

HFA-152a as a Sustainable pMDI Propellant

Stuart Corr

Koura, Chester, UK

KEYWORDS: sustainability, HFA-152a, carbon footprint, metered dose inhaler

INTRODUCTION

There is increasing attention on the environmental impact associated with pressurized metered dose inhalers (pMDIs) with some proposals to encourage transitioning towards alternative delivery technologies [1]. Before embarking on any significant change to prescription of inhalation drugs, we need to understand the environmental implications of the options available as well as their potential impact on patients.

ENVIRONMENTAL IMPACT: LIFE CYCLE ANALYSIS (LCA)

The carbon footprint of a number of inhalers has been reported previously [2]. These studies indicate that the carbon footprint per dose of medicine delivered (as the equivalent number of grams of CO₂ (gCO₂eq)) is in the range of 200–300gCO₂eq for an HFA-134a pMDI, 600–800gCO₂eq for a HFA-227ea pMDI and 8–60gCO₂eq for dry powder (DPI) inhalers. Detailed LCA analysis to ISO 14040/14044 methodology has shown that using HFA-152a results in a >90% reduction in carbon footprint when compared with an equivalent HFA-134a formulation [3]. Clearly, the reduction in carbon footprint will be significantly higher when an HFA-227ea-based product is replaced. This magnitude of reduction puts the HFA-152a pMDI squarely within the range of the DPI products studied in the United Nations Environment Programme reference. In the most recent study [4], Jeswani compares the environmental impacts of pMDIs using HFA-134a, HFA-227ea and HFA-152a with those of a particular DPI device. The comparison in this study was between a weighted-average pMDI impact versus a specific DPI device (Diskus®) at the lower-end of the range of reported DPI carbon footprints. It should be recognized that like DPIs, not all pMDIs have the same carbon footprint. For example for 200-dose reliever pMDIs (Figure 1).

The carbon footprint of these pMDI products varies by around a factor of three but the prescription profile in the UK is such that weighted average is towards the top of the range. In looking to (re)formulate pMDI products to use HFA-152a in place of current propellants, it may be possible to use less propellant per dose than some of the current products. Clearly the success of this approach will depend on the technical performance of the new formulation but also on patient preference factors. Using published data [4, 5] the carbon footprint per dose across a number of delivery platforms can be compared (Figure 2).

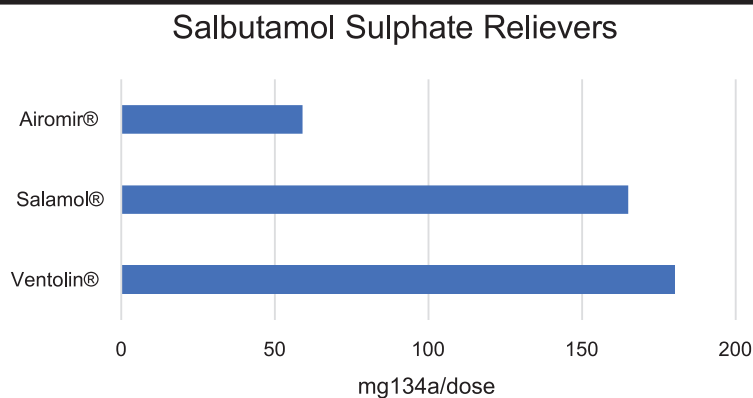


Figure 1. Propellant use per dose for pMDI products.

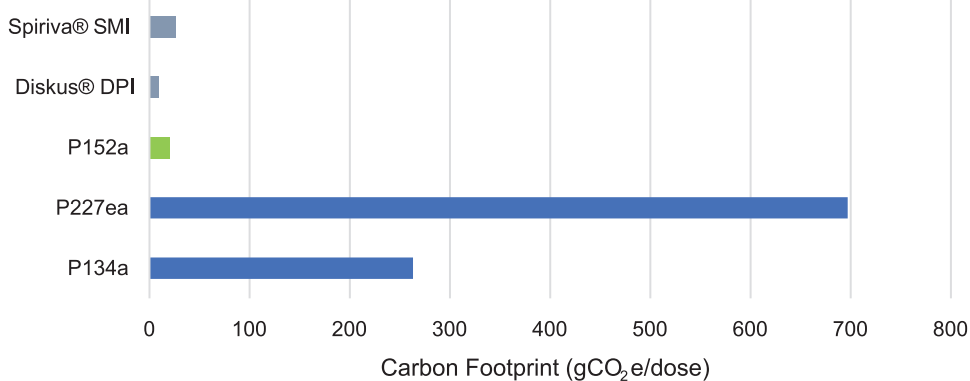


Figure 2. Carbon footprint per dose for inhalation delivery platforms.

Based on the inhaler usage data from the United Kingdom National Health Service (NHS), Jeswani [4] considered the environmental impact of a number of inhaler use change scenarios (Figure 3). Whilst pMDI replacement by DPI gave an attractive reduction, it did not recognize that DPIs are not universal in their patient applicability [6] and the magnitude of carbon footprint reduction of (A) is unlikely to be achievable. Taking a more pragmatic level of replacement where 20–30% of inhalers remain as pMDI reduces the carbon saving of the DPI replacement approach significantly (D). Scenarios E and F where the ratio of pMDIs to DPIs remains the same as present but using HFA-152a as the propellant provide the greatest potential mitigation.

In assessing the options for carbon footprint mitigation it is essential to consider the potential consequences for patients and health care providers. Scenarios (B), (C), (E) and (F) all maintain the current treatment platform and would be expected to minimize the requirements for device use retraining. The reduced propellant charge per dose, with possibly the use of additional or increased levels of excipients in (B) and (C) may have some effect on patient perception. Similarly, the change in propellant itself (HFA-152a) may also be perceived to be different by patients ((E) and (F)). Since they require a change in delivery platform, (A) and (D) will require significant investment of time and money into retraining and with the potential to result in an increase in exacerbations with consequential cost and health impacts [7, 8].

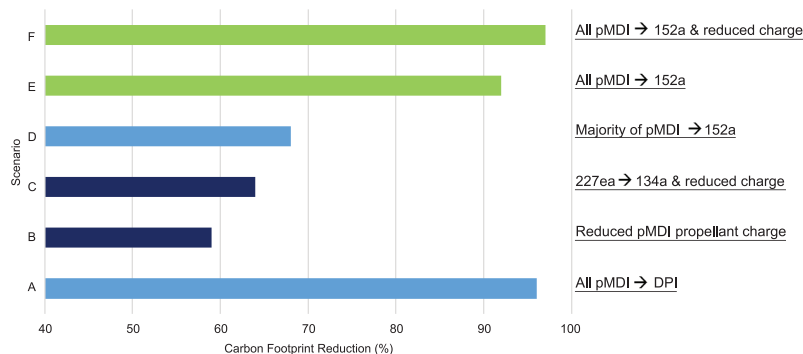


Figure 3. UK NHS inhaler carbon footprint mitigation scenarios.

INHALATION SAFETY PROGRAM

Clearly, any new pMDI propellant must not come at the cost of any significant compromise to patient inhalation safety. A medical-grade of HFA-152a from Koura has been the subject of an extensive suite of inhalation safety testing with the chronic two-year animal study already underway. Results to date on both acute and sub-chronic safety tests have been very encouraging with HFA-152a behaving in a similar manner to HFA-134a. Propellant-only clinical trials are already approved by the US FDA. It is anticipated that the program data will be available to support the commercial use of medical-grade HFA-152a with completion of a Drug Master File (DMF).

Other potential low-carbon propellants have been proposed including the hydrofluoroolefin HFO-1234ze(E) (1,3,3,3-tetrafluoropropene) [2]. Whilst the acute toxicity of HFO-1234ze is acceptable for use in industrial applications, some questions remain including the effects of chronic exposure at the levels relevant to pMDI inhalation. In a series of rat studies, focal and multifocal mononuclear cell infiltrates in the heart were observed [9]. The significance of these observations would require further investigation.

HFA-152a manufactured to cGMP is already available in small quantities for research purposes. Although it is expected that the DMF for HFA-152a will be finalized in 2022, there will still be much work to be done before a commercial pMDI based on HFA-152a can be made available. This development and regulatory stage will go beyond the 2022 propellant timescale, perhaps to 2025 or so, before new products based on HFA-152a will appear on the market[10].

CONCLUSION

The development of HFA-152a for use in pMDIs has made significant progress over the last few years with many of the hurdles either already overcome or looking to be manageable going forward. By reducing the environmental impact of pMDIs to levels comparable with other delivery technologies, HFA-152a enables the pMDI platform to remain as an invaluable option that gives patients and medical practitioners the freedom to choose their medication on the basis of clinical efficacy, patient preference and cost whilst avoiding the costs and potentially adverse impact on patients associated with an imposed change in inhaler delivery technology.

ACKNOWLEDGEMENTS

The author would like to acknowledge Prof. Adisa Azapagic and Dr Harish Jeswani (Manchester University) for their input, and Koura for permission to publish.

REFERENCES

1. UK Progress on Reducing F-gas Emissions [<https://www.parliament.uk/business/committees/committees-a-z/commons-select/environmental-audit-committee/news-parliament-2017/f-gases-report-published-17-19/>]. Accessed December 31, 2019.
2. United Nations Environment Programme. UNEP: Report of the Medical Technical Options Committee (MTOC) 2014 assessment report. UNEP Ozone Secretariat.
3. Noakes T, Corr S: The future of propellants for pMDIs. In *Drug Delivery to the Lungs 2016*. The Aerosol Society, Bristol, UK: 2016, 61–64.
4. Jeswani HK, Azapagic A: Environmental impacts of inhalers in the UK. *J Cleaner Production* 2019, 237: 117733.
5. Hansel M, Bambach T, Wachtel H: A comparison of product carbon footprints of Respimat® versus pressurized metered dose inhalers. In *Respiratory Drug Delivery 2018*. Edited by Dalby RN, Byron PR, Hindle M, Peart J, Traini D, Young PM, Farr SJ, Suman JD, Watts A. DHI Publishing; River Grove, IL: 2018, 321–24.
6. United Kingdom NICE Patient Decision Aid [<https://www.nice.org.uk/guidance/ng80/resources/inhalers-for-asthma-patient-decision-aid-pdf-6727144573>]. Accessed December 31, 2019.
7. Usmani OS, Scullion J, Keeley D: Our planet or our patients-is the sky the limit for inhaler choice? *The Lancet* 2019, 7(1): 11–13.
8. Bjermer L: The importance of continuity in inhaler device choice for asthma and chronic obstructive pulmonary disease. *Respiration* 2014, 88.
9. Rusch GM, Tveit A, Muijser H, Tegelenbosch-Schouten MM, Hoffman GM: The acute, genetic, developmental and inhalation toxicology of trans-1,3,3,3-tetrafluoropropene (HFO-1234ze). *Drug Chem Toxicol* 2013, 36(2): 170–80.
10. Chiesi Farmaceutici: Chiesi outlines €350 million investment and announces first carbon minimal pressurised Metered Dose Inhaler (pMDI) for Asthma and COPD 04/12/2019. [<https://www.chiesi.com/en/chiesi-outlines-350-million-investment-and-announces-first-carbon-minimal-pressurised-metered-dose-inhaler-pmdi-for-asthma-and-copd/>]. Accessed December 31, 2019.