A Greener Future for the Inhalation Industry: A Critical Year for our Climate

The urgent threat of climate change is the age-defining issue of our generation, and we are reaching a defining moment for our industry. The inhalation industry is committed to reducing their carbon footprint and establishing processes which are more sustainable. A global commitment to establishing a greener future *must* happen now; the industry's proactive approach will address the major environmental concerns of pMDI manufacture – the carbon footprint of the propellant.

The adverse effects of greenhouse gases on our climate are well documented. This is not a new revelation, rather, this industry has gone through a similar issue before! The issue being adapting the way we formulate MDIs to develop more sustainable products, whilst maintaining the safety and functionality.

Figure 1

This article explores the legislative and economic drivers of why the industry needs to adapt, and crucially why now is the time to act. It is also important to ground ourselves and remember why we develop medicines; to better the health of the public and save lives. The effective delivery of medicines still remains the priority. The challenge to produce sustainable products cannot compromise the safety, efficacy and patient adherence of inhaled medicines.

The 1987 Montreal Agreement was the catalyst for the first-wave development of sustainable pMDIs. The successful phase out of CFCs with F-gases had a positive impact on ozone depletion and to some extent the carbon footprint[1]. Through significant investment by the industry, less ozone-depleting alternatives were developed (HFA-134a, HFA-227 & DPIs). Manufacturers of pMDIs understand that sustainable products cannot be developed on sentiment alone – it is the commitment to invest that ultimately allows the change to alternative propellant systems!

Two major pharmaceutical companies, Astra Zeneca and Chiesi Group, have recently committed to investing in alternative propellant pMDIs. Both companies have committed to launch a 'greener' inhaler by 2025[2,3]. Other major companies have yet to publicise their commitment. Given the timelines for pharmaceutical product development and regulatory approval of new medicines, 2025 may seem challenging. The importance of acting now is evident for both environmental and economic issues. It is clear the environmental crisis cannot wait; if and when the current propellant supply is phased out, commercial production of current inhalers becomes unrealistic.

As a producer of reliever medication, Pharmaserve North West has committed to future-proofing our facilities, products and processes. The importance of safeguarding the supply of critical medicines has been highlighted through the COVID-19 crisis. It is a collective responsibility to ensure global delivery of life-saving pMDIs. The issues and challenges posed by the investment into two prospective greener propellants have been addressed as a matter of urgency. Working closely with industry leaders to ensure our approach to the 'greener' inhaler does not impact the health of the public.

Proposed Solutions

HFO-1234ze and HFA-152a have been highlighted as potential replacements of HFA-134a and HFA-227ea. Isobutane was also considered and is currently used in topical aerosols; the inhalation safety concerns make this a less favourable option[1]. Both propellants address the environmental concerns of pMDIs, however each has limitations and challenges which must be overcome before commercial production.

	HFA-134a	HFA-152a	HFO-1234ze
Liquid Density (g/mL)	1.21	2.7	1.29
ODP	0	0	0
GWP	1300	138	< 1
Atmospheric Lifetime	13 years	1.4 years	18 days
Flammability	n/a	LFL 3.8%	n/a

Table 1

It has been well documented that HFA-152a is actively being developed for use in pMDIs. The properties are similar to those of HFA-134a – but critically for suspension formulations, the liquid density is significantly lower. Despite this, early formulation studies have shown that the performance is surprisingly good[4]. Although the data is promising, it is critical that further studies are performed to understand the propellant performance for more inhaled APIs and also solution formulations. The performance of HFO-1234ze may look more promising, given the closeness of its properties to HFA-134a. The transferability, due to these similarities, may expedite the development process.

Both propellants have been shown to have good compatibility with currently used materials in MDI componentry. Particular focus has been on the behaviour observed when the propellant contacts elastomer and polymer materials used in the valve constructions. In light of the change, the concern of compatibility is actively being addressed by componentry suppliers, with commitment to understanding and developing new 'sustainable' componentry. The critical path activity of the development of a new propellant is the generation of long-term safety data. HFA-152a is expected to finalise the DMF in 2022; the FDA granted approval to proceed with clinical trials which began in February 2020[5]. The generation of the toxicological data package is also backed by Chiesi to help achieve their target of a commercial product launch in 2025[3,6].

The current uses for HFO-1234ze are focused on commercial and industrial products, although the manufacturer does have a pharmaceutical division and patents for use as a medical propellant. The initial safety data shows that it has a low acute toxicity. Any timelines for extensive toxicological assessment have yet to be published and will no doubt be the rate-limiting step.

The appeal of HFO-1234ze is clear – due to its lower flammability the propellant can be directly transferred to existing equipment and facilities. Whereas, HFA-152a is considered flammable and significant investment is required to mitigate the flammability risks and ensure safe handling. Although the technology is established for topical sprays (historically this technology has been used to safely fill cans with isobutane), the timeline to scale up production is somewhat hindered by the safety requirements. Novel manufacturing methods using 'tablet dispersion drug loading' are also being considered, which form stable suspensions when the propellant is added – the separation of the propellant filling stages, reduced batch sizes and mixing requirement mitigates some safety concerns[7].

It is also important to consider the DPI approach. Whilst the product, technology and processes are established today, there are considerations to be made to ensure the global access to inhaled medications to all demographics. The breathing ability of paediatric and geriatric patients makes DPIs less feasible, particularly in reliever medicines. The economic impact of a wholesale switch was studied, showing the prescribing costs of the switch would increase around 10% on average[8]. It is also important to note this is not feasible for all patients – the pMDI must remain and hence the environmental challenge remains.

Legislative & Environmental Drivers

With the rising concern in the urgency of the environmental crisis, the Kigali amendment to the Montreal protocol was signed in 2016 and presented the industry with a new challenge – tackling greenhouse gas emissions. The amendment aims to *phase out* global consumption of HFA by around 85% by 2047 to address the environmental concerns[9,10].

There is currently no legal or regulatory requirement to change propellant outside of the Montreal agreement in the US. More and more pressure is being applied by environmental lobbyists to phase out these high global warming potential propellants. The corporate responsibility to protect the environment is evident – however the 'choice' of the solution has commercial motivation. It is clear that all solutions are positive; for the environment and the enhancement to patient. Multiple therapeutic solutions allow additional factors to be considered when prescribing medicines: patient ability, preference, costs and adherence.

Economic Drivers

Besides from the moral obligations as residents of this planet, there are also commercial incentives to act promptly. The economic driving factors of propellant price increases and supply chain issue serve as a warning sign for currently marketed products.

Figure 3 (Koura) is based on probable phased withdrawal of 'F' gas quota exemption

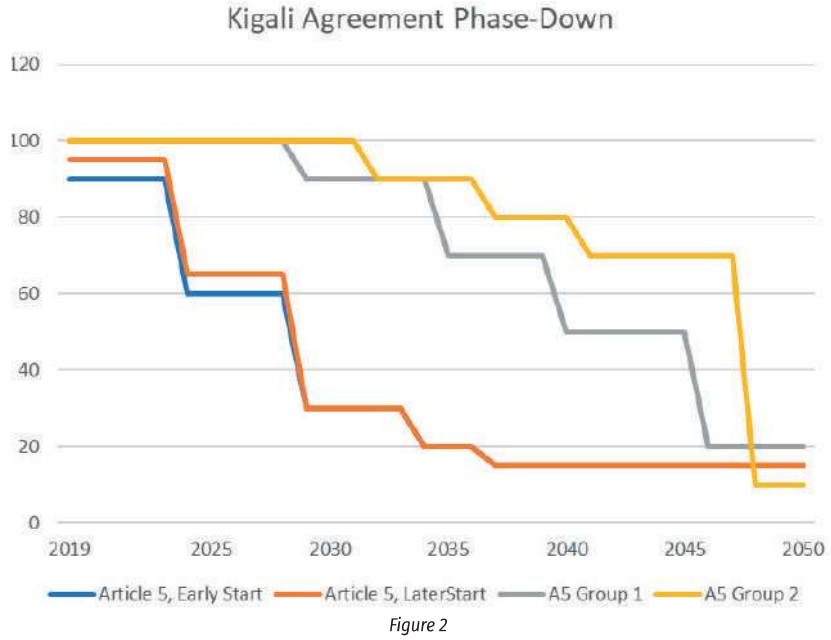

Figure 2

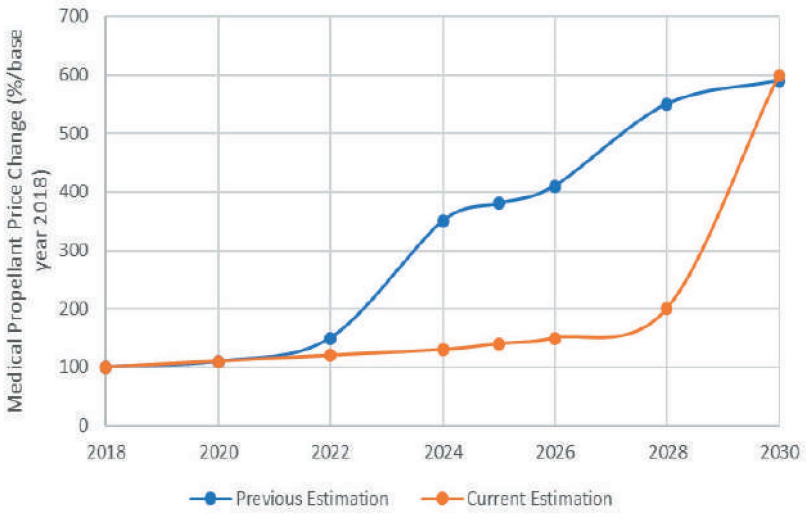

Figure 3

by the EU commission over six years. The increase in cost is mainly due to the need, under the revised regulation, to purchase quotas. This also applies to HFA-227ea, which may lead to it becoming unavailable for medical use. This is a median case; there are more aggressive scenarios. This applies to both 134a and 227ea. In addition, regulation of industrial uses of 227ea may lead to it becoming unavailable for medical use.

By performing early-stage feasibility studies, a commercial strategy can be defined. The translation of existing medicines can follow several routes (DPI, alternative propellant, nasal spray). It is critical for both the patient and business to have assurance that their current product portfolios are safeguarded against the industrial change. The initial investment to assess the feasibility of product translations to sustainable alternatives is relatively small, with relatively big dividends. The focus on being the 'first-to-market' for each medicine is becoming more evident. The market share of current HFA-134a pMDIs cannot be maintained going forward. Capitalisation on this industrial change ensures businesses are not cannibalised by the lack of agility on this issue.

Safeguarding Approach

Pharmaserve have outlined a safeguarding approach to streamline the development and supply of sustainable pMDIs. Through working closely with industry leaders and suppliers, a suggested approach and timeline has been outlined, primarily to ensure the maintenance and supply of **safe** sustainable products, whilst maintaining a commercially viable operation within the inhalation industry.

Figure 4

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