Navigating the Transition to Low Global Warming Potential Propellants

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Disclaimers

This presentation reflects the views of the presenter and should not be construed to represent FDA's official views or policies.

Any representation of brand name drugs in this talk are for purposes of scientific discussion and specific comparison.

Introduction – Complex Drug Product Dosage Form - Metered Dose Inhalers

- Since the FDA approval of Medihaler Epi and Medihaler Iso in 1956, metered dose inhalers (MDIs) have been a safe and effective method for respiratory drug delivery for close to 70 years
- Account for two-thirds of all respiratory therapy doses prescribed
- Main target diseases are asthma and chronic obstructive pulmonary disease (COPD)
- Formulated to deliver a range of active pharmaceutical ingredients (APIs) with differing mechanisms of action
  - Inhaled corticosteroids (ICS)
  - Short- and long-acting bronchodilators
- Provide a fast and convenient aerosolization system for drug delivery by using a propellant-driven mechanism

https://www.pikpng.com/downpngs/hiRwxbo_asthma-attackers-swim-class-asthma-inhalers-clipart/

Propellants – Critical Drivers of MDI Performance

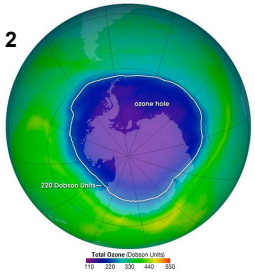
An MDI's propellant performs multiple functions:

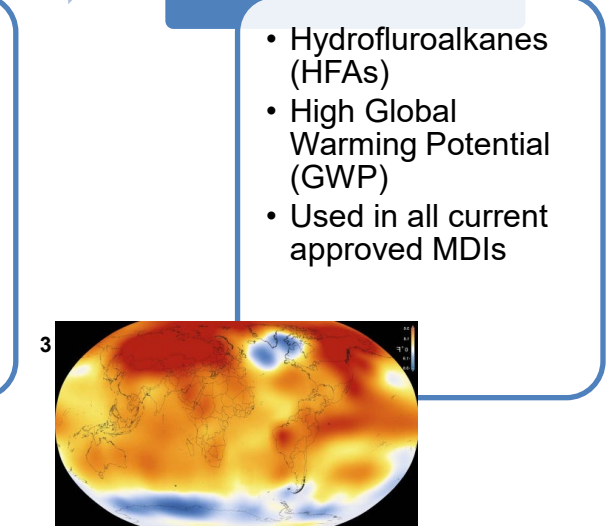
- **Driving force for releasing the drug from the actuator device**
- **Facilitator for atomization of the formulation into aerosolized droplets and maturation of the droplets to their subsequent depositing forms**
- **Constitute the bulk of an MDI's formulation, providing a solubilizing medium for either dissolving or dispersing the API in the formulation**

Propellant History for MDIs

1st Generation

- Chloroflurocarbons (CFCs)
- Deplete Ozone Layer
- 1987 Montreal Protocol for CFC phase out





CCl_3F CCl_2F_2 $F_2ClC-CClF_2$

CFC-11 CFC-12 CFC-114

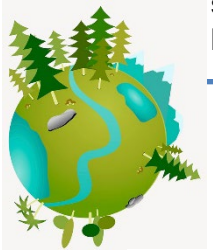
2nd Generation

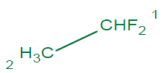
- Hydrofluroalkanes (HFAs)
- High Global Warming Potential (GWP)
- Used in all current approved MDIs

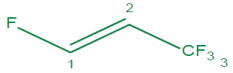
HFC-227ea HFA-134a

3rd Generation

- Phase down 2nd Gen HFAs by 80-85% by 2047 (Kigali Amendment to Montreal Protocol)
- Potential supply shortages of HFAs and cost increases
- Manufacturers drive to seek alternative propellants for MDIs







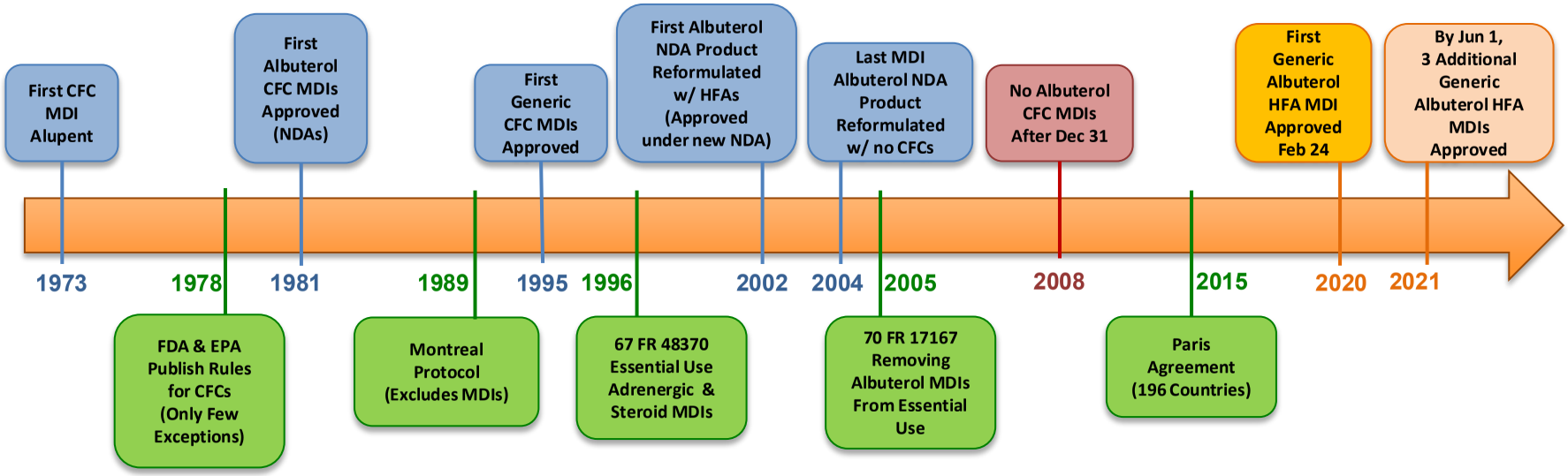
HFA-152a HFO-1234ze

https://images.rawpixel.com/image_800/cznmcy1wcml2yxrlL3Jhd3BpeGVsX2ltYWdlcy93ZWJzaXRlX2NvbnRlbnQvbHIvam9iNjgzLTAxODEteC5qcGc.jpg

Phase Out of CFCs in MDIs

- Removal of CFC propellant MDIs from the market was a complex multi-year process (beginning in 2005) that had a variable timeline based on the specific API
- To remove CFCs, each MDI required reformulation to either use new propellants or develop another platform for delivery
- Hydrofluoroalkanes (HFAs), which include hydrofluorocarbons (HFCs), became new propellants
  - Due to the different chemical properties between CFCs and HFAs, redesign of the MDI device was sometimes necessary in addition to the reformulation
- The new reformulated MDIs required full clinical development programs
  - Patents and exclusivity for new HFA propellant MDIs were listed in FDA Orange Book

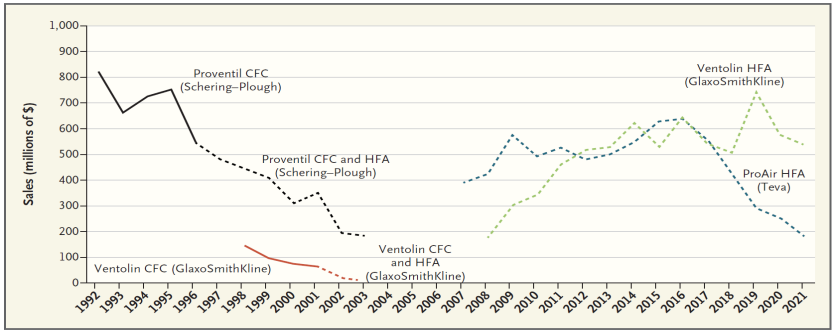
Albuterol MDI History and the Impact of the CFC Phase Out on Generics



- The phase-out of CFC propellant MDIs from the market impacted generic MDIs in two ways
  - Removed existing generic MDIs from the market
  - Patents and exclusivity for the HFA propellant MDIs contributed to delays for generic versions

Impact of the CFC Phase Out on Generic MDIs

- The net result from the CFC phase out for MDIs was an increased cost to patients
  - For albuterol MDIs[4,5], the increased cost occurred rapidly for patients following removal of the last CFC based albuterol MDI in 2008
  - In 2018, the monthly cost of a branded HFA based albuterol MDI was approximately $200
- The approval of three HFA based generic albuterol MDIs in 2020 has led to reduced costs for patients
  - In 2022, the average cost for a generic HFA based albuterol MDI was less than $25



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

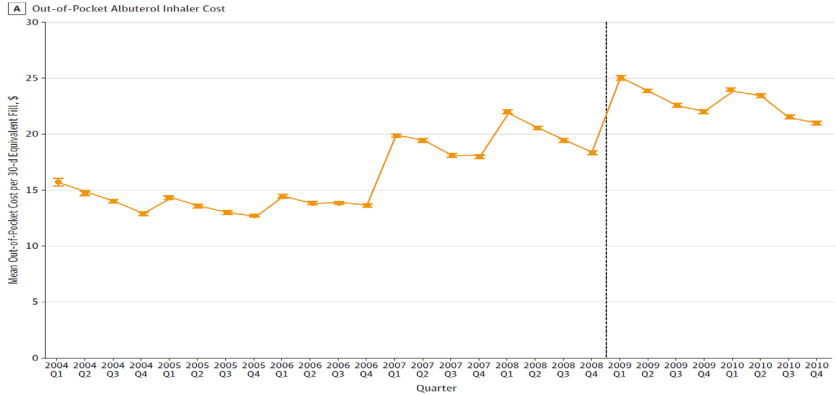


Figure 1 from Wouters et al[4] and figure 1a from Jena et al[5] – Albuterol MDI sales 1992-2021 *(top)* and mean out of pocket costs *(bottom)*.

Wouters, J., et al. Product Hopping in the Drug Industry – Lessons from Albuterol. NEJM. 2022. 387(13): 1153-1156.

Jena, A., et al. The Impact of the US Food and Drug Administration Chlorofluorocarbon Ban on Out-of-Pocket Costs and Use of Albuterol Inhalers Among Individuals with Asthma. JAMA Intern Med. 2015. 175(7): 1171-1179.

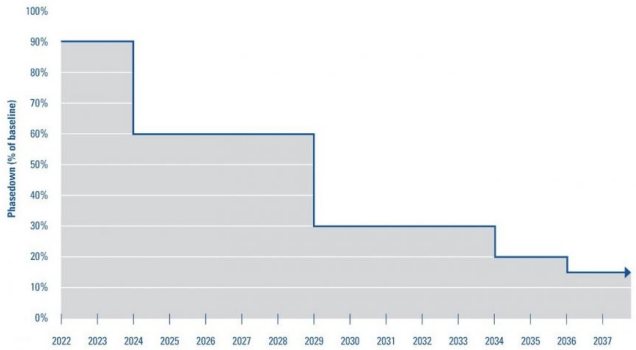
The Next Propellant Transition – The HFC Phase-Down

HFC PHASEDOWN
American Innovation & Manufacturing (AIM) Act
A U.S. Environmental Protection Agency Program

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

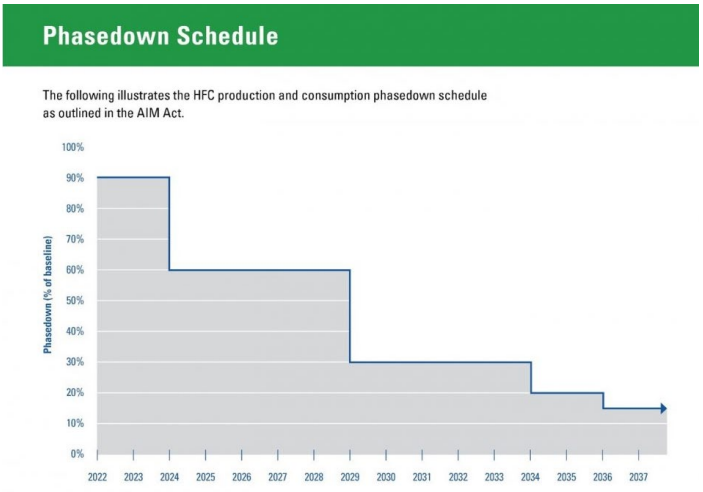
Phasedown Schedule

The following illustrates the HFC production and consumption phasedown schedule as outlined in the AIM Act.



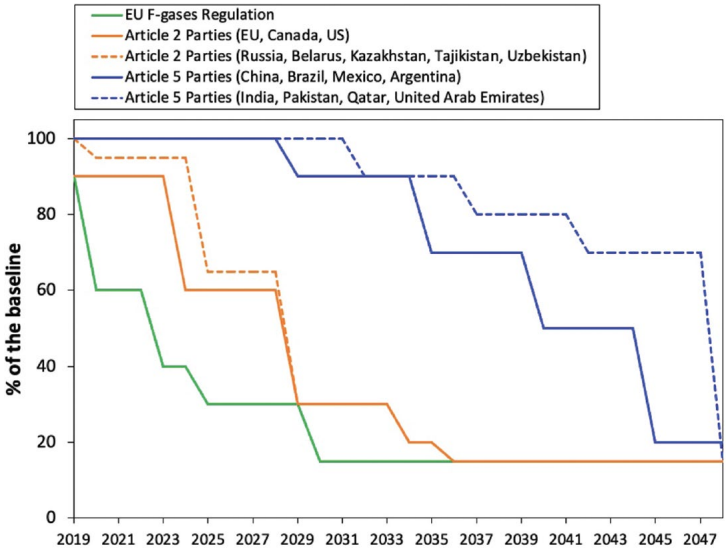
- HFCs (which include the HFA propellants) found to be potent greenhouse gases that can contribute to climate change
- While HFC emissions from MDIs represent <0.1% of the total greenhouse emissions[6], efforts to reduce their use are underway to address their environmental impacts
- 2019: Kigali Amendment to the Montreal Protocol
  - Gradual reduction (**phase-down**) in consumption and production of HFCs
  - Countries allowed exemptions for certain essential uses
- 2020: American Innovation Manufacturing (AIM) Act enacted
  - Directs EPA to address the HFC **phase-down**

The Next Propellant Transition – The HFC Phase-Down



- 2021: EPA published a Final Rule for phase-down of HFCs[7]
  - Mandates the phase-down of HFCs to 15% of their baseline levels over a period ending in 2036
  - MDIs received application-specific allowances through 2025
- 2023: HFC Allocation Final Rule published[8]
  - EPA reviewing application-specific allowance allocation; potential for renewal beyond 2025
- Communication between EPA and FDA is ongoing to minimize effects of the HFC phase-down on the MDI market
  - Prevention of any potential for drug shortages due to the propellant transition is important
  - HFC allocation for MDI drug developers, along with drug development timelines for completing a propellant transition, have been discussed

Implications from a Global HFC Phase Down



Phase down for different parties following Kigali amendment and EU F-gas regulation indicated as reduction % of the baseline.[6]

- Countries around the world are working to phase-down HFC use
- Differences in phase-down timelines and regulatory requirements across health agencies can lead to challenges for brand and generic developers
- Coordination and communication among health agencies is important for an efficient transition
  - Generic Drug Cluster (international regulatory agencies) have discussed the approaches different agencies are considering to support drug propellant transition
- Health agencies are beginning to provide guidance to industry
  - In 2023, EMA published its scientific guidelines, *Questions and Answers on Data Requirements When Transitioning to Low Global Warming Potential (LGWP) Propellants in Oral Pressurised Metered Dose Inhalers*[9]

What Does this Phase-Down Mean for Reference (NDA) and Generic (ANDA) HFA-based MDIs?

- Importantly, this transition is a **phase-down** of HFCs, not a **phase-out** as previously done with the CFC propellants
- Therefore, at this time, HFA MDIs can remain on the market, including generics
- However, as this phase-down of HFCs is occurring globally, there is the expectation that this process will impact both the supply and cost of HFAs
- The increase in cost for HFA propellants is likely to impact manufacturing decisions for HFA-based MDIs that could increase the cost of these treatments for patients

A Public Health Perspective

- Ideally, this current phase-down/phase-in propellant change is conducted in an orderly fashion, maintaining access to these important, life-saving, disease-treating medications for our patients in the United States
- We strive for a balance with regards to least burdensome approach, but yielding products that are therapeutically equivalent to the ones they are replacing

ACKNOWLEDGEMENTS

- Our Inhalation Product Team in DTP/ORS/OGD led by Dr. Bryan Newman
- Dr. Robert Lionberger, who was one of the first to mention that we need to be prepared for this transition for generics as far back as 2019
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- Our EPA, academic, and industry collaborators

Thank You

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