Responding to challenges in developing lower global warming potential pressurized metered dose inhalers (pMDIs)

Legislative and commercial drivers for propellant change and a novel approach to formulation and manufacturing of lower GWP pMDIs

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Legislative drivers for change

As discussed by Mao, et al in the June 2021 issue of *Inhalation* [1], the hydrofluorocarbon (HFC) propellants used today in pressurized metered dose inhalers (pMDIs) have global warming potential (GWP) many times that of carbon dioxide. Their use, together with all other emissive uses of HFCs, is being phased down under the Montreal Protocol. In both the European Union (EU) and the United States (US), this phase down has been enshrined in legislation according to the timetable shown in Figure 1. For both regions, the use of HFCs in pMDIs has been recognized as essential. However, the EU fluorinated greenhouse gas (F-gas) regulations are currently under review, while in the US, under the American Innovation and Manufacturing Act (2020), it is proposed that the US Environmental Protection Agency (EPA) will review essentiality in the light of available alternatives.

By 2015, more than 90% of F-gas contributions to greenhouse emissions were from HFCs. However, the majority were used in refrigeration or air conditioning applications. Aerosol usage accounted for less than 10% and the emissive use of pMDIs comprised only 2.3% of the F-gas contribution to greenhouse emissions [2]. Nevertheless, demand for pMDIs and other aerosols will grow with increasing population and disease prevalence. This has been modeled under a business-as-usual scenario by the United Nations Technical and Economic Assessment Panel (TEAP) [2]. The Panel projects that contribution to greenhouse gas emissions from the Western world could grow to about 15% of the total HFCs by 2035 as other uses are eliminated [2].

Commercial drivers for change

While this legislation should not necessarily cause the pharmaceutical industry to panic, the biggest single factor that drove the timing of transition away from chlorofluorocarbon (CFC) propellants in pMDIs was the increasing price of propellant and associated CFC components. As it became more expensive to manufacture CFC pMDIs than HFC pMDIs, industry replaced CFCs with HFCs so CFC pMDIs disappeared from the supply chain. It is highly likely that scenario will also contribute to the timing of a transition to low GWP pMDIs. Currently, HFC 134a propellant accounts for approximately 30% of the $0.80 it costs to manufacture a pMDI [3]. With fewer non-medical uses for HFC 227ea, its cost is 3-4 times that of HFC 134a, a gap that is currently widening as those industrial uses are replaced by liquefied gases with lower GWP.

In 2018, there was also a warning of things to come. In the EU, the price of industrial grade HFC 134a rose rapidly towards the end of the year in anticipation of the 40% reduction in quotas (Figure 1), peaking at a 5-fold increase compared to 2015 levels. However, this trend was largely reversed in 2019, due to a loophole allowing import of HFCs from outside of the EU. It is anticipated this may be resolved within the current F-gas legislative review in the EU, so the potential exists for prices to rise once more.

Under the Kigali Amendment [4], the 40% reduction would be repeated in the US (and other parts of the Western world) in 2025 (Figure 1). There are no exemptions for any type of application under the Montreal Protocol so it is very likely that price

increases will ensue. Furthermore, as the HFCs in these industrial uses are changed to low GWP alternatives, production will be switched from continuous manufacturing to batch manufacturing campaigns. Consequently, there will likely be additional costs for underused assets, with increasing maintenance bills and lower purchasing power on feedstocks, all of which must be amortized across the reducing tonnes that are manufactured.

Even if there are no other price increases but propellant costs rise 6-fold in 2025, the cost to manufacture an HFC 134a pMDI would rise almost 3-fold to $2.88, while that of a 227ea pMDI would rise almost 4-fold to $5.40 [5]. Therefore, it has been suggested that 2025 could be a tipping point for pMDI cost of goods in the Western world [6]. Two companies [7, 8] have announced plans to transition away from the use of HFCs 134a and 227ea as of that date.

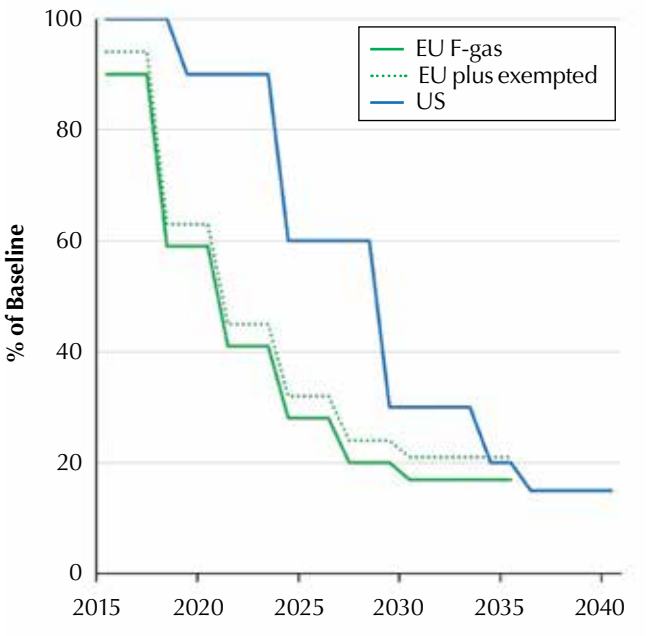
Rescue medications are the primary concern

pMDIs containing only salbutamol account for more than half of all doses of inhaler medication and two-thirds of pMDI doses [6]. Therefore, to have a major impact on global emissions, this product is the priority. Furthermore, the average selling price of a salbutamol pMDI dispensed annually, across the globe, is approximately $0.06 per dose, compared to that of a long-acting β-agonist/inhaled corticosteroid (LABA/ICS) combination, which is at least $1.07 per dose [6]. Today, salbutamol pMDIs represent 10% of the total global inhaler market value. So a 3-fold increase in price, to match the rising costs calculated above, would result in a major increase of the overall medication cost to payors, and potentially further reduce the accessibility to life-saving medication for some patients. Following the submission of this article, it was announced that an R&D program to redevelop and redesign current salbutamol pMDIs with a lower greenhouse gas propellant was underway. The developed pMDIs have the potential to reduce emission by 45% from asthma patients using rescue pMDIs: https://www.gsk.com/en-gb/media/press-releases/gsk-announces-major-renewable-energy-investment-and-low-carbon-inhaler-programme-alongside-life-sciences-sector-race-to-zero-breakthrough-at-nyc-climate-week.

It has been suggested that patients could switch to dry powder inhalers (DPIs) because of their lower carbon footprint [9]. However, this is impractical because a) in many markets, rescue medications are not available in DPI form, b) where available, there would likely be a significant increase in cost and c) it is questionable whether a patient undergoing an exacerbation can generate adequate inspiratory flows through a DPI [6]. Indeed, during an exacerbation, the Global Initiative for Asthma (GINA) guidelines recommend the use of repeat doses of a short-acting β-agonist (SABA), usually administered via a pMDI with a spacer [10], while the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for chronic obstructive pulmonary disease (COPD) recommend the use of SABAs, with or without a short-acting muscarinic agent (SAMA) [11]. GINA has updated their guidelines to recommend starting a newly diagnosed asthma patient on either low-dose ICS alongside a SABA, or as needed low-dose combinations of ICS with formoterol. However, the price differential between doses of LABA/ICS and salbutamol quoted above would again likely provide a significant barrier to adoption.

Figure 1

Phase down of HFC use under the EU F-gas regulations and the Kigali Amendment to the Montreal Protocol.



Technical solutions for pMDIs with low GWP

On the basis that salbutamol pMDIs are required both from clinical and economic perspectives, there is a need to find a low GWP replacement propellant. Historically, when propellants were needed to replace CFCs, two consortia (IPACT I and IPACT II) were formed by a number of pharmaceutical companies to generate a package of safety data on pharmaceutical grade propellants in order to meet regulatory requirements [6]. Pharmaceutical grade HFC 134a was approved for use in pMDIs by the EU in 1994 and HFC 227ea in 1995, but it took an additional decade to complete the phase out of CFCs in that region. At present, there is no equivalent initiative and no industry-wide approach to this problem. While hydrocarbons and dimethyl ether are used in consumer and topical aerosols, both are very flammable, have poten-

tial cardiac side effects and some have taste issues. There are also developments in valve technology to create a metering valve capable of using compressed gases such as CO_2 [12]. Non-metered variants of this technology have recently reached the market [13]. Not-in-kind alternatives, such as soft-mist inhalers (SMIs), also address the issue of effort-independence. Several companies are pursuing this approach.

Potential propellants for low GWP pMDIs

This leaves only two leading candidates as propellants for pMDIs with significantly lower GWP: HFO 1234ze(E) and HFC 152a. The former is the more attractive from an emissions perspective, as it has the lowest GWP. HFO 1234ze(E) also appears to be closer to HFCs 134a and 227ea in key physical properties (density, vapor pressure, moisture solubility and dipole moment). That may make the path to development faster, if the materials and processes developed for use with HFCs can be directly transferable. However, as a new propellant, it is extremely likely that medical regulators will expect long term human safety data to be collected before granting market authorization. This will undoubtedly be critical path activity. Given that HFO 1234ze(E) is not widely available in pharmaceutical-grade material, nor yet has a comprehensive inhalation safety data package, these requirements may make the projected launch date of 2025 a stretch target.

At present, HFO 1234ze(E) uses appear to be more focused on non-medical applications such as refrigeration; its aerosol use is also non-medical, such as in party streamers. Although there are patent applications relating to its use as a medical propellant, there have been few publications on pMDI applications, other than one or two academic research papers. However, it is known to be in active development by at least one pharmaceutical company [14].

On the other hand, HFC 152a is well publicized to be in active development for applications in pMDIs [15]. HFC 152a is made at large scale for industrial uses, including use as a precursor in the chemical synthesis of polymers, and so is comparable in price to HFC 134a. Data on prototype formulations have shown good pharmaceutical performance in the laboratory despite a significant density difference between the propellant and most commonly prescribed respiratory drugs [16]. Nonetheless, there may still be significant valve and product development required. Product chemical stability and compatibility with existing pMDI components also appear promising. One company has initiated propellant-only clinical trials of their pharmaceutical grade of HFC 152a with a view to creating a Drug Master File [17].

During the transition from CFC propellants, HFC 152a was also considered alongside HFCs 134a and 227ea but was not adopted at the time. One issue is the flammability of this propellant, with a lower explosive limit (LEL) of 3.9% by volume in air at room temperature (whereas isobutane is 1.8%). In particular, there are risks associated with off-loading and storage of bulk propellant, and then in manufacture of the bulk formulation and in pMDI filling. However, these latter two tasks are difficult to fully automate, leaving some risk to personnel.

Unlike some ethanolic pMDI formulations, HFC 152a does not cause flame extension during a standard flame test. Nonetheless, safe manufacturing processes for HFC 152a will need to be developed. Given that many millions of aerosol cans are safely filled with isobutane, the technology exists to overcome this problem. Normally, a paste is filled into the can and a valve crimped on, then the cans pass to an isolated explosion shed where an automated, highly ventilated gassing facility adds the liquefied propellant [18]. Cold fill of the propellant is not recommended for flammable aerosols [19], so to replicate the process of pre-loading cans with a drug formulation in pMDIs, ethanol could be used. However, not all drugs are compatible with ethanol due to formulation instability [18]. Furthermore, ethanol is also flammable with an LEL of 3%, so is likely to raise additional safety concerns if used with HFC 152a.

A novel technology for pMDI formulation and manufacturing

The Respitab® technology platform (i2c Pharmaceutical Services, Cardiff, UK) [20], provides a novel approach to pMDI formulation and manufacturing that can reduce the challenges and complexities associated with using HFC 152a, while producing high performance pMDIs. Respitab is a propellant dispersible tablet consisting of one or more jet-milled, micronized, active pharmaceutical ingredients (APIs) and approved inhalation excipients such as lactose and menthol. The technology does not require bespoke engineered particles but focuses on careful selection of excipients that have regulatory approval for use in inhalation products.

The API, in tablet form, is added to the pMDI canister followed by crimping of the metering valve and pressure-filling the propellant. Dispersion of the Respitab occurs as the propellant is pressure-filled into the canister. This simplified approach to dispense API into the canisters in the absence of propellant and pressure-filling of propellant alone into crimped canisters can provide a lower risk since the volumes of propellant present in the formulation preparation/filling area are much lower than in a traditional mixing vessel process. In addition, there can be fewer potential hazard sources such as static, mechanical moving parts, electrical sources, etc. Eliminating the need to use a bulk formulation mixing tank removes the requirements for production of drug/ethanol and/or propellant concentrates,

and initial propellant charging of and within batch top-up of pressurized mixing vessels. Decreasing the number of processing steps and their complexity reduces the risk of propellant escape and possible sources of ignition i.e., there is no need for homogenizers associated with a mixing vessel or for concentrate production. For propellant filling alone, the process can be fully automated and performed in a highly ventilated explosion shed gassing facility, thereby, the process can be inherently safer overall.

Studies with Respitab Salbutamol HFC 152a

Using the Respitab formulation process, a powder mixture containing jet-milled salbutamol sulphate with excipients menthol and lactose was tableted, producing 100 mg tablets with sufficient salbutamol for a product of 200 doses. Tablets were individually dispensed into plain, pMDI canisters with Aptar DF 316 valves (Aptar Pharma, Le Vaudreuil, France) then crimped and HFC 152a pressure-filled through the valve. Subsequently, the canisters underwent 2 weeks of quarantine prior to standard testing of through-life dose content uniformity (DCU) and aerodynamic particle size distribution (APSD) using a pharmacopoeial DCU apparatus and Next Generation Impactor (NGI; Copley Scientific Limited, Nottingham, UK), respectively. DCU data obtained from the single tablet batch are presented in Figure 2, in which limits have been placed on the graph for reference, based on ± 25% and ± 35% of the overall mean metered dose of salbutamol per actuation.

The data show that the metered dose of salbutamol per actuation was close to a target metered dose of 100 µg, with good agreement among the ten inhalers tested, and comparable to currently marketed salbutamol products. The DCU of Respitab salbutamol in HFC 152a was within acceptable limits (as defined in the Pharmacopoeia). All individual pMDI canisters complied with the Pharmacopoeial specification, i.e., 9 out of 10 results were within ± 25% of the overall mean value and no values were outside ± 35% of the overall mean value. DCU data showed consistent through canister life metered doses of salbutamol, confirming both the dispersion and suspension stability of Respitab. Further DCU data (not shown) demonstrated stable metered doses up to 6 months at accelerated storage conditions of 40 °C/75% RH.

Aerodynamic particle size distributions (APSDs) from the Respitab Salbutamol HFC 152a pMDI and a currently marketed, salbutamol HFC 134a pMDI were measured using the NGI. The Respitab formulation and pMDI hardware were selected with the aim of producing aerosol characteristics similar to the marketed product. Three inhalers were tested from each product and the APSD data obtained are presented in Figure 3. The mean fine particle fraction (FPF; % < 5 µm) and mass median aerodynamic distribution (MMAD) values of salbutamol from the Respitab product were 48.3% and 2.38 µm respectively, while for the marketed product FPF and MMAD were 48.5% and 2.33 µm respectively. As anticipated, the APSD characteristics of salbutamol from Respitab and the marketed

Figure 2

Dose content uniformity (DCU) of Respitab Salbutamol HFC 152a pMDIs through can life (n=10).

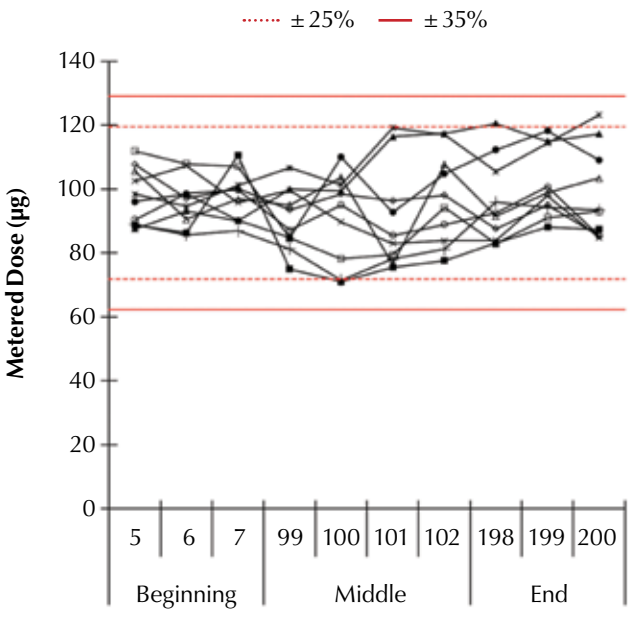
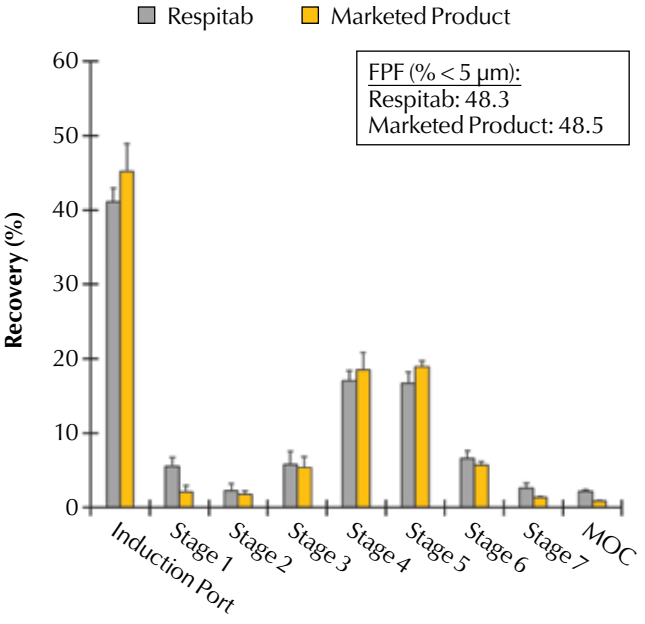


Figure 3

Summary of aerodynamic particle size distribution (APSD) data from Respitab and a marketed salbutamol product (mean ± SD, n=3).



product were similar. Further data (not shown) have been collected that demonstrated stable APSD up to 6 months at accelerated storage conditions of 40 °C/75% RH, illustrating that the Respitab technology has the potential to provide a like-for-like HFC 152a replacement for the HFC 134a product. Additional optimization of the factors critical for tablet production, as well as for and DCU and APSD characteristics, are ongoing.

Considerations for use of Respitab

The Respitab approach has potential to be adaptable and scalable, with the use of standard tableting machinery, to produce various batch sizes. Tablet production does not require a high-speed tablet press since one propellant dispersible tablet typically provides a month's supply of inhaled medication. Quality control checks are performed to ensure API content of the tablets is within specified limits and ensure the API content of each pMDI canister is precisely controlled. This avoids the requirements of real-time analytical in-process controls, essential to determine the API quantity dispensed into each canister during traditional pMDI filling. Following Respitab production and quality control release, batches of tablets can either be stored in bulk form or stored after being dispensed and crimped in standard, non-coated pMDI canisters. Dispensing and crimping may be performed at a different facility from that used for propellant filling. Units from these batches can be dispensed when needed for the production of pMDIs, which can range from small laboratory scale or clinical trial scale batches through large scale commercial batches.

The avoidance of pressure bulk mixing vessels in pMDI manufacture has the potential to eliminate bridging studies with different size pressure vessels, as used in a traditional pMDI development process. In addition, the absence of bulk mixing pressure vessels removes the requirement to compensate for propellant evaporation in pressure vessels during the filling process, in order to maintain the correct concentration of API and ensure accurate and reproducible filling of API into canisters. The elimination of mixing vessels can reduce waste and loss of API and propellant, and result in simplified cleaning processes because the API is only present in canisters and not in propellant filling lines. This can also facilitate rapid and safe switching of production between different product lines, thereby increasing efficiency and minimizing the carbon footprint associated with pMDI manufacture.

Manufacturing of Respitab

The manufacture of Respitab starts with production of an ordered blend of micronized API(s) and larger excipient particles, prepared by low shear mixing. The resultant homogeneous powder blend is quantitatively sampled to ensure content uniformity of API(s). The excipients include menthol as a tablet dispersant and lactose as a suspension stabilizing agent. Menthol has been selected as an appropriate dispersant since it is an approved inhalation excipient and has solubility in the propellant, which promotes tablet disintegration and generates a homogeneous dispersion of the API(s) and excipient. Lactose plays a dual role, acting as a tableting agent and stabilizing the suspension through physical interactions with the API(s) in the propellant environment. Therefore, stable pMDI suspension formulations are produced without the requirement for ethanol or surfactants.

At a convenient time after the addition of one Respitab, containing one month's supply of the API(s), to a canister, the filling of propellant results in immediate disruption of the tablet and following a standard quarantine period, the API(s) will be fully dispersed within the canister. The remaining pMDI manufacturing procedures such as quarantine, actuator fitting, spray testing and packaging are the same as those used in traditional processes. Upon actuation and aerosolization, the API(s) detach from the lactose particles. The particle size properties of the lactose have been carefully selected to optimize both the tableting process and subsequent suspension stability. The size range is such that upon dosing, the majority of the lactose will not be deposited in the lungs, similar in principle to DPI formulations. The amount of lactose emitted per dose from Respitab is considerably lower than that from a typical DPI. Through specific selection of excipients, the Respitab technology may be suitable for the formulation of API(s) with a range of physicochemical properties and potencies, e.g., high-dose inhaled corticosteroids, highly potent long-acting β-agonists, long-acting muscarinic antagonists and combinations of these API(s). Respitab formulations also can be modified to provide aerosol performance appropriate to various API(s) and comparator products.

Conclusions

The emissive use of HFCs as propellants in pMDIs is regulated under the Kigali Amendment to the Montreal Protocol. A new propellant used in a lower GWP pMDI must be both clinically and economically feasible. Development of reliever medications presents a particular challenge, as DPIs are not recommended for use during an exacerbation and propellant prices will very likely have to rise from 2025. In many markets, this may make this life-saving medicine unaffordable for poorer communities.

Consequently, there is a clear need for alternatives to the current reliever pMDIs that are both affordable and have a lower GWP. An option for the near-term is to reformulate salbutamol with HFC 152a using a tablet formulation approach that has potential for advantages over conventional filling technologies. Not only might this reduce manufacturing risks, it could provide an opportunity to mitigate the risk of future price increases of HFCs 134a and 227ea and

thereby may help ensure continuity of affordable care. This approach also could be used to develop other pMDIs with low GWP propellants.

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