REFORMULATING pMDIS WITH NEXT-GENERATION SUSTAINABLE PROPELLANTS

In this article, Ross Errington, Head of Drug Product Development, and Simon Gardner, Business Development Director, both at Bespak, discuss sustainability and the reformulation of pMDIs with low-GWP propellants.

The global incidence of respiratory diseases is rising, with chronic obstructive pulmonary disease (COPD) the third leading cause of death worldwide.[1] This trend is exacerbated by airborne pollution, an ageing population and improving accessibility to accurate diagnoses. Against this backdrop, pressurised metered dose inhalers (pMDIs) are invaluable. These devices represent a highly effective means of pulmonary delivery independent of inspiratory effort by the patient, which is particularly relevant for very young and elderly patients.[2] pMDIs also offer a cost-effective option for payers.[3] In the UK, 71% of patients with asthma are treated using only pMDIs. However, efficacy and affordability are not the only bars by which pMDIs are measured – sustainability is of increasing concern.[4,5]

The basis for sustainability issues in pMDIs lies in their propellants, a key component of the formulation that provides the required pressure to atomise the active drug substance into micron-sized droplets for optimal delivery to the lung.[6] The propellants used in pMDIs are hydrofluorocarbons (HFCs), also known as F-gases, and have high global warming potential (GWP). As a result, an industry-wide global transition to low-GWP propellants in pMDIs is gaining momentum. While a positive step forward for the environment, challenges must be overcome to embark on successful reformulation projects.

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TRANSITIONING TO GREENER PROPELLANTS

Climate-friendly propellants are vital to the long-term sustainability of the pMDI industry. The two most promising low-GWP alternatives are HFA-152a and HFO-1234ze, which can work with modified pMDI designs to achieve effective pulmonary delivery while greatly reducing emissions. Although highly promising from a technical perspective, there are many factors to consider beyond the availability of effective alternatives when making the transition. Chief among these is the need to update manufacturing and formulation processes for compatibility with greener propellants. By preparing effectively and getting ahead of regulatory mandates, pharmaceutical companies can avoid disruption to business continuity and safeguard the accessibility of life-saving medicines.

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Through driving factors and key collaborations, barriers to the adoption of greener propellants are being overcome:

- The removal of supply chain restrictions now enables low GWP adoption, as the two candidate propellants progress towards commercialisation
- Companies are already offering an end-to-end supply chain of low-GWP components and product development and commercialisation services, including commercial-scale pMDI filling with HFA-152a and HFO-1234ze
- Regulators are defining product approval processes.

It is therefore unlikely that legacy propellants will continue to be available or affordable for the pharmaceutical sector, given the speed of adoption for industrial uses. The demand for more climate-friendly propellants will increase significantly in the coming years and, within the industry, there is a responsibility to ensure that the continued delivery of cost-effective medicine to patients globally. As such, the industry must transition before the legislation mandates it.

THE RISK OF DECISION DELAY

Until recently, the pMDI industry has enjoyed protection from the change to low-GWP propellants under regulations such as the EU F-gas Regulation ((EU) No 517/2014) and the US American Innovation and Manufacturing Act of 2020. However, these protections are starting to fall away as low-GWP propellants come to market. With changing legislative and regulatory demands, high-GWP HFCs could become more difficult to acquire as suppliers start to reduce production. Diminished availability and the subsequent increased cost associated with these propellants will likely impact pMDI cost of goods as well.

It is possible that some patients could switch from pMDIs to alternative devices. This is being encouraged across certain healthcare systems but may not be appropriate in many instances. For example, dry powder inhalers are not suitable for all patients, tend to be more expensive to the payer and the need for a particular medication may restrict device choice. There are also mixed results for patients who switch between different inhaler devices.[7] Switching inhalers on non-medical grounds can lead to reduced adherence, loss of disease control and subsequent demand for additional healthcare resources, all of which add to the cost and carbon footprint of the patient's treatment. It is therefore vital that pMDIs continue to be accessible to those who need them most, and that means ensuring the availability of low-GWP pMDIs as soon as possible.

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OPPORTUNITIES CREATED BY REFORMULATING pMDIS

The conversation around patient health is not limited to the problems associated with switching to different kinds of devices. Pollution plays a role in respiratory diseases; therefore, sustainability is intrinsically linked with patient outcomes. Action to minimise climate change demonstrates a genuine desire to protect patients and the planet, which helps to meet corporate responsibility expectations.

From a business point of view, reformulations with greener propellants are also able to achieve intellectual property protection, opening up new possibilities across the industry for companies both big and small. Developers willing to take a proactive approach to the shift can take advantage of this increasingly complex landscape and discover new routes to commercial success.

MODIFYING FORMULATIONS AND COMPONENTS FOR LOW-GWP pMDIS

There are clear opportunities to reformulate with greener propellants and there is a strong sense of time pressure in the evolving industry landscape. Once the decision is made, the real work begins. Pharma companies must re-evaluate and adapt formulations, device components – such as valves and actuators – and manufacturing processes to ensure safety and performance during the lifetime of the product.

Developing a formulation with a performance closely matching that of existing marketed products provides a higher chance of clinical and regulatory success and a smooth transition for the patient in terms of usability and, therefore, compliance.[8] In recent feasibility studies conducted by Bespak, pMDIs using both of the new low-GWP propellants were investigated. One of these studies explored the development of albuterol sulphate pMDIs using the greener propellant HFA-152a. The through-inhaler-life (TIL) delivered doses (DDs) and aerodynamic particle size distribution (APSD) were evaluated in formulations containing different levels of ethanol.[9] The results showed that the TIL DDs became more consistent when ethanol content increased. For APSD, fine particle fraction reduced as the ethanol content increased. By using in-house expertise and extensive experience to optimise formulations, it was possible to achieve consistent performance comparable with that of existing HFA pMDIs.

A second study investigated the impact of device design on the aerosolisation of fluticasone propionate suspensions using both HFA-152a and HFO-1234ze.[10] Actuator design proved critical to controlling throat deposition and droplet size distribution produced by pMDIs. As droplet size is not the sole factor affecting throat deposition, other influencers of this should be explored, such as the spray pattern and plume velocity. To truly control key parameters and understand the compatibility between formulation, device and component design, and low-GWP propellants, collaborating with pMDI specialists will be beneficial during the transition.

THE NEED FOR ROBUST MANUFACTURING PROCESSES

After optimising the formulation and device components, it is necessary to develop robust manufacturing processes for low-GWP pMDIs. For this, understanding the properties of the propellants and their impact on the API, is vital. The physical properties of both greener propellants are similar to existing ones, but formulation development work will need to be undertaken. Of additional concern is that

both have flammable properties that must be considered.[11] HFA-152a is classified as an extremely flammable gas, whereas HFO-1234ze has a narrow flammability range. The flammability of the propellants may necessitate a large investment to make production sites compliant with safety regulations, such as Dangerous Substances and Explosive Atmospheres Regulations (DSEAR).[12]

In addition to the cost of converting manufacturing equipment, some companies may find it hard to meet transition timelines as current available manufacturing capacity is quickly taken up. At the same time, securing timely manufacturing capacity for both clinical trials and commercial supply is crucial to success.

Contract development and manufacturing organisations dedicated to extending their low-GWP manufacturing capacity offer a flexible solution. This investment can help alleviate capital expenditure and engineering project management concerns for developers, securing the supply chain and avoiding a shortage of safe, affordable pMDI medications for patients.

PROGRESS IN THE GREEN TRANSITION

With the opportunities created by new greener propellants and growing demand for change, the race to stake claims to markets and products is already underway. AstraZeneca recently announced completion of its clinical programme to support the transition of Breztri Aerosphere (budesonide/glycopyrrolate/formoterol fumarate) – a triple-combination therapy for COPD – to a next-generation propellant. Clinical programmes for the transition of AstraZeneca's wider pMDI portfolio to the new propellant have also started.[13]

The rapid adoption of sustainable low-GWP propellants will place increasing pressure on global supply chains and capabilities, including product development and testing, clinical batch production, scale-up capability and new production equipment.[14] As such, it is expected that there will be a major gap between demand and the available manufacturing capacity for low-GWP pMDIs in the short to medium term.

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GETTING AHEAD OF THE CURVE

Significant progress has been made in the transition to greener propellants, with companies such as AstraZeneca making huge strides. Over the next few years, pMDI developers will need to simultaneously consider clinical outcomes for patients, cost effectiveness for the payer and environmental impact, and understand how they can optimise all aspects for stakeholders.

From selecting a low-GWP candidate propellant to securing manufacturing capacity, collaborating with experts who can use up-to-date industry and technical knowledge can provide the means to successfully transition. By working together, a greener future can be secured that simultaneously increases the chances of achieving commercial success with a pMDI product.

ABOUT THE COMPANY

Bespak is a specialist inhalation contract development and manufacturing organisation solely focused on inhaled and nasal drug delivery. Offering a fully integrated seamless service for developing and manufacturing drug products, devices and components for the global pharmaceutical industry, the company specialises in pMDIs, dry powder inhalers, and pulmonary and nasal soft mist inhalers. Bespak has established capacity and ongoing expansions to enable the manufacture of pMDIs with low-GWP propellants.

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ABOUT THE AUTHORS

Ross Errington, Head of Drug Product Development, is a chemist by training. He has over 30 years' experience in pharmaceutical product development and manufacture, specialising in inhaled delivery systems. He has deep experience of pMDI product development and commercialisation, having supported numerous customers to successfully design, develop, register and commercialise products across global markets. Mr Errington is also an International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) board member.

Simon Gardner, Business Development Director, is a chemical engineer by training. He has over 25 years of experience in the global pMDI industry, including process engineering, plant management and business management roles in the medical propellants sector. He is a subject matter expert in propellant market dynamics and environmental regulation, and now focuses on supporting Bespak's customers to transition to sustainable propellants. Mr Gardner is also an IPAC board member.

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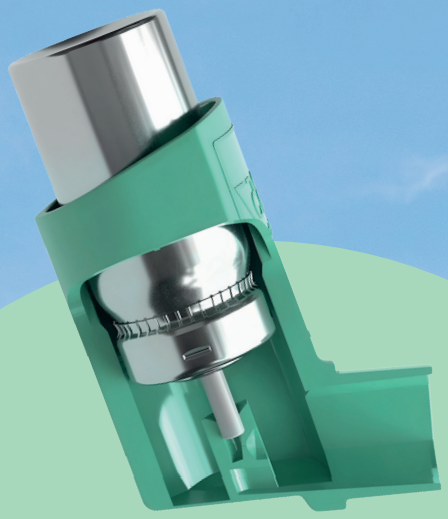

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