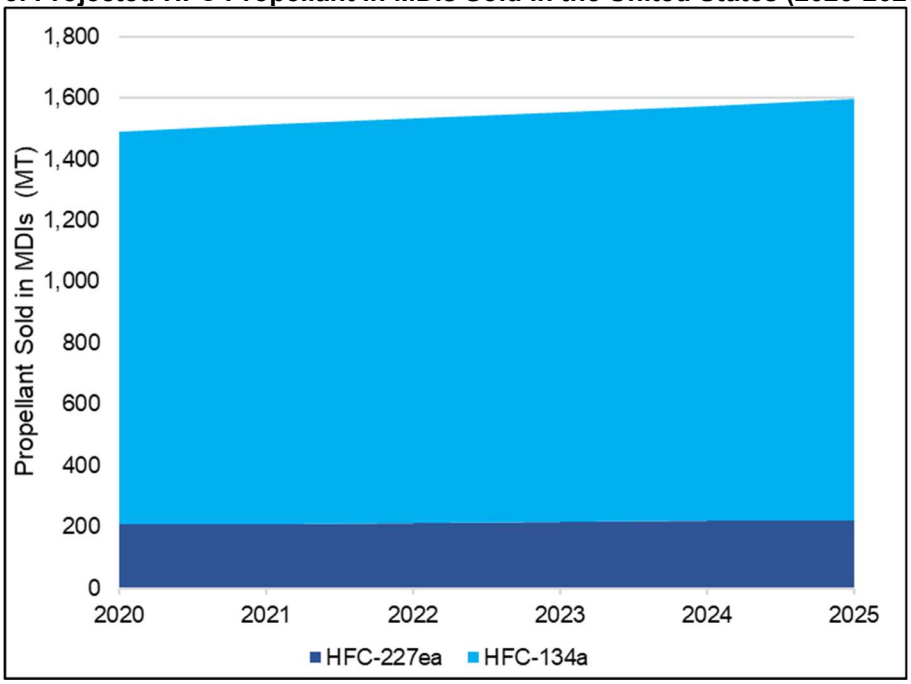
	2020	2021	2022	2023	2024	2025
Amount of HFC Sold in MDIs (MT)						
HFC-134a	1,284	1,301	1,319	1,337	1,355	1,373
HFC-227ea	207	210	213	216	219	222
Total	**1,491**	**1,511**	**1,532**	**1,552**	**1,574**	**1,595**
Amount of HFC Sold in MDIs (MMT CO_2 Eq.)						
HFC-134a	1.84	1.86	1.89	1.91	1.94	1.96

[13] Data provided by IQVIA to the MCTOC indicates that of inhalers worldwide, approximately 16% are sold in the United States, of which 70% are MDIs (MCTOC 2018). In addition, MCTOC (2018) estimates that approximately 800 million HFC MDIs (data provided by Mexichem Fluor, now Koura) and 450 million DPIs are manufactured annually worldwide. Assuming that inhalers manufactured are sold and used in that same year, the estimated annual inhaler use is 200 million inhalers (i.e., 140 million HFC MDIs and 60 million DPIs).

	2020	2021	2022	2023	2024	2025
HFC-227ea	0.67	0.68	0.69	0.69	0.70	0.71
Total	**2.50**	**2.54**	**2.57**	**2.61**	**2.64**	**2.68**

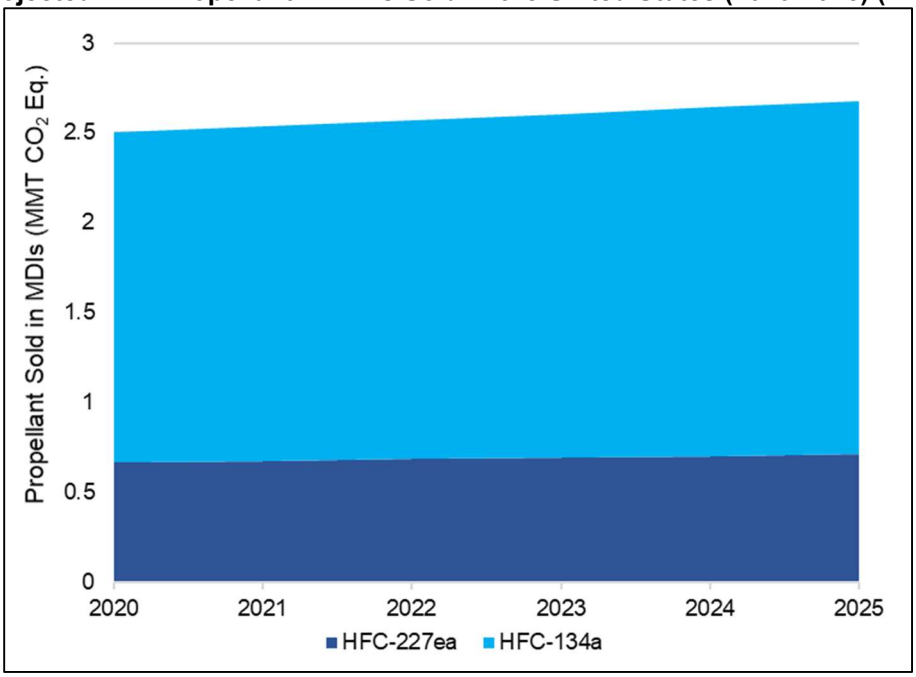
Note: Totals may not sum due to independent rounding.

Figure 3. Projected HFC Propellant in MDIs Sold in the United States (2020-2025) (MT)



Sources: EPA (2020), MCTOC (2018).

Figure 4. Projected HFC Propellant in MDIs Sold in the United States (2020-2025) (MMT CO_2 Eq.)



Sources: EPA (2020), MCTOC (2018).

For comparison, approximately 123 ± 12 million HFC MDIs (i.e., 97 million HFC-134a MDIs and 26 million HFC-227ea MDIs, corresponding to 1,018 MT ± 89 MT of HFC-134a and 250 MT ± 38 MT of HFC-227ea, respectively) were manufactured in and imported into the United States in 2019 as derived from Koura bulk gas and imported MDI estimates (Koura 2021a).[14] The values estimated by Koura take into consideration several assumptions that may be overestimated (e.g., amount of MDI product imported into the United States by manufacturers) (Koura 2021a). In addition, the annual estimates by Koura model medical grade HFCs used for manufacturing, which may not necessarily reflect the consumer inhaler market that year (e.g., does not account for inventory of MDI products) (Koura 2021a). Given the various assumptions and uncertainties associated with EPA (2020) and the Koura model, it is likely that actual annual HFC MDI use in the United States is between 111 and 142 million MDIs.

MDI manufacturers have suggested that future therapies may benefit from the delivery of medication by MDIs for patient groups beyond asthma and COPD, including but not limited to the delivery of biologic therapies via the lung. There are numerous therapy areas, both topical and systemic, that pharmaceutical manufacturers may address via MDI for lung or nasal delivery more effectively than by other means (Kindeva Drug Delivery LP 2021). In addition, medical conditions in which HFC MDIs may be used as therapy per the American Thoracic Society include: acute viral infections (including COVID-19), bronchiectasis, idiopathic pulmonary fibrosis, non-specific shortness of breath, post-COVID-19 infection, post-infection chronic cough, and sarcoidosis (ATS 2021).[15]

Due to the low prevalence of some of these additional medical conditions compared to asthma and COPD (e.g., more than 150 times more people diagnosed with asthma than idiopathic pulmonary fibrosis per 100,000 in the United States [CDC 2019, CDC 2021]); the high comorbidity rates of these conditions with COPD and asthma; as well as the use of alternative treatments (e.g., prednisone is the most common drug for sarcoidosis [Stanford Medicine n.d.,]), it is unlikely that these additional medical conditions will significantly alter the growth rate of HFC use in MDIs. The prevalence of other conditions will be monitored in the future to ensure that the growth rate of HFC use is accurately predicted. In addition, if there is an expansion in the use of MDIs for treatment of medical conditions beyond asthma and COPD, propellant use, which may include HFC use, may be higher than what is forecasted using the conservative growth rate established based on the incidence of asthma and COPD only.

[14] Koura (2021) estimates are in metric tonnes and have been converted to MDI units assuming the same HFC charge per MDI as in the MDI sales analysis (i.e., 10.5 g for HFC-134a and 9.6 g for HFC-227ea). The analysis assumes that all HFC use estimated by Koura for manufacturing uses were used in MDIs sold and used in that same year (i.e., no manufacturing nor leak losses).

[15] Koura commented on the proposed HFC phasedown rule indicating other uses for HFC based medical propellants such as laser ablation treatment (Koura 2021b). It should be noted, however, that MDIs are the largest application sector for HFC based medical propellants (Koura 2021b).

4.3. Imports and Exports of MDI Products in the United States

As noted above in Section 3.2, the manufacture of MDIs occurs in the United States, and the United States also imports HFC MDIs from EU member states and other countries. It is estimated that the amount of MDI products manufactured in the United States is approximately equal to the amount of MDI products imported to the United States (Koura 2021a).

Table 5 summarizes the countries exporting HFC MDIs into the United States. Countries from which MDIs are imported into the United States were identified from available import/export information databases[16] and cross-referenced with the Drug Establishments Current Registration Site (DECRS)[17] to determine if the products exported from these countries were also manufactured there (SeAir 2021, Zauba 2021, FDA 2020d). MDIs imported into the United States come from two regions, the EU (Belgium, France, Germany, Spain, Sweden, and the Netherlands) and Asia (China, India, Japan, and Singapore) (SeAir 2021, Zauba 2021). It was determined that MDIs imported to the United States were most likely manufactured in China, France, Germany, India, Singapore, and Sweden (FDA 2020d). Mexico also exports medical grade HFCs to the United States for the manufacture of MDIs (Armstrong 2021).

Table 5. Origin of HFC MDIs Imported into the United States

Manufacturer[a]	MDI Product Name[a]	Exporting Countries[b]	Manufacturing Facility Found on DECRS List?
HFC-227ea[c]			
AstraZeneca	Symbicort®	Belgium, Germany, Sweden	Belgium: No Germany: No Sweden: Yes
Merck Sharp and Dohme	Asmanex® HFA	Singapore	Yes
Merck Sharp and Dohme	Dulera®	No Import Records Found	
HFC-134a			
Sunovion Pharmaceuticals Inc.	Xopenex®	India	Yes
AstraZeneca	Bevespi Aerosphere®	Belgium	No
AstraZeneca	Breztri Aerosphere®	No Import Records Found	
Boehringer Ingelheim	Atrovent®	The Netherlands	No
Covis Pharma B.V.	Alvesco®	No Import Records Found	
GlaxoSmithKline	Advair®	China, Japan	China: Yes Japan: No
GlaxoSmithKline	Flovent®	France	Yes
GlaxoSmithKline	Ventolin®	Japan, Spain	Japan: No Spain: No
Kindeva Drug Delivery LP	Proventil®	No Import Records Found	
Teva	ProAir®	Belgium, Germany	Belgium: No Germany: Yes

[16] Exporting country represents the country of the final port before entry into the United States and does not necessarily represent the country where the product was manufactured.
[17] The Drug Establishments Current Registration Site (DECRS) is a database of current information submitted by drug firms to register establishments (facilities) which "manufacture, prepare, propagate, compound or process drugs that are commercially distributed in the U.S. or offered for import to the U.S." FDA (2020d).

Manufacturer[a]	MDI Product Name[a]	Exporting Countries[b]	Manufacturing Facility Found on DECRS List?
Norton Waterford LTD	QVAR® Redihaler™	Records Found but not Viewable	
Armstrong Pharmaceuticals Inc.	Primatene Mist	Mexico[d]	No
Cipla LTD	Generic Albuterol Sulfate Inhaler	India	Yes
Lupin Inc	Generic Albuterol Sulfate Inhaler	No Import Records Found	
Perrigo Pharmaceuticals Co	Generic Albuterol Sulfate Inhaler	No Import Records Found	

Note: Due to limited availability of import/export information, the data provided may not be a total representation of all importers of HFC MDIs into the United States.
[a] FDA (2020c).
[b] Based on U.S. import information found from Seair EXIM Solutions (Seair 2021) and Zauba Technologies Pvt Ltd (Zauba 2021).
[c] The vast majority of HFC-227ea MDIs are imported into the United States mostly from the EU and most recently from India (Koura 2021a).
[d] Armstrong Pharmaceuticals Inc. imports HFC-134a from Mexico for use in their Primatene Mist MDI products rather than importing finished MDI products (Armstrong 2021).

U.S. producers in the global supply chain for MDI propellants manufacture and export finished HFC propellants and designated specialized grades of HFCs for further purification to become medical propellants to MDI manufacturers in other countries, later importing the finished product for use on the U.S. healthcare market (Koura 2021b).

5. References

American Thoracic Society. 2021. Comments on Proposed Rule: Phasedown of Hydrofluorocarbons: Establishing the Allowance Allocation and Trading Program Under the American Innovation and Manufacturing Act (AIM). July 6, 2021. Available online at: https://www.regulations.gov/comment/EPA-HQ-OAR-2021-0044-0181

Armstrong Pharmaceuticals Inc (Armstrong). 2021. Communication to EPA from Armstrong Pharmaceuticals.

Catalent Pharmaceuticals. 2021a. Dry Powder Inhalers. Available online at: https://www.catalent.com/specialty/inhalation/dry-powder-inhalers/

Catalent Pharmaceuticals. 2021b. Metered Dose Inhalers (MDIs). Available online at: https://www.catalent.com/specialty/inhalation/metered-dose-inhalers/

Centers for Disease Control and Prevention (CDC). 2014a. Use of long-term control medication among persons with active asthma. Available online at: https://www.cdc.gov/asthma/asthma_stats/longterm_medication.htm.

Centers for Disease Control and Prevention (CDC). 2014b. Frequent use of quick-relief medication among persons with active asthma. Available online at: https://www.cdc.gov/asthma/asthma_stats/overuse.htm.

Centers for Disease Control and Prevention (CDC). 2018a. Summary Health Statistics Table for U.S. Adults: National Health Interview Survey, 2018, tables A-2b, A-2c. Available online at: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2018_SHS_Table_A-2.pdf

Centers for Disease Control and Prevention (CDC). 2018b. Summary Health Statistics Table for U.S. Children: National Health Interview Survey, 2018, tables C-1b, C-1c. Available online at: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2018_SHS_Table_C-1.pdf.

Centers for Disease Control and Prevention (CDC). 2019. Idiopathic Pulmonary Fibrosis (IPF) Among Dental Personnel. February 14, 2019. Available online at: https://www.cdc.gov/niosh/topics/ipf/default.html#:~:text=In%20the%20United%20States%2C%20an,100%2C000%20are%20living%20with%20IPF.

Centers for Disease Control and Prevention (CDC). 2020. Asthma Action Plans. Available online: https://www.cdc.gov/asthma/actionplan.html.

Centers for Disease Control and Prevention (CDC), National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health. 2021. Chronic Disease Indicators (CDI). Available online at: https://nccd.cdc.gov/cdi/rdPage.aspx?rdReport=DPH_CDI.ExploreByTopic&islTopic=COPD&islYear=9999&go=GO

Corr, Stuart. 2020 HFA-15a as a Sustainable pMDI Propellant. Koura. Available online at: https://www.zephex.com/wp-content/uploads/2020/07/Corr-2020-1.pdf.

De Marco et al. 2013 The coexistence of asthma and chronic obstructive pulmonary disease 9COPD): Prevalence and risk factors in young, middle-aged, and elderly people from the

general population. PLoS One. Available online at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3651288/#!po=32.3529.

Department of Health & Human Services (DHHS) Centers for Medicare & Medicaid Services. 2006. Medicaid Drug Rebate Program. Release No. 73: Bulletin for Participating Drug Manufacturers. Available online at: https://www.medicaid.gov/medicaid-chip-program-information/by-topics/prescription-drugs/downloads/rx-releases/mfr-releases/mfr-rel-073.pdf.

Department of Health & Human Services (DHSS) Centers for Medicare & Medicaid Services. 2010. Medicaid Drug Rebate Program. Release No. 82: Bulletin for Participating Drug Manufacturers. Available online at: https://www.medicaid.gov/medicaid-chip-program-information/by-topics/prescription-drugs/downloads/rx-releases/mfr-releases/mfr-rel-082.pdf.

Giraud and Allaert. 2009. Improved asthma control with breath-actuated pressurized Metered Dose Inhaler (pMDI): The SYSTER Survey. European Review for Medical and Pharmacological Sciences. September 2009. Available online at: https://www.researchgate.net/profile/Francois_Allaert/publication/40448031_Improved_asthma_control_with_breath-actuated_pressurized_Metered_Dose_Inhaler_pMDI_The_SYSTER_survey/links/5ad58ee3a6fdcc293580ad2c/Improved-asthma-control-with-breath-actuated-pressurized-Metered-Dose-Inhaler-pMDI-The-SYSTER-survey.pdf.

GlaxoSmithKline. 2019, GSK Public policy positions: respiratory products and global warming. Available online at: https://www.gsk.com/media/2962/respiratory-products-and-global-warming-policy.pdf.

Honeywell Fluorine Products. 2021. Comment on Notice of Data Availability Relevant to the United States Hydrofluorocarbon Baselines and Mandatory Allocations. Available online at: https://www.regulations.gov/comment/EPA-HQ-OAR-2021-0044-0011

ICF International. 2016. Preliminary Assessment of Global HFC Consumption in Aerosols. Prepared by ICF International for the U.S. Environmental Protection Agency (EPA). September 2016.

ICF. 2020. Observed Trends for HFC-227ea Emissions in the United States and HFC-227ea and HFC-134a Emissions from the MDI Aerosols End-Use in EPA's Vintaging Model. Prepared by ICF for the U.S. Environmental Protection Agency (EPA). June 24, 2020.

International Pharmaceutical Aerosol Consortium (IPAC). Ensuring Patient Care: The Role of the HFC MDI 2nd edition. 1999. Available online at: https://f1856665-a297-420b-a480-7c0957181470.filesusr.com/ugd/495d79_cecf8e047cd84c67999dec8cc7f03ef1.pdf.

Kindeva Drug Delivery L.P. 2021. Comment on Notice of Data Availability Relevant to the United States Hydrofluorocarbon Baselines and Mandatory Allocations. Available online at: https://www.regulations.gov/comment/EPA-HQ-OAR-2021-0044-0027

Koura. 2021a. Personal communication between Tim Noakes (Koura), Richard Greenhough (Koura), Maureen Hardwick (International Pharmaceutical Aerosol Consortium (IPAC)), Mark Wagner (ICF), and Paula Garcia-Holley (ICF). February 2, 2021.

Koura 2021b. Comments on Proposed Rule: Phasedown of Hydrofluorocarbons: Establishing the Allowance Allocation and Trading Program Under the American Innovation and Manufacturing Act (AIM). July 6, 2021. Available online at: https://www.regulations.gov/comment/EPA-HQ-OAR-2021-0044-0143

Levinson, D.R. 2005. Medicaid Drug Price Comparisons: Average Manufacturer Price to Published Prices. June 2005. Available online at: https://oig.hhs.gov/oei/reports/oei-05-05-00240.pdf.

Levy et. al. 2013. Asthma patients inability to use a pressurized metered-dose inhaler (pMDI) correctly correlates with poor asthma control as defined by the Global Initiative for Asthma (GINA) strategy: a retrospective analysis. US National Library of Medicine. National Institutes of Health. Available online at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6442852/#!po=6.25000.

Medicaid. 2020a. State Drug Utilization Data. Available online at: https://www.medicaid.gov/medicaid/prescription-drugs/state-drug-utilization-data/index.html.

Medicaid 2020b.November 2019 medicaid & CHIP Enrollment Data Highlights. Available online at: https://www.medicaid.gov/medicaid/program-information/medicaid-and-chip-enrollment-data/report-highlights/index.html.

Medical and Chemicals Technical Options Committee (MCTOC). Report of the Medical and Chemical Technical Options Committee 2018 Assessment Report. 2018. Nairobi, Kenya: United Nations Environment Programme (UNEP). Available online at: https://ozone.unep.org/sites/default/files/2019-04/MCTOC-Assessment-Report-2018.pdf.

Mexichem Fluor. 2015. Response to Charge Letter: Request for Data on HFC Consumption in the Global Aerosols Sector sent on December 1, 2015. Correspondence with Tim Noakes. December 11, 2015.

National Center for Environmental Health (NCEH). 2021. National Health Interview Survey (NHIS) Data. Last reviewed January 19, 2021. Available online at: https://www.cdc.gov/asthma/nhis/default.htm

National Institutes of Health (NIH). 2021. U.S. National Library of Medicine DailyMed Database. Available online at: https://dailymed.nlm.nih.gov/dailymed/index.cfm. Accessed January 7, 2021.

Noakes, Tim. n.d. HFA Propellants: Manufacture, storage, and use. Avoiding problems. Mexichem Fluor. Available online at: http://www.unido.ru/upload/files/d/2day_mexichem.pdf.

Ozone Secretariat. 1987. The Montreal Protocol on Substances that Deplete the Ozone Layer. United National Environment Programme (UNEP). Available Online at: https://ozone.unep.org/treaties/montreal-protocol.

Pritchard, John. 2020. The Climate is Changing for Metered-Dose Inhalers and Action is Needed. US National Library of Medicine. National Institutes of Health. Available online at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7410333/.

Sandoz. 2021. Sandoz in-licenses brand and authorized generic of respiratory medicine Proventil® HFA (albuterol sulfate) Inhalation Aerosol from Kindeva Drug Delivery, with

immediate generic availability in US. March 16. Accessed August 10, 2021. https://www.sandoz.com/news/media-releases/sandoz-licenses-brand-and-authorized-generic-respiratory-medicine-proventil-hfa.Stanford Medicine. n.d. About Sarcoidosis: How is sarcoidosis treated? Accessed August 20, 2021. Available online at: https://med.stanford.edu/sarcoidosis/about-.html

SeaAir EXIM Solutions. Global Trade Data. Available online at: https://www.seair.co.in/global-trade-data/usa-import-data.aspx. Accessed January 8, 2021.

U.S. Census. 2017. 2017 National Population Projections Tables: Main Series. Available online at: https://www.census.gov/data/tables/2017/demo/popproj/2017-summary-tables.html

U.S. Environmental Protection Agency (EPA). 2020. Vintaging Model. Version VM IO file_v5.1_10.08.20.

U.S. Food and Drug Administration (FDA). 2020a. Current Good Manufacturing Practice (CGMP) Regulations. Available online at: https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations.

U.S. Food and Drug Administration (FDA). 2020b. Drugs@FDA: FDA-Approved Drugs. Available online at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

U.S. Food and Drug Administration (FDA). 2020c. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm.

U.S. Food and Drug Administration (FDA). 2020d. Drug Establishments Current Registration Site (DECRS). Available online at: http://www.accessdata.fda.gov/cder/drls_reg.zip.

Zauba Technologies Pvt Ltd. U.S. Import Data. Available online at: https://www.zauba.com/USA-imports-exports/Imports. Accessed January 8, 2021.

Appendix A: Analysis of the DPI Market

An analysis of the DPI market was performed to inform the total medical inhaler market size and market penetration of NIK inhalers. The analysis is based on sales data for DPI products from annual manufacturer reports and the SDUD of Medicaid. The estimates derived using this approach were then compared with the total potential inhaler market estimated for the U.S. population with asthma and COPD.

DPI Product Sales Analysis

A total of 25 proprietary DPI products were identified in the United States (see Table 6). In 2019, only 15 of the 25 proprietary DPI products were available in the market as the remainder were discontinued or were not reported due to low sales volumes.

Table 6. Manufacturers of DPIs

Manufacturer[a]	DPI Product Name[a]	Active Ingredient[a]	FDA Approval Date[a]
AstraZeneca	Pulmicort® Flexhaler®	Budesonide	7/12/2006
	Tudorza Pressair®	Aclidinium Bromide	7/23/2012
	Duaklir Pressair®	Aclidinium Bromide; Formoterol Fumarate	3/29/2019
Boehringer Ingelheim	Spiriva®	Tiotropium Bromide	1/30/2004
Catalent Inc.[b]	N/A	N/A	N/A
GlaxoSmithKline	Breo Ellipta®	Fluticasone Furoate; Vilanterol Trifenatate	5/10/2013[b] 4/30/2015[c]
	Flovent Diskus®	Fluticasone Propionate	9/29/2000
	Advair Diskus®[d]	Fluticasone Propionate; Salmeterol Xinafoate	8/24/2000
	Incruse® Ellipta®	Umeclidinium Bromide	4/30/2014
	Relenza®	Zanamivir	7/26/1999
	Arnuity® Ellipta®	Fluticasone Furoate	8/20/2014[c] 5/17/2018[d]
	Trelegy Ellipta	Fluticasone Furoate; Umeclidinium Bromide; Vilanterol Trifenatate	9/18/2017[e] 9/9/2020[f]
	Anoro® Ellipta®	Umeclidinium Bromide; Vilanterol Trifenatate	12/18/2013
	Serevent®	Salmeterol Xinafoate	9/19/1997
Merck Sharp and Dohme	**Asmanex Twisthaler**	Mometasone Furoate	3/5/2005[g] 2/1/2008[h]
Mylan Pharmaceuticals Inc	TOBI® Podhaler	Tobramycin	3/22/2013
	Wixela Inhub	Fluticasone Propionate; Salmeterol Xianfoate	1/30/2019
Sunovion Pharmaceuticals Inc.	Arcapta® Neohaler	Indacaterol	7/1/2011[i]
	Seebri Neohaler	Glycopyrrolate	10/29/2015[j]
	Utibron Neohaler®	Indacaterol/ Glycopyrrolate	10/29/2015[k]
Teva	**Proair Digihaler**	Albuterol Sulfate	12/21/2018

Manufacturer[a]	DPI Product Name[a]	Active Ingredient[a]	FDA Approval Date[a]
	Proair Respiclick®	Albuterol Sulfate	3/31/2015
Teva	Armonair Digihaler	Fluticasone Propionate	2/20/2020
	ArmonAir® RespiClick®	Fluticasone propionate	1/27/2017[l]
	Airduo Digihaler®	Fluticasone Propionate; Salmeterol Xinafoate	6/12/2019
	Airduo Respiclick®	Fluticasone Propionate; Salmeterol Xinafoate	1/27/2017

N/A: Not Applicable
Note: Bolded manufacturer entries represent manufactures that produce both DPIs and MDIs. Bolded DPI products represent product lines that consist of both DPIs and MDIs.
[a] FDA (2020c).
[b] Catalent Pharmaceuticals manufactures DPI products as a contractor to other pharmaceutical companies, which may include other DPI products listed in this table (Catalent 2021a).
[c] FDA approval of Breo Ellipta 0.1mg/inhale; EQ 0.025 mg base/inhale on 5/10/2013.
[d] FDA approval of Breo Ellipta 0.2mg/inhale; EQ 0.025 mg base/inhale on 4/30/2015.
[e] FDA approval of Arnuity Ellipta 0.1 mg/inhale and 0.2 mg/inhale on 8/20/2014.
[f] FDA approval of Arnuity Ellipta .05 mg/inhale on 5/17/2018.
[g] FDA approval of Trelegy Ellipta 0.1 mg/inhale; EQ .0625 mg base/inhale; EQ .025 mg base/inhale on 9/18/2017.
[h] FDA approval of Trelegy Ellipta 0.2 mg/inhale; EQ .0625 mg base/inhale; EQ .025 mg base/inhale on 9/9/2020.
[i] FDA approval of Asmanex Twisthaler 0.22 mg/inhale on 3/30/2005.
[j] FDA approval of Asmanex Twisthaler 0.11 mg/inhale on 2/1/2008.
[k] Arcapta® Neohaler, Seebri Neohaler, and Utibron Neohaler® were discontinued 3/10/2020.
[l] Armonair® RespiClick® was discontinued in 2017.

Sales data, in dollars, for DPI products were obtained from annual reports of their respective manufacturing companies. If sales data for certain products were not publicly available (i.e., Serevent®, Relenza®, TOBI® Podhaler, Asmanex® Twisthaler®, and Wixela™ Inhub™), data from the SDUD of Medicaid were used as a proxy. The SDUD provides information on the number of units of DPI product that Medicaid is reimbursing (e.g., 22,320,652 units of Anoro® Ellipta® of Alvesco® reimbursed in 2019), the number or prescriptions, and the amount reimbursed. When sales data from annual reports were lower than the reimbursement value from the SDUD (i.e., Tudorza Pressair®), the larger value was applied.

Using this approach, approximately 18.9 million DPIs were assumed to be sold and used in the United States in 2019. Considering that the estimated HFC MDI market size by EPA (2020) in 2019 is 55.3 million inhalers, the total market size for inhalers in the United States was 74.2 million (see **Error! Reference source not found.**). Therefore, the market share of DPIs is 25%while that of HFC MDIs is 75%. This market share is close to that reported for the United States market in MCTOC (2018) (i.e., 30% DPIs).

Table 7. Estimated MDI and DPI Use in the United States (2019)

	Number of Inhalers	Percent of Total
HFC MDIs	55,344,000[a]	75%
DPIs	18,904,000	25%
Total Inhalers	**74,248,000**	**100%**

[a] EPA (2020).

Medical Inhaler User Population

In 2018, approximately 12.8 and 24.7 million people had COPD and asthma, respectively, in the United States (CDC 2018a, CDC 2018b). Based on this data, potential annual inhaler use was estimated under four different scenarios, as shown in Table 8. In the most conservative scenario (Scenario 1), 100% of the population with COPD and/or asthma was assumed to use one inhaler per month for 12 months (i.e., 12 inhalers per year).[18] In the most realistic scenario (Scenario 4), 50% of the population with COPD and/or asthma was assumed to use one inhaler a month for three months of the year.[19] This analysis results in a large range of annual inhaler use, from 19.1 million to 450 million units annually (see Figure 5).

Some people can have both asthma and COPD[20] and others do not use medication.[21] Furthermore, some medications are administered differently from inhalers (e.g., use of nebulizer). In addition, although it is estimated that DPIs last for a month[22] and HFC MDI inhalers for long-term control are also consumed within a month, when inhalers are used as a rescue (i.e., quick-relief) medication, they may last longer.

A summary of the assumptions for the four scenarios and two analyses conducted to estimate the size of the U.S. medical inhaler market are summarized in Table 8, and is followed by Figure 5, which compares the resulting estimates of each approach.

Table 8. Assumptions for Analyses on Estimated Annual Inhaler Use in the United States

Scenario/Analysis	Assumptions
Scenario 1	100% of population with COPD and/or asthma use one inhaler per month for 12 months (2018)
Scenario 2	50% of population with COPD and/or asthma use one inhaler a month for 12 months (2018)
Scenario 3	100% of population with COPD and/or asthma use one inhaler per month for 3 months (2018)

[18] Although some asthma and COPD patients may be prescribed multiple inhalers a month as part of their asthma action plans, including a long-term control and a quick-relief inhaler, use of one inhaler a month is assumed to be a reasonable scenario because some patients may not use prescribed inhalers (CDC 2020).

[19] Over 60% of MDI patients in a study were unable to use their MDI device and there is evidence that poor inhalation technique impacts both asthma control and patient adherence to treatment (Giraud and Allaert 2009, Levy et al. 2014). Therefore, it is likely that although treatments may be prescribed for long-term control, the actual use period is shorter and a 3-month treatment was assumed.

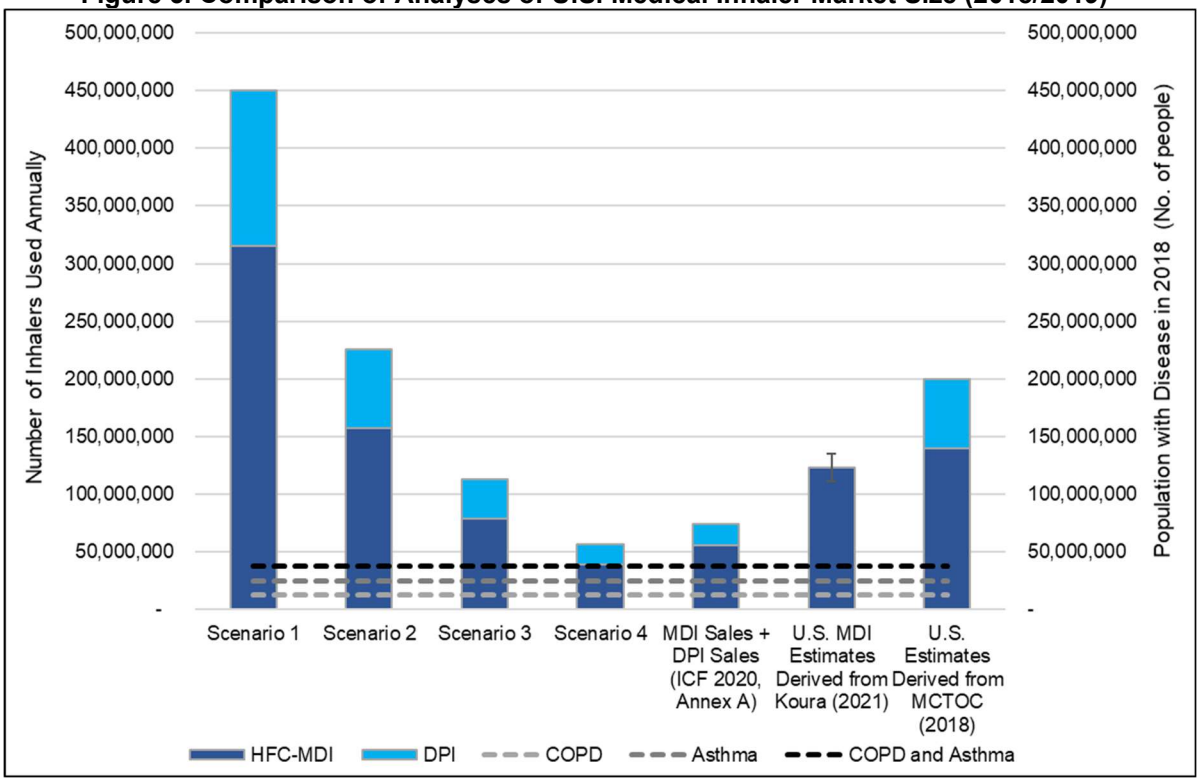
[20] De Marco et al. (2013) indicate that for subjects with asthma the percentage of the asthma-COPD overlap syndrome was 16%, 30%, and 61% for ages 20-44, 45-64, and 65-84, respectively. In addition, De Marco et al. (2013) report that for subjects with COPD the percentage of the asthma-COPD overlap syndrome was 33%, 27%, and 25% for ages 20-44, 45-64, and 65-84, respectively.

[21] Nearly 39.0% of all adults and 40.2% of all children with self-reported active asthma used at least one kind of Long Term Control medication in the past 3 months (CDC 2014a). Furthermore, nearly 24.3% of all adults and 18.7% of all children self-reported active asthma used quick-relief medications (QRMs) frequently in the past 3 months and using more than 2 days per week is considered frequent use (CDC 2014b).

[22] Multi-dose DPIs typically contain enough doses for at least one month's treatment (MCTOC 2018).

Scenario/Analysis	Assumptions
Scenario 4	50% of population with COPD and/or asthma use one inhaler a month for 3 months (2018)
MDI Sales + DPI Sales	Combined results from ICF (2020) MDI sales analysis (see Section 4.2) and DPI sales analysis (see Appendix A)
U.S. Estimates Derived from MCTOC (2018) Derived Estimates for USA	Reflects assumptions reported in MCTOC (2018) for the global and U.S. MDI and DPI markets (see Footnote **Error! Bookmark not defined.**)
U.S. MDI Estimates Derived from Koura (2021a)	Reflects MDI estimates derived from Koura (2021a) bulk gas and MDI import estimates

Figure 5. Comparison of Analyses of U.S. Medical Inhaler Market Size (2018/2019)[a]



The estimated worst-case scenario described above (i.e., scenario 1) results in more than double the estimated total inhaler use (i.e., approx. 200 million inhalers)[23] than estimates derived from MCTOC (2018) and results in MDI use almost 2.5 times larger than those modeled by Koura (2021a) (i.e., 123 ± 12 million MDIs). It is likely that scenario 1 does not portray an accurate representation of MDI use in the United States. In addition, estimates for total inhaler use from the MDI and DPI sales analyses (i.e., 74 million inhalers), may be underestimating use of MDI inhalers, are larger than estimates for scenario 4, indicating that these scenarios are also

[23] Data provided by IQVIA to the MCTOC indicates that of inhalers worldwide, approximately 16% are sold in the United States, of which 70% are MDIs (MCTOC 2018). In addition, MCTOC (2018) estimates that approximately 800 million HFC MDIs (data provided by Mexichem Fluor, now Koura) and 450 million DPIs are manufactured annually worldwide. Assuming that inhalers manufactured are sold and used in that same year, the estimated annual inhaler use is 200 million inhalers (i.e., 140 million HFC MDIs and 60 million DPIs).

unrealistic. Therefore, it is likely that actual inhaler use in the United States (i.e., MDIs and DPIs) is between 111 and 225 million inhalers annually with DPI use ranging from 24 to 68 million inhalers annually.

ICF recognizes several assumptions may warrant further review and refinement, including:

- Five of the 25 DPI products identified have generics available (i.e., Flovent Diskus®, Advair Diskus®,[24] Wixela™ Inhub™, AirDuo Digihaler®, and AirDuo RespiClick®). The analysis assumed that sales from the generics were negligible, although it is possible that they are sizable and calculated DPI volumes are underestimated.
- One "prescription" as reported in the SDUD corresponds to one inhaler and one "unit" corresponds to one dose. The *Unit Type Each* as defined by Medicaid Manufacturer Release No. 73 and Manufacturer Release No. 82 do not indicate if a unit is an inhaler or a dose (DHHS 2006, DHHS 2010). Furthermore, Release No. 73 indicates that labelers erroneously report drugs using the *Unit Type Each* (DHHS 2006). Should a "unit" be equivalent to an inhaler rather than a dose, results of the analysis would be underestimated.
- As of September 2020, only 21% of the United States population was enrolled in the Medicaid program and there is no readily available information on how much of the DPI market is met with Medicaid reimbursed products (Medicaid 2020b). Thus, the DPI sales, and therefore, use estimated from SDUD data for these products (i.e., Serevent®, Relenza®, TOBI® Podhaler, Asmanex® Twisthaler®, and Wixela™ Inhub™) is likely underestimated.

[24] A generic version of Advair Diskus is available from Hikma Pharmaceuticals and was approved by the FDA on 12/17/2020.