the FDA are committed to performing the studies needed to assure that our expectations are borne out. In the meantime, we urge people who are at the highest risk for infection to receive both doses of the two-dose vaccine, and we encourage manufacturers to consider routinely testing intradermal dose administration in future clinical vaccine trials, in order to expand our understanding of this operationally attractive option. The currently available evidence suggests that shifting to intradermal dosing that requires less vaccine is not a lesser option. Rather, it is a rational, evidence-informed means of advancing access, equity, and our chances of controlling the monkeypox outbreak.

Disclosure forms provided by the authors are available at NEJM.org.

From the Multinational Monkeypox Outbreak Response (J.T.B.) and the Office of the Director (R.H.G., R.P.W.), Centers for Disease Control and Prevention, Atlanta; and the Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, MD (P.M.).

This article was published on August 31, 2022, at NEJM.org.

1. Frey SE, Wald A, Edupuganti S, et al. Comparison of lyophilized versus liquid modified vaccinia Ankara (MVA) formulations and subcutaneous versus intradermal routes of administration in healthy vaccinia-naïve subjects. Vaccine 2015;33:5225-34.
2. Frey SE, Stapleton JT, Ballas ZK, et al. Human antibody responses following vaccinia immunization using protein microarrays and correlation with cell-mediated immunity and antibody-dependent cellular cytotoxicity responses. J Infect Dis 2021;224:1372-82.
3. Wilck MB, Seaman MS, Baden LR, et al. Safety and immunogenicity of modified vaccinia Ankara (ACAM3000): effect of dose and route of administration. J Infect Dis 2010;201:1361-70.
4. Garg S, Thongcharoen P, Praphasiri P, et al. Randomized controlled trial to compare immunogenicity of standard-dose intramuscular versus intradermal trivalent inactivated influenza vaccine in HIV-infected men who have sex with men in Bangkok, Thailand. Clin Infect Dis 2016;62:383-91.
5. Amoah S, Mishina M, Praphasiri P, et al. Standard-dose intradermal influenza vaccine elicits cellular immune responses similar to those of intramuscular vaccine in men with and those without HIV infection. J Infect Dis 2019;220:743-51.

DOI: 10.1056/NEJMp2211311

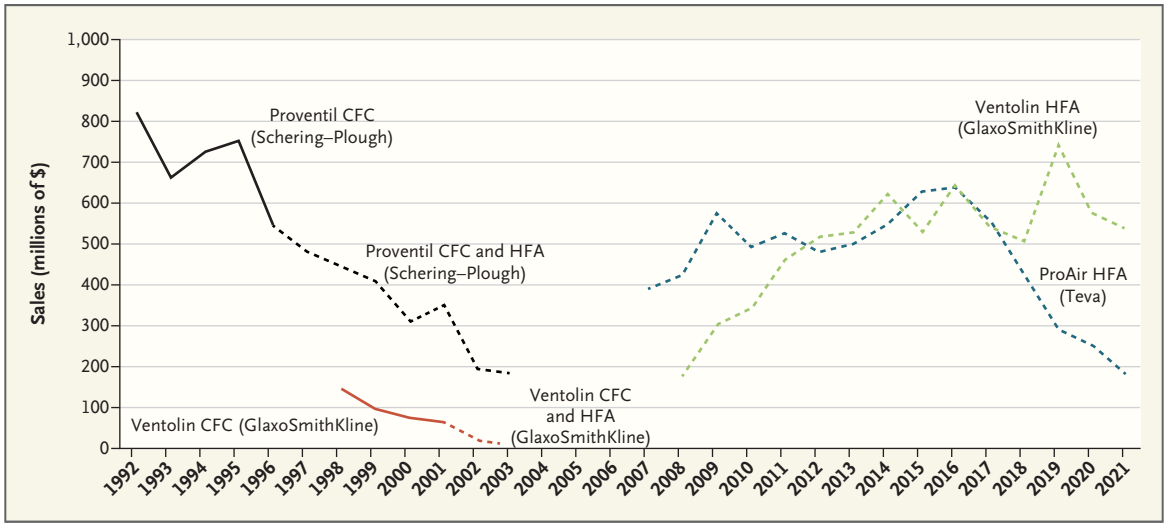
Product Hopping in the Drug Industry — Lessons from Albuterol

Olivier J. Wouters, Ph.D., William B. Feldman, M.D., D.Phil., M.P.H., and S. Sean Tu, J.D., Ph.D.

Many patients with asthma or chronic obstructive pulmonary disease (COPD) rely on albuterol, a short-acting β_2-agonist, to relieve acute symptoms of bronchospasm. The Food and Drug Administration (FDA) approved the first two albuterol inhalers — Ventolin (Glaxo Wellcome) and Proventil (Schering–Plough) — in 1981. Each went off patent in 1989, and by 1997 there were four generic albuterol inhalers on the U.S. market, typically priced at $15 or less.

These inhalers contained ozone-depleting chlorofluorocarbons (CFCs) but were initially allowed to remain on the U.S. market after the 1987 passage of the Montreal Protocol (a global environmental treaty banning CFC-containing products) because patients with asthma or COPD had few good therapeutic alternatives. However, pharmaceutical manufacturers soon developed inhalers with hydrofluoroalkane (HFA) rather than CFC propellants and sought to shift patients to these newer products. Several inhaler manufacturers formed the International Pharmaceutical Aerosol Consortium, a lobbying group dedicated to, among other goals, persuading lawmakers and regulators to ban inhalers with CFCs. The group spent hundreds of thousands of dollars,[1] and in 2005, the FDA ruled that CFC inhalers would be phased out beginning in 2009.[2] As a result of the ban, newer albuterol products — including Proventil HFA (which was approved in 1996), Ventolin HFA (approved in 2001), and ProAir HFA (approved in 2004) — would be free from competition from inexpensive CFC-containing generics. HFA inhalers were protected by new patents on both the HFA propellants and the devices themselves, and they generally cost much more than generic CFC inhalers.

Over the quarter-century since the first HFA-containing albuterol inhalers were approved, manufacturers have reaped immense financial rewards. The resulting "product hops" to the new albuterol inhalers generated approximately $14 billion in U.S. sales between 2007 and 2021 (see graph). Annual revenue from sales of brand-name albuterol inhalers was on the decline in the 1990s (when sales data first became publicly available), and it



Net Sales of Brand-Name Albuterol Inhalers in the United States, 1992–2021.

Sales figures are from annual reports to investors published on company websites or 10-K forms filed with the Securities and Exchange Commission; these documents contained data on product sales net of any discounts or rebates. Teva's sales figures reflect sales in the United States and Canada and include sales of ProAir RespiClick and ProAir Digihaler from 2015 onward. No information was available on sales of Proventil CFC and HFA in 1998, so we imputed an amount corresponding to the midpoint between sales in 1997 and 1999. Data on sales of Proventil HFA were unavailable in most years after 2003 and are therefore not shown. Ventolin was sold by Glaxo Wellcome in 1998 and 1999; GlaxoSmithKline was formed in 2000 through the merger of Glaxo Wellcome and SmithKline Beecham. Yearly average exchange rates were used to convert foreign currencies to U.S. dollars; all amounts were inflation-adjusted to 2021 dollars with the use of the U.S. consumer price index. CFC denotes chlorofluorocarbon, and HFA hydrofluoroalkane.

had dipped below $200 million by the early 2000s. But with the increased uptake of HFA devices in the years leading up to and following the 2009 CFC ban, sales rebounded to almost $1 billion by 2010. Annual sales figures remained between $800 million and $1.3 billion for the entire decade until the first generic HFA-containing albuterol inhaler was approved in 2020.

Had the FDA delayed the CFC ban by several years, until generic HFA inhalers were closer to becoming available, payers and patients would probably have saved billions of dollars. The FDA estimated in 2005 that CFC inhalers accounted for approximately 1200 metric tons of CFC emissions each year in the United States[2] — a total that corresponded to approximately 0.1% of the nearly 1.1 million metric tons of global CFC emissions in 1986, before other CFC products were first pulled from the market.[3] Under the Montreal Protocol, the ban could have been delayed further, since lifesaving products such as inhalers were given special dispensation to remain on the market as long as there were no economically viable alternatives.

We worry that without patent and regulatory reform, this pattern is likely to be repeated. The history of albuterol over the past 40 years offers a cautionary tale for regulators and policymakers seeking to ensure access to prescription drugs while still meeting other goals such as environmental protection.

Giving the makers of HFA inhalers the same degree of market protection as the manufacturers of the very first albuterol inhalers (or, for that matter, any newly discovered treatment) runs contrary to what we believe is the commonly accepted view of how pharmaceutical markets are supposed to operate: innovators are rewarded for making risky investments by being granted the freedom to charge high prices for a limited time, after which generics manufacturers can legally provide patients with low-cost substitutes. In this case, innovators had already been compensated for their initial investment in albuterol inhalers with monopoly pricing that remained in place for most of the 1980s. But in the late 2000s, patients with asthma or COPD (and their insurers) were again forced to pay monopoly prices, as new patent clocks started. These prices were permitted even though the new inhalers were therapeutically equivalent to the older ones.

To be fair, brand-name manufacturers did invest in research and development to bring their new HFA-based metered-dose inhalers to market; several companies claimed to have spent $250 million to $400 million to develop their products, though few details were provided.[2] But the many billions of dollars in additional revenue earned by brand-name manufacturers over the past decade far exceeded these investments.

Several brand-name manufacturers are now touting the development of even "greener" inhalers, since HFA-based products also emit greenhouse gases. For example, AstraZeneca and GlaxoSmithKline, two of the largest manufacturers of brand-name inhalers, are developing next-generation, low-carbon inhalers. Unless policymakers work to minimize the extent to which any new patents on these products delay the approval of generic equivalents, the United States may end up spending billions more in the coming decades on a product whose active ingredient was first approved in 1981. The same could happen for other medications currently delivered by HFA-based metered-dose inhalers.

To avoid another surge in spending on inhalers, the federal government could take several steps. First, the FDA could refrain from banning HFA-based metered-dose inhalers, at least until generic versions of greener alternatives become available; alternatives may include not only future inhalers that are more eco-friendly but also existing options, such as dry-powder inhalers.

Second, lawmakers could promote early entry of greener generic inhalers by increasing the 180-day exclusivity period awarded to the first generics manufacturer to successfully challenge the patents on a particular drug–device combination. The Hatch–Waxman Act of 1984 instituted 180-day exclusivity periods as a reward for generics manufacturers to pursue patent challenges, which can be associated with costly and risky litigation. Increasing the rewards for challenging the extensive patent "thickets" on complex products like inhalers would better reflect the added costs to firms and could expedite market entry by generics.

Third, the U.S. Patent and Trademark Office could pursue reforms, including the introduction of a specialized team — a so-called art unit — dedicated to examining drug–device combinations, to help ensure the quality of patents issued on new inhalers. The FDA and the Patent and Trademark Office recently announced their intention to pursue joint initiatives to promote competition in the pharmaceutical industry and lower drug prices, and these initiatives could serve as one pathway for implementing reforms.[4]

Fourth, the Centers for Medicare and Medicaid Services (CMS) could determine what reimbursement rate is appropriate for any greener inhalers that gain approval (over and above reimbursement rates for HFA inhalers), considering the environmental benefits they provide. Such assessments could eventually guide Medicare negotiations under the Inflation Reduction Act of 2022, which will allow CMS to directly negotiate the prices of certain drugs. Though many products will be excluded from negotiation — for example, drugs that have been on the market for less than 9 years — individual Medicare Part D plans and other payers, including private insurers, could still negotiate over greener metered-dose inhalers on the basis of CMS assessments (even when these products are not subject to centralized CMS negotiation). Payers have leverage, since they can always use formulary design to steer patients away from new metered-dose inhalers toward older dry-powder equivalents, such as ProAir RespiClick, which do not emit greenhouse gases. The United Kingdom has adopted a strategy of encouraging use of dry-powder inhalers for precisely this reason, and some commentators have called for the same approach in the United States.[5]

Such a multipronged effort could help avert a repeat of the unnecessary and harmful financial excesses that followed the ban on CFC inhalers. Albuterol is one of many drug–device combinations now on the U.S. market; we believe that limiting costly product hops on complex therapies should be a priority for both the FDA and the Patent and Trademark Office.

Disclosure forms provided by the authors are available at NEJM.org.

From the Department of Health Policy, London School of Economics and Political Science, London (O.J.W.); the Program on Regulation, Therapeutics, and Law, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School — both in Boston (W.B.F.); and the College of Law, West Virginia University, Morgantown (S.S.T.).

This article was published on September 24, 2022, at NEJM.org.

1. Open Secrets. Client profile: International Pharm Aerosol Consortium. 2022 (https://www.opensecrets.org/federal-lobbying/clients/summary?cycle=2020&id=D000052304).

2. Food and Drug Administration. Use of ozone-depleting substances: removal of essential-use designations. Final rule. Fed Regist 2005;70:17167-92.
3. United Nations Environment Programme. Production and consumption of ozone depleting substances under the Montreal Protocol 1986–2004. November 2005 (https://wedocs.unep.org/handle/20.500.11822/8109).
4. United States Patent and Trademark Office. Drug pricing initiatives. 2021 (https://www.uspto.gov/initiatives/drug-pricing-initiatives).
5. Rabin AS, Harlan EA, Ambinder AJ. Small devices, big problems: addressing the global warming potential of metered-dose inhalers. Ann Am Thorac Soc 2022;19:1090-2.

DOI: 10.1056/NEJMp2208613