Manufacturer revenue on inhalers after expiration of primary patents, 2000-2021

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Inhalers remain the cornerstone therapy for asthma and chronic obstructive pulmonary disease (COPD). Over the past several decades, brand-name manufacturers have continued to sell most inhalers at high prices without the threat of direct generic competition. They have arranged for long periods of market exclusivity by obtaining patents not just on the active ingredients ("primary patents") but also on peripheral aspects of these products such as the propellants and delivery devices ("secondary patents"), and by shifting active ingredients to different devices ("device hops").[1, 2] Delays in generic competition have reduced patient access and led to unnecessary health care spending.[2, 3] To better understand the financial value of patents to inhaler manufacturers, we quantified the revenue earned on all brand-name inhalers approved by the Food and Drug Administration (FDA) from 2000-2021 and compared earnings before and after expiration of primary patents on these products.

Methods

We identified patents on FDA-approved inhalers for the treatment of asthma and COPD using the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). We extracted the claims of each patent from LexisNexis Total Patent One and Google Patents to determine whether patents covered the active ingredients or other aspects of the product in question. Data on sales revenue (net of rebates) earned in the US were obtained from 10-K filings to the Securities and Exchange Commission and company annual reports. Individual products with the same active ingredients marketed by a single manufacturer were classified as the same inhaler line. Because manufacturers reported aggregated revenue on inhaler lines—e.g., on Advair (fluticasone-salmeterol) rather than providing a breakdown for Advair Diskus and Advair HFA—we focused on inhaler lines as the primary unit of analysis. Within each inhaler

line, we recorded the number of device hops (eMethods). In years when data on US revenue were missing, imputations were performed (eMethods). The main analysis compared revenue earned when primary patents were active vs. revenue earned after primary patent expiration. In a sensitivity analysis, we quantified revenue on products with only active secondary patents that were free from generic competition (eMethods). Revenue was adjusted for inflation to 2021 dollars using the Consumer Price Index for All Urban Consumers. Analyses were performed in Excel version 16 (Microsoft).

Results

The FDA approved 39 brand-name inhalers across 32 inhaler lines from 2000 to 2021 (Table). These products were linked to 18 primary patents and 239 secondary patents.

Revenue data were available for 21 inhaler lines, which represented more than 90% of the US market based on a prior analysis of Medicare Part D spending.[4] Manufacturers earned $179.3 billion on inhalers during the study period: $67.8 billion (38%) when primary patents were active, $110.8 billion (62%) after primary patents had expired but when secondary patents were active, and $614 million (<1%) after all patents had expired (Figure). Advair (fluticasone-salmeterol) had the highest revenue at $68.8 billion (38% earned before primary patent expiration and 62% after) followed by Spiriva (tiotropium) at $31.0 billion (85% earned before primary patent expiration and 15% after). Ninety-eight percent of the $110.5 billion earned by manufacturers on inhaler lines that were protected exclusively by secondary patents accrued during periods when these products faced no generic competition.

Discussion

Manufacturers of brand-name inhalers listed many more secondary patents than primary patents with the FDA from 2000-2021 and earned substantially more revenue on inhalers after active ingredients went off-patent compared to revenue generated when primary patents remained active. The analysis was limited by missing revenue data on a subset of inhalers, though these inhalers represented a small fraction of the overall market.

The current patent and regulatory system rewards minor changes to the delivery systems of existing molecules, diverting incentives for investments in new therapeutic breakthroughs.[2] Regulators and lawmakers have begun to scrutinize the patenting practices of drug-device combinations.[5, 6] Without substantial reform, patients and payers may continue spending large sums on inhaled products with active ingredients developed decades ago.

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Table: Expiration of key patents on FDA-approved inhalers, 2000-2021

			Regulatory events			Revenue			
Inhaler line	**Active ingredient**	**Products per inhaler line[a]**	**Year of first approval in line[a]**	**Expiration of primary patents[c]**	**Expiration of secondary patents[c]**	**Revenue earned with primary patents active (Billions, $)**	**Revenue earned with only secondary patents active (Billions, $)**	**Revenue earned after all patents have expired (Billions, $)**	**Total revenue (Billions, $)**
ICS									
Qvar	beclomethasone	2	09/15/2000	Pre-approval	01/25/2039	0.0	4.0	0.0	4.0
Pulmicort	budesonide	1[b]	07/12/2006	Pre-approval	05/08/2018	0	10.9	0.3	11.2
Alvesco	ciclesonide	1	01/10/2008	01/09/2013	02/01/2028	0.1	0.4	0.0	0.5
Aerospan	flunisolide	1	01/27/2006	Pre-approval	07/07/2015	N/A	N/A	N/A	N/A
ArmonAir[d]	fluticasone	1	01/27/2017	Pre-approval	08/16/2036	N/A	N/A	N/A	N/A
Arnuity[d]	fluticasone	1	08/20/2014	08/03/2021	10/11/2030	0.3	<0.1	0.0	0.3
Flovent[d]	fluticasone	2[b]	09/29/2000	05/14/2004	08/26/2026	3.9	11.6	0.0	15.5
Asmanex	mometasone	2	04/25/2014	Pre-approval	03/17/2018	N/A	N/A	N/A	N/A
LABA									
Foradil	formoterol	2	02/16/2001	Pre-approval	11/28/2020	0.0	0.3	0.0	0.3
Arcapta	indacaterol	1	07/01/2011	10/10/2020	10/11/2028	N/A	N/A	N/A	N/A
Striverdi	olodaterol	1	07/31/2014	05/12/2025	10/16/2030	N/A	N/A	N/A	N/A
LAMA									
Tudorza	aclidinium	1	07/23/2012	02/10/2025	03/13/2029	0.5	0.0	0.0	0.5
Seebri	glycopyrrolate	1	10/29/2015	Pre-approval	10/20/2028	N/A	N/A	N/A	N/A
Spiriva	tiotropium	2	01/30/2004	07/30/2018	04/16/2031	25.7	4.7	0.0	30.5
Incruse	umeclidinium	1	04/30/2014	12/18/2027	10/11/2030	1.3	0.0	0.0	1.3
ICS-LABA									
Symbicort	budesonide-formoterol	1	07/21/2006	Pre-approval	10/07/2029	0	15.6	0.0	15.6
Advair[d]	fluticasone-salmeterol	2	08/24/2000	08/12/2008	08/26/2026	26.1	42.1	0.0	68.2
AirDuo[d]	fluticasone-salmeterol	1	01/27/2017	Pre-approval	08/16/2036	N/A	N/A	N/A	N/A
Breo[d]	fluticasone-vilanterol	1	05/10/2013	05/21/2025	10/11/2030	4.3	0.0	0.0	4.3
Dulera	mometasone-formoterol	1	06/22/2010	Pre-approval	11/21/2020	0	3.1	0.2	3.3
LAMA-LABA									
Duaklir	aclidinium-formoterol	1	06/21/2002	02/10/2025	03/13/2029	<0.1	0.0	0.0	<0.1
Bevespi	glycopyrrolate-formoterol	1	04/25/2016	Pre-approval	03/17/2031	0	0.2	0.0	0.2
Utibron	glycopyrrolate-indacaterol	1	10/29/2015	02/25/2025	10/20/2028	N/A	N/A	N/A	N/A
Stiolto	tiotropium-olodaterol	1	05/21/2015	05/12/2025	10/16/2030	N/A	N/A	N/A	N/A

Anoro	umeclidinium-vilanterol	1	12/18/2013	12/18/2027	11/29/2030	2.4	0.0	0.0	2.4
ICS-LAMA-LABA									
Breztri Aerosphere	budesonide-glycopyrrolate-formoterol	1	07/23/2020	Pre-approval	03/17/2031	0	0.1	0.0	0.1
Trelegy[d]	fluticasone-umeclidinium-vilanterol	1	09/18/2017	12/18/2027	11/29/2030	2.6	0.0	0.0	2.6
SABA									
ProAir	albuterol	2	10/29/2004	Pre-approval	08/16/2036	0	7.7	0.0	7.7
Ventolin	albuterol	1[b]	04/19/2001	Pre-approval	08/26/2026	0	7.3	0.1	7.4
Xopenex	levalbuterol	1	03/11/2005	Pre-approval	10/08/2024	0	2.4	0.0	2.4
SAMA									
Atrovent	ipratropium	1[b]	11/27/2004	Pre-approval	01/17/2030	N/A	N/A	N/A	N/A
SAMA-SABA									
Combivent	albuterol-ipratropium	1[b]	12/31/2020	Pre-approval	10/16/2030	N/A	N/A	N/A	N/A

ICS indicates Inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta agonist; SAMA, short-acting muscarinic antagonist

a. Inhalers with different strengths or device-types under the same New Drug Application (NDA) were considered a single product.

b. All patents listed in the Orange Book through the 2021 edition were analyzed when determining the expiration dates of last-to-expire patents. Expiration dates reflected 6-month pediatric extensions, where relevant. Expiration dates of primary patents were considered "pre-approval" when no patents on the active ingredients in a given inhaler line were listed in the Orange Book during the study period. In some cases, such patents had been listed on earlier products in the Orange Book but had subsequently expired before the study period; in other cases (for example, older products like glycopyrrolate, which was first approved in 1961), no patents on the active ingredients were listed in the Orange Book.

c. Some of the revenue during the study period was generated on products that were approved in the inhaler line before 2000, including products with ozone-depleting chlorofluorocarbons (CFCs) that were phased out by the FDA beginning in 2009. The five inhaler lines in the cohort with one or more products approved before 2000 were Flovent (a CFC-containing version was approved in 1996; Flovent Rotadisk was approved in 1997), Ventolin (a CFC-containing version was approved in 1981; Ventolin Rotahaler was approved in 1988), Pulmicort (Pulmicort Turbuhaler was approved in 1997), Atrovent (a CFC-containing version was approved in 1986), and Combivent (a CFC-containing version was approved in 1996). Inhaler lines with only products approved before 2000 were excluded from the analysis.

d. Advair, AirDuo, ArmonAir, and Flovent all contain fluticasone propionate, while Arnuity, Breo, and Trelegy contain the longer-acting fluticasone furoate.

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