Supporting a Sustainability Switch – A Laboratory Assessment of HFO-1234ze(E)-based Formulation Performance used with a Commonly Referenced Valved Holding Chamber (VHC)

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BACKGROUND

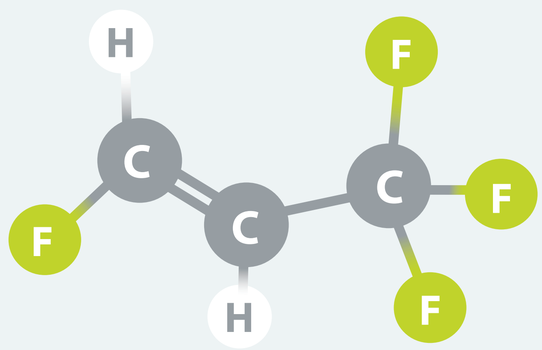
- The current transition to low GWP propellant is the result of the Kigali Amendment to the Montréal Protocol.
- A key requirement for any new propellant having the potential to reduce environmental carbon footprint is to maintain or improve upon the performance of existing inhalers.
- pMDIs are widely used with a VHC to overcome poor patient coordination of actuation with the onset of inhalation, especially prevalent with children.

OBJECTIVE

- To assess if a change in propellant affects the mass of medication contained in fine particles capable of penetrating beyond the oropharynx

HFO-1234ze(E)

Solstice Air (HFO-1234ze(E)), cGMP is an environmentally preferable, ultra-low Global Warming Potential (GWP) alternative to HFCs that reduces greenhouse gas emissions of MDIs by up to 99.9%.



MATERIALS & METHODS

PART 1: pMDI Canister Preparation at Honeywell

- The TEST propellant was ultra-high purity grade HFO-1234ze(E). The REFERENCE was propellant grade HFA-134a
- Beclomethasone dipropionate (BDP) was the model active pharmaceutical ingredient (8%w/v solution in 2 mg/mL ethanol)
- Fluorocarbon polymerised (FCP) plasma process coated cans each with 63 µL metering valve. Canisters were agitated to ensure adequate mixing and then left to equilibrate under 2-week quarantine.

PART 2: Evaluation at Trudell Medical International

- An anatomically correct 4-year-old child Model (ADAM) was used to measure the mass of BDP contained in fine particles capable of penetrating to a filter located at the model exit (**fig. 1**).
- A single measurement for each of 5 canisters for each formulation was made with the following standard child settings:
  - tidal volume = 155 mL,
  - inspiratory/expiratory ratio = 1:2,
  - rate = 25 breaths/min.
- In all cases, actuation of the inhaler coincided with the onset of the recorded inhalation waveform and 5 complete respiratory cycles were allowed to elapse before terminating the sampling process.
- The mass of BDP recovered from the pMDI mouthpiece, VHC, facemask, face surface, oropharyngeal airway and filter were separately recovered and subsequently assayed via HPLC-UV spectrophotometry.

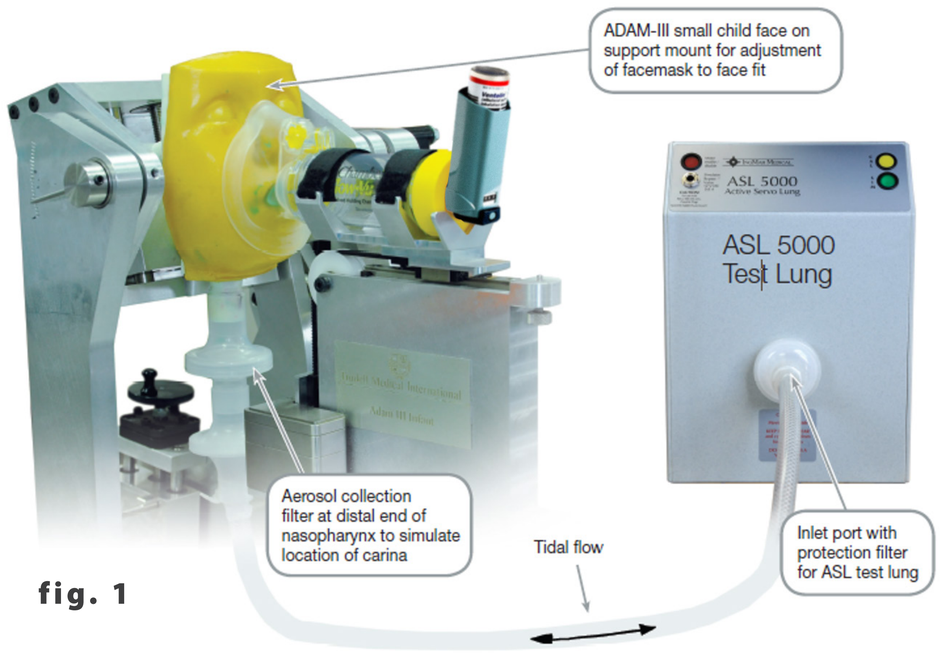
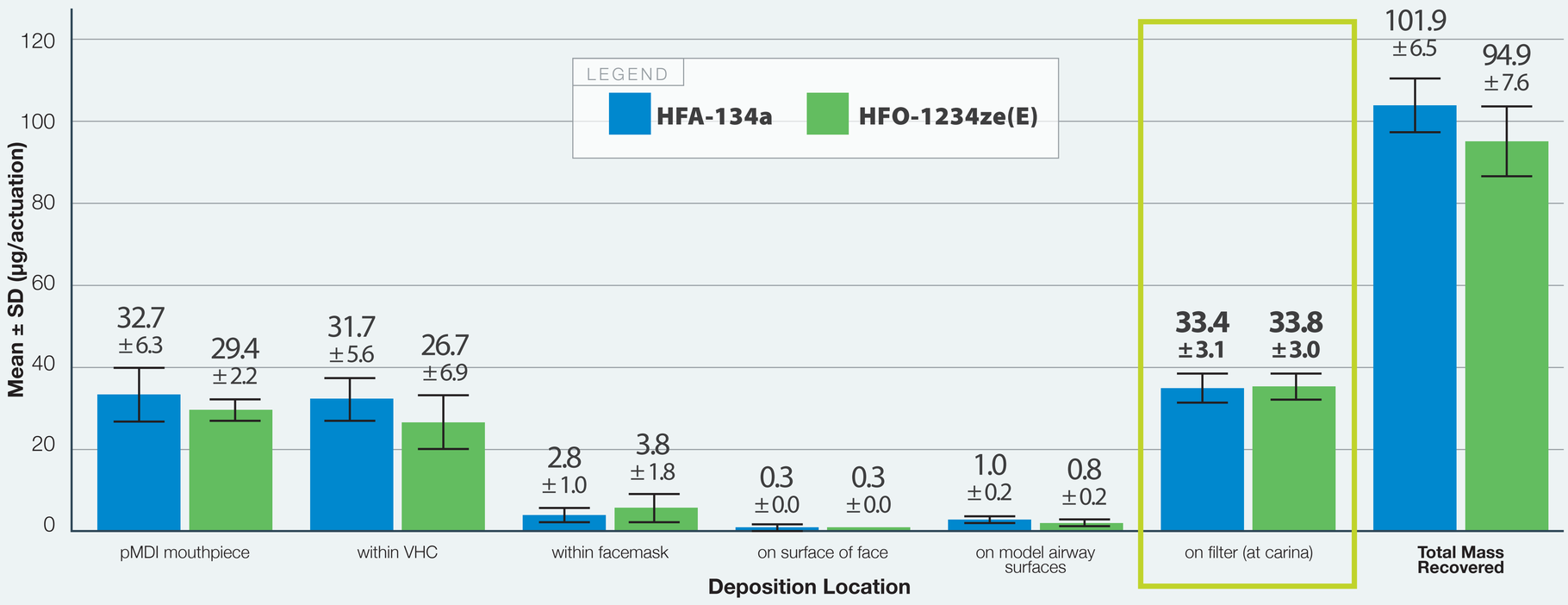


fig. 1

RESULTS

- The total mass of BDP recovered from all components of the sampling apparatus is summarized in **fig 2**.
- The total mass recovery (mass balance) values for both products were all within ±15% of the targeted metered dose for the formulations.
- There was no statistical difference in the mass/actuation of BDP recovered from the filter,
  - **This mass represented the mass of fine particles capable of reaching the carina and therefore available for deposition in the lungs between the two formulations (un-paired t-test, p (2-sided) = 0.82).**

fig. 2 Mass of BDP/actuation Recovery Profiles for HFA-134a and HFO-1234ze(E) pMDIs



DISCUSSION

- Information on the delivery of inhaled medication by pMDI products when used with a spacer or VHC is crucial for laboratory and clinical programs supporting inhaler development.
- In Europe, such testing with an add-on device is now a regulatory requirement for quality performance testing and *in vitro* equivalence.
  - EMA draft guideline 'Pharmaceutical Quality of Inhaled and Nasal Products'. 2024. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-pharmaceutical-quality-inhalation-nasal-medicinal-products_en.pdf.
  - EMA draft guideline 'Documentation for Demonstrating Therapeutic Equivalence Between Orally Inhaled Products in Asthma and COPD'. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-requirements-demonstrating-therapeutic-equivalence-between-orally-inhaled-products-oip-asthma-chronic-obstructive-pulmonary-disease-copd_en.pdf.
- **We found that changing the propellant from HFA-134a to HFO-1234ze(E) did not significantly affect the mass of fine BDP particles delivered to the lungs, a promising result for the adoption of HFO-1234ze(E).**

CONCLUSIONS

- We undertook our comparison of BDP delivered by pMDI with either HFA-134a or HFO-1234ze(E) propellants via a VHC with facemask using a child face model with anatomically correct oropharyngeal airway
- Our finding of comparability between the two propellants provides encouraging support for equivalence in the delivery of fine particles distal to the airway at the carina and potentially available for lung delivery when transitioning to low GWP propellants

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