Exploring new pMDI propellants for a greener future

Considerations for developers and manufacturers

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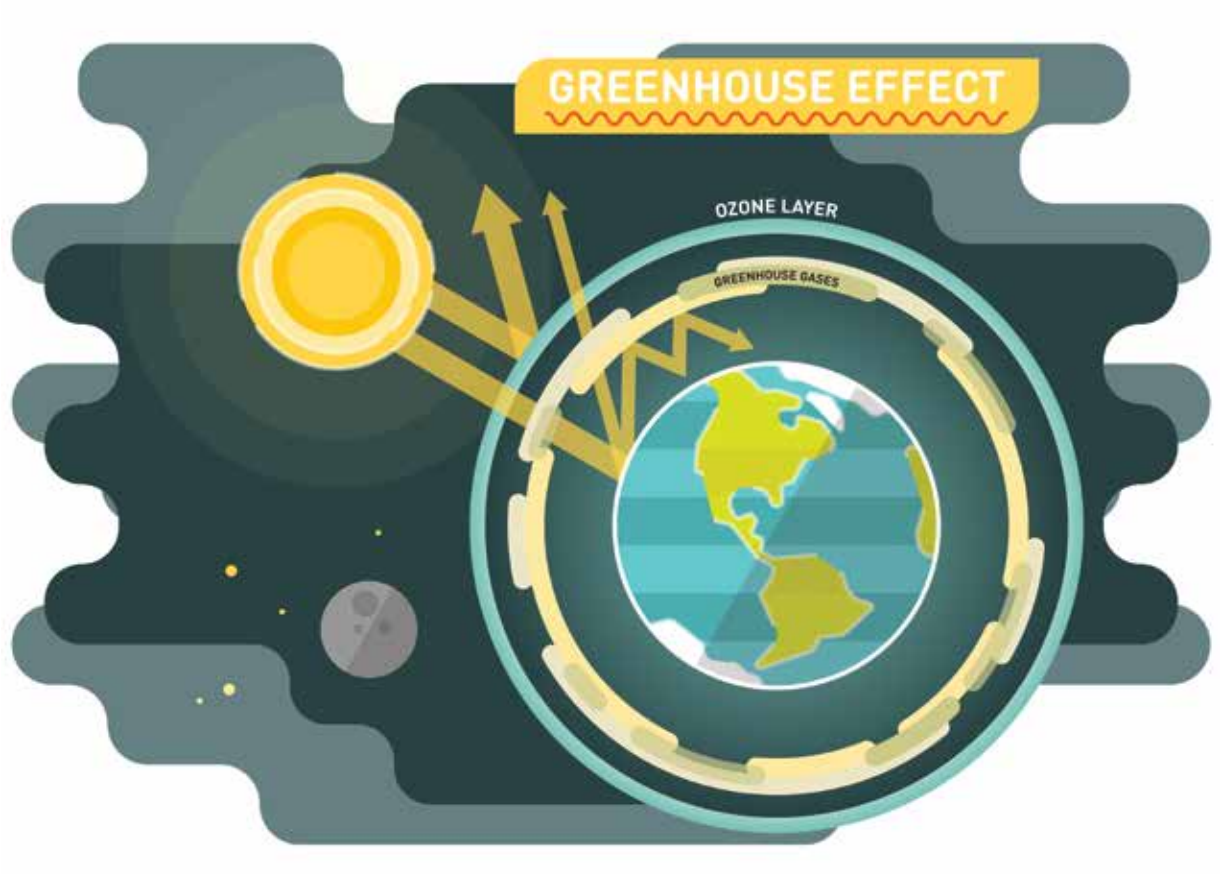

Propellants such as chlorofluorocarbons (CFCs) and hydrofluoroalkanes (HFAs) or F-gases have been used as propellants in inhalation products for many years. However, both have been shown to have an impact on global warming due to their high Global Warming Potential (GWP) and long atmospheric life (AL). The Kigali Amendment to the Montreal Protocol, agreed upon by the United Nations (UN) countries in 2016, aims to phase-down global HFA consumption by 80-85% by 2047 [1].

While the volumes of these gases used by the inhalation and respiratory healthcare industry are relatively small, it is likely we will see supply shortages, as other industries completely phase out their use. With this in mind, pharmaceutical companies will need access to tried-and-tested alternative propellants to ensure there is no disruption to medication supply.

This article discusses ways the inhalation industry can prepare for and be ready to adopt new propellants in order to guarantee the continued, reliable manufacture and supply of vital medicines for patients.

The continuing need for pMDIs

Pressurized metered dose inhalers (pMDIs) have become one of the major inhalation dosage forms for respiratory disease treatment since the first epinephrine and isoproterenol inhalers (Medihaler Epi and Medihaler Iso) were launched in 1956.

Using the UK as an example, in 2017, approximately 50 million inhalers were dispensed, of which 70% (35 million) were pMDIs and 30% (15 million) were dry powder inhalers (DPIs) [2]. From a patient compliance perspective, it is critical to sustain the supply

of pMDIs since, due to compromised lung function and breathing capacity, not all patients are able to use other inhalation products, such as DPIs. In fact, the need for pMDIs is expected to grow by 6.5% annually between 2017 and 2023 [2].

Current pMDIs use HFAs, namely 1,1,1,2-tetrafluoroethane (HFA-134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA-227ea), as propellants to aerosolize and deliver medicines. The amount of HFAs used in pMDIs is only a very small portion (1 megatons or 0.2%) of the annual CO_2 emission, according to a survey conducted in the UK in 2017 [3].

However, as other industries phase out the use of HFAs, supplies could become limited and result in situations where inhalation products formulated with these propellants are no longer available to patients. Therefore, the pharmaceutical industry should be actively investigating alternative propellants to ensure that equivalent pMDIs with new propellants are available.

Potential alternative propellants

Multiple factors need to be considered when selecting alternative propellants. These include safety and compatibility between the new propellants and container closure systems as well as the medicines to be formulated. It is also important to evaluate optimal vapor pressure for respiratory delivery and optimal molecular weights to reduce diffusion through solids (leakage), as well as GWP and toxicity, which should both be low. It is, of course, vital that any propellant be safe for human ingestion and have no detrimental impact/interaction with the active pharmaceutical ingredients (APIs).

There are at least two potential alternatives, 1,1-difluoroethane (HFA-152a) and 1,3,3,3-tetrafluoropropene (HFO-1234ze(E)) currently being developed by Koura [4] and Honeywell [5]. Both products are undergoing safety evaluation. Both HFA-152a (GWP: 124, AL: 1.5 years) [6, 7] and HFO-1234ze(E) (GWP: 6, AL: 18 days) [6, 8] have a lower GWP and shorter AL compared to the existing propellants HFA-134a (GWP: 1430, AL: 14.6 years) [6, 9] and HFA-227ea (GWP: 3220, AL: 33 years) [1, 6].

In addition to safety and impact on the environment, the physical and chemical properties of the propellants are important when formulating medicines into pMDIs. Fortunately, both HFA-152a and HFO-1234ze(E) have similar properties to HFA-134a and HFA-227 in terms of vapor pressure, density and compatibility with surfactants and solvents such as ethanol, which can limit these concerns in terms of formulation development.

Compared to inert HFO-1234ze(E), HFA-152a is more flammable, which means more attention should be given to engineering controls during process development, scale-up and commercial manufacturing of pMDIs.

Technical challenges

While exploring and anticipating the potential industry changes around the application of existing propellants and the introduction of new alternatives is complex, companies need to actively prepare so they can tackle these hurdles head on.

Among the technical challenges in applying new propellants, the key factors to consider are:

- Compatibility between the propellants and container closure systems
- Compatibility between the propellants and active pharmaceutical ingredients
- Developing a process and scale-up manufacturing in a safe way

Compatibility between the new propellants and container closure systems is ensured by maintaining the seal integrity and valve delivery performance throughout product shelf life. Acceptable levels of leachables and extractables are also key.

Propellant vapor pressure and molecular weight are two key factors determining the propellant leak rate, which can be evaluated by exposing the filled canisters to extreme temperatures and pressures and testing them at different time points. Calculations for propellant leakage can then be generated to understand and predict the leak rate as well as to establish the root cause of any deviation from the acceptance criteria.

An example of a best practice approach for a successful evaluation would be:

- Understanding the essential requirements for propellants to be successfully used in inhalers and key aspects of product performance to be achieved [10].
- Risk assessment/understanding of the product performance that will be affected by a propellant change.
- Risk assessment of the wider impacts on manufacturing, assembling and testing.
- Evaluating the impact of the new propellant by conducting product performance tests and comparing results against a control/acceptance criterion.
- First principle assessment (e.g., building a model) to identify the root cause of the product performance tests and identify and predict any potential improvements to current design.

Compatibility between propellants and active pharmaceutical ingredients is determined by the physical and chemical properties of the new propellants and all formulation components. Using suspension pMDI products as an example, compatibility of micronized APIs, selection of proper surfactants and necessary co-solvents must be considered along with container closure selection during initial formulation screening.

Process development, scale-up and commercial manufacturing need to bring safety, process design and risk control into consideration. Commercial manufacturing facilities must follow specific guidance such as the European Aerosol Federation's Guidelines on

Basic Safety Requirements in Aerosol Manufacturing [11], The Dangerous Substances and Explosive Atmospheres Regulations 2002 [12], and Directive 99/92/EC & Directive 94/9/EC on operating aerosol manufacturing [13].

In terms of safety, occupational exposure limits (OELs), lowest-observed-adverse-effect level (LOAEL) and acute inhalation toxicity must be evaluated.

For process design, vapor/liquid pressure, temperature relationship of the new propellants, suitable equipment contact materials and pressure-containing systems e.g., vessels, pipework, relief stream, etc. must be fully assessed and design changes may be necessary.

In terms of risk control, a special approach must be taken when handling flammable propellants such as HFA-152a. This includes but is not limited to evaluation of the:

- Minimum ignition energy
- Lower and upper flammable limit (LFL/UFL)
- Lower explosive limit (LEL) and Upper explosive limit (UEL)
- Auto ignition temperature (AIT)
- Velocity of detonation (VoD) and
- Rate of pressure rise

Corresponding measures such as ATEX (ATmospheres EXplosible) certification of electrical equipment as well as special design of isolated storage/mixing, filling areas and leak detection can then be taken.

Additional considerations

To date, no specific regulatory guidance has been issued regarding the use of new propellants in pMDIs. However, from safety and efficacy standpoints, it is important to follow the United States Food and Drug Administration (FDA) Guidance on MDI and DPI Products - Quality Considerations [14] when determining a development strategy.

In addition, it is advisable to match the performance of inhalers with alternative propellants to that of existing pMDIs as much as possible. This can help ensure the safety and efficacy of new inhalers and make it easier for patients to adapt to the new products.

Preparing now for the future

There is a need to adopt more environmentally friendly pMDI propellants, not only to reduce carbon footprint, but also to mitigate supply issues that may result from the decline in the use of existing propellants. HFA-152a and HFO-1234ze(E) are two potential candidates. It is critical that drug developers and manufacturers prepare their facilities for the use of these propellants, considering factors such as container closure compatibility, flammability and challenges in process development and scale-up. Those who prepare now can help "future-proof" their operations, continuing to bring pMDIs to patients who depend on them.

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