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A GREENER FUTURE: INCREASING PRESSURE FOR PHARMA TO ADOPT ENVIRONMENTALLY FRIENDLY PROPELLANTS

THE PUSH FOR A GREENER FUTURE FOR PHARMA

In recent years there has been a global focus on adopting sustainable processes, reducing carbon footprint and ultimately creating a 'greener' world for the future. The prominence placed on discussion around environmentally friendly operations has prompted widespread reviews of current practices across all industries, including the pharmaceutical industry. For example, the inhalation and respiratory healthcare sector has historically utilised chlorofluro-carbons (CFCs) to deliver medicines using inhalation devices. In 1987 the Montreal Protocol prohibited the use of these gases and they were eventually replaced by hydrofluorocarbons (HFAs) or F-gases.

However, these F-gases have also been shown to have an impact on global warming due to their high Global Warming Potential (GWP) and long atmospheric life (AL). To resolve the issues, a Kigali Amendment to the Montreal Protocol was agreed by the United Nations (UN) countries in 2016 which aims to phase down global HFA consumption by 80–85% by 2047.[1]

As a result, the pharma industry is under increasing pressure to find a suitable replacement for these gases for pressurised metered dose inhalers (pMDIs) which utilise HFAs as propellants.

In this whitepaper, Recipharm's Lei Mao, Ph.D., Director of Inhalation Science and Product Development, Ron Roscher, Head of Engineering and HSE and Mark Knowles, Head of Product Engineering at Bespak by Recipharm discuss how the inhalation industry is adapting by exploring new propellants in order to guarantee the continued, reliable manufacture and supply of vital medicines.

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THE INHALATION LANDSCAPE AND THE IMPORTANCE OF pMDIS AS A DELIVERY ROUTE

Over the last few years more and more companies are exploring inhalation as a potential administration route for existing products as well as new ones entering the drug pipeline. Along with their inherent ability to effectively treat respiratory diseases, the ability of inhalation and nasal medications to avoid the first pass effect of the liver means that this delivery route can offer enhanced bioavailability and efficacy using lower doses, which ultimately means less side effects for patients. In addition, new regulatory approval routes such as the 505 (b)(2) legislation, which permits faster approval for recognised APIs being used in inhalation devices, has further propelled the increasing popularity of these products.

pMDIs have become one of the major inhalation dosage forms for respiratory disease treatments since the first epinephrine and isoproterenol inhalers launched (Medihaler Epi and Medihaler Iso) 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). That being said, from an administration perspective it is essential that patients can easily and effectively administer the full dose of medication. With this in mind, it is critically important to sustain supply of pMDIs, since not all patients are able to use other inhalation products such as DPIs because of their compromised lung function and breathing capability. In fact, the need for pMDIs is expected to grow by 6.5% annually between 2017–2023.[2]

PHASING OUT HFA: THE FUTURE OF PMDIS

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 deliver and aerosolise medicines. Although the amount of HFAs used in pMDIs is only a very small portion (1Mt or 0.2% of the annual CO2 emission) as reported from a survey conducted in the UK in 2017[3], there are external challenges to consider. For example, as other industries phase out the use of HFAs, limited supply could result in a situation where supply is no longer available. It is, therefore, important to ensure that equivalent pMDIs with new propellants are available.

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THE AVAILABILITY OF NEW PROPELLANTS AND THEIR POTENTIAL: KEY CONSIDERATIONS AND PRACTICALITIES

To date, there are at least two potential alternatives to the current propellants used in pMDIs that have shown promising results. Both 1,1-difluoroethane (HFA-152a) and 1,3,3,3-tetrafluoropropene (HFO-1234ze(E)) are currently being developed by Koura[4] and Honeywell[5] and are going through 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)[6,11], and therefore are more environmental friendly.

However, the selection process is not straightforward, several aspects need to be considered when selecting alternative propellants to ensure availability of safe and effective medications for patients, these include:

Safety and impact on the environment

As with all medications, safety is a key consideration. This includes the combination of the new propellant, container closure system and the medicines being delivered, as well as individually. This dual focus has always been a challenge when formulating combination products, however the addition of relatively unknown propellants further complicates the process.

It is also important to consider the evaluation of optimal vapour pressure for respiratory delivery, optimal molecular weights to reduce diffusion through solids (leakage), low GWP and low toxicity. It is of course vital that any propellant is safe for human ingestion and that there is no detrimental impact/interaction with drugs.

From a technical perspective, occupational exposure limits (OELs), lowest-observed-adverse-effect level (LOAEL) and acute inhalation toxicity need to be evaluated. And, during process design, vapour/liquid pressure, the lower and upper explosure limit (LEL and UEL), and temperature relationship of the new propellants, suitable equipment contact materials, pressure containing systems e.g. vessels, pipework and relief stream etc. need to be fully assessed and design changes may be required if necessary. This is essential to ensure safe scale-up later down the line.

In terms of risk control, a different approach needs to be taken when handling flammable propellants such as HFA-152a. This includes but is not limited to evaluation of the minimum ignition energy, the lower and upper flammable limit (LFL/UFL)/lower explosive limit, auto ignition temperature (AIT), velocity of detonation (VoD), and rate of pressure rise. Corresponding measures such as ATEX certification of electrical equipment, special design of isolated storage/mixing, filling areas and leak detection can then be taken.

Compatibility

As mentioned, compatibility between the propellants and container closure systems such as cans and valves as well as compatibility between the propellants and actives are key factors to be considered.

Functionally, compatibility between the actives, formulation and new propellants needs to be considered. This is determined by the physical and chemical properties of the new propellants and all formulation components. For example, suspension MDI products rely on the compatibility of micronised actives, selection of proper surfactants and necessary co-solvents, along with container closure selection during initial formulation screening. Special considerations such as use of a gasket with less permeability or secondary packaging may be necessary if the active particles are sensitive to moisture ingression, i.e. tend to form agglomeration.

Compatibility between the new propellants and container closure systems can be ensured by maintaining the seal integrity and valve delivery performance through the product shelf life. Acceptable levels of leachables and extractables are also key, making comprehensive testing essential.

Propellant vapour pressure and molecular weight also need to be considered when determining the propellant leak rate. This can be evaluated by exposing the filled canisters to extreme temperatures and pressures and then testing them at different points in time. However, ahead of this process it is possible to use calculations to accurately predict propellant leakage rate, as well as establish the root cause of any deviation from the acceptance criteria.

Below is the best practice approach to evaluation adopted at Recipharm

- Understand the essential requirements for propellants to be successfully used in inhalers and key aspects of product performance to be achieved [10]
- Carry out a comprehensive risk assessment and understanding of the product performance that will be affected by a propellant change
- Ensure risk assessment of the wider impacts on manufacturing, assembling and testing in conducted
- Evaluate the impact of the new propellant by running product performance tests and comparing results against a control/acceptance criterion
- Carry out 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.

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 work to prepare so that they can tackle these hurdles head on.

The potential for these changes to become regulation, or at the very least a necessary adaption, is growing increasingly likely and it is essential that companies explore the application of alternative propellants actively. Preparation is key and by starting to work with these potential propellants and documenting preliminary findings now, supply chain partners can map out the journey required to secure the supply of essential medicines while ensuring environmental compliance.

Physical and chemical properties

In addition to the safety, compatibility and impact to the environment, the physical and chemical properties of the propellants are important when formulating medicines into MDIs. Since both the lead propellant candidates to replace HFA-134a and HFA-227 have similar properties in terms of the vapour pressure, density, and compatibility with surfactants and solvents such as ethanol, it suggests that radical changes to formulation platforms may not be required. This should now be established through the appropriate studies.

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

Process development, scaling up and commercial manufacturing

Process development, scaling up and commercial manufacturing need to bring safety, process design and risk control into consideration. Commercial manufacturing facilities must follow specific guidance such as European Aerosols Federation's Guidelines on Basic Safety Requirements in Aerosol Manufacturing, The Dangerous Substances and Explosive Atmospheres Regulations 2002, and Directive 99/92/EC & Directive 94/9/EC on operating aerosol manufacturing.

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THE RECIPHARM APPROACH

Recipharm is working with suppliers and pharmaceutical companies to prepare for the upcoming propellant changes likely to impact in the pharma industry. The impact on the individual parts of the container closure systems that Bespak by Recipharm supplies is also being closely investigated to avoid surprises and get a head start in any reformulation project that are required. Recipharm has already analysed, using predictive modelling, and tested, at extreme temperatures and pressures over time, HFO-1234ze(E) and HFA-152a in order to provide an alternative commercial pDMI device that offers optimal low GWP.

Recipharm also regularly performs formulation screening to investigate the interactions between the APIs, the excipients and container closure system to provide further insight into the magnitude of change in behaviour as a result of replacing the current propellant. Supportive studies are also offered to investigate new extractables and leachables (E&L) and adapt analytical methods to the modified formulations to ensure customer products continue to meet expectations.

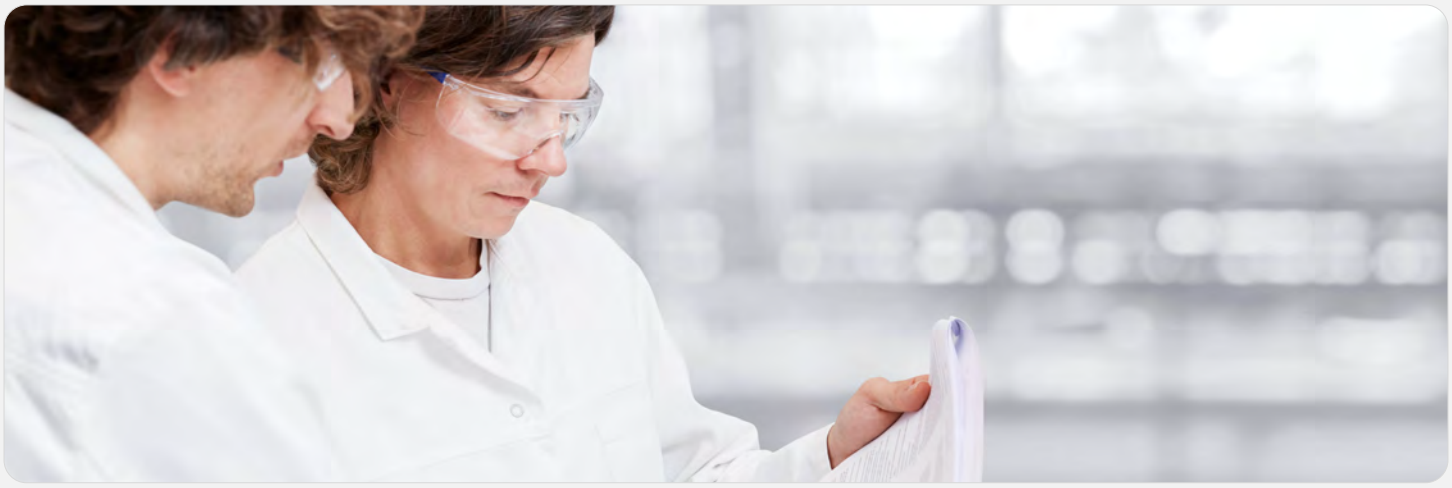
By applying enhanced safety measures, process scale-up can be offered and material for the necessary clinical trials can be supplied to enable the marketing authorisation holder to ultimately submit the updated dossier to the relevant authorities. The change of propellant in a current pMDI product is a large scope of work which will take several years to perform, including generating the necessary stability data and clinical results, hence it is important to consider this challenge in immediate strategic plans for any pMDI company.

DEVELOPING NEW PROPELLANTS: A REGULATORY VIEW

No specific regulatory guidance has been issued regarding the use of new propellants in MDIs. However, from safety and efficacy standpoints, it is important to follow the latest FDA guidance on MDI and DPI Products – Quality Considerations[11] when determining a development strategy. It is advisable to match the performance to that of existing MDI products as much as possible. This not only ensures the safety and efficacy of the products but also will make it easier for patients to adapt to the new product versions.

SUMMARY

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



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AUTHOR BIOGRAPHIES

Lei Mao, Director of Inhalation Science and Product Development at Recipharm

Lei Mao is the Director of Inhalation Science and Product Development at Recipharm Laboratories. With over twenty years of experience, Lei has a wealth of knowledge in formulation and inhalation product development within the pharmaceutical industry. He started a career working as a senior scientist, where he developed particulate formulations for inhalation applications and has since held managerial positions for big pharma companies. He also holds a Ph.D. in Pharmaceutical Sciences and a degree in pharmacy.

Mark Knowles, Head of Product Engineering – Bespak at Recipharm

Mark Knowles works for Bespak as the Head of Product Engineering, furthering technology and product offerings to support Bespak's respiratory, drug delivery and in vitro diagnostic device portfolio. Mr Knowles has over 30 years' experience in R&D, the last 20 years in medical device development. Previous to working at Bespak he worked at Cambridge Consultants (medtech diagnostics) and Elekta Ltd (invasive radiotherapy). Mr Knowles has a great deal of experience translating customer needs into technology solutions, designed for high-volume manufacturing in highly regulated environments. He has an MBA in technology management.

Ron Roscher, Head of Engineering & HSE at Recipharm

Ron Roscher is Head of Engineering & HSE at Recipharm. He has over thirty years of operations, manufacturing and engineering experience across the chemicals, specialty chemicals, explosives, pharmaceutical propellants and inhalation manufacturing sectors. He has extensive experience in plant design and commissioning, engineering, production and operations management and has significant experience and knowledge in the areas of Process Safety and Occupational Safety management. He holds a Bsc Mechanical Engineering.

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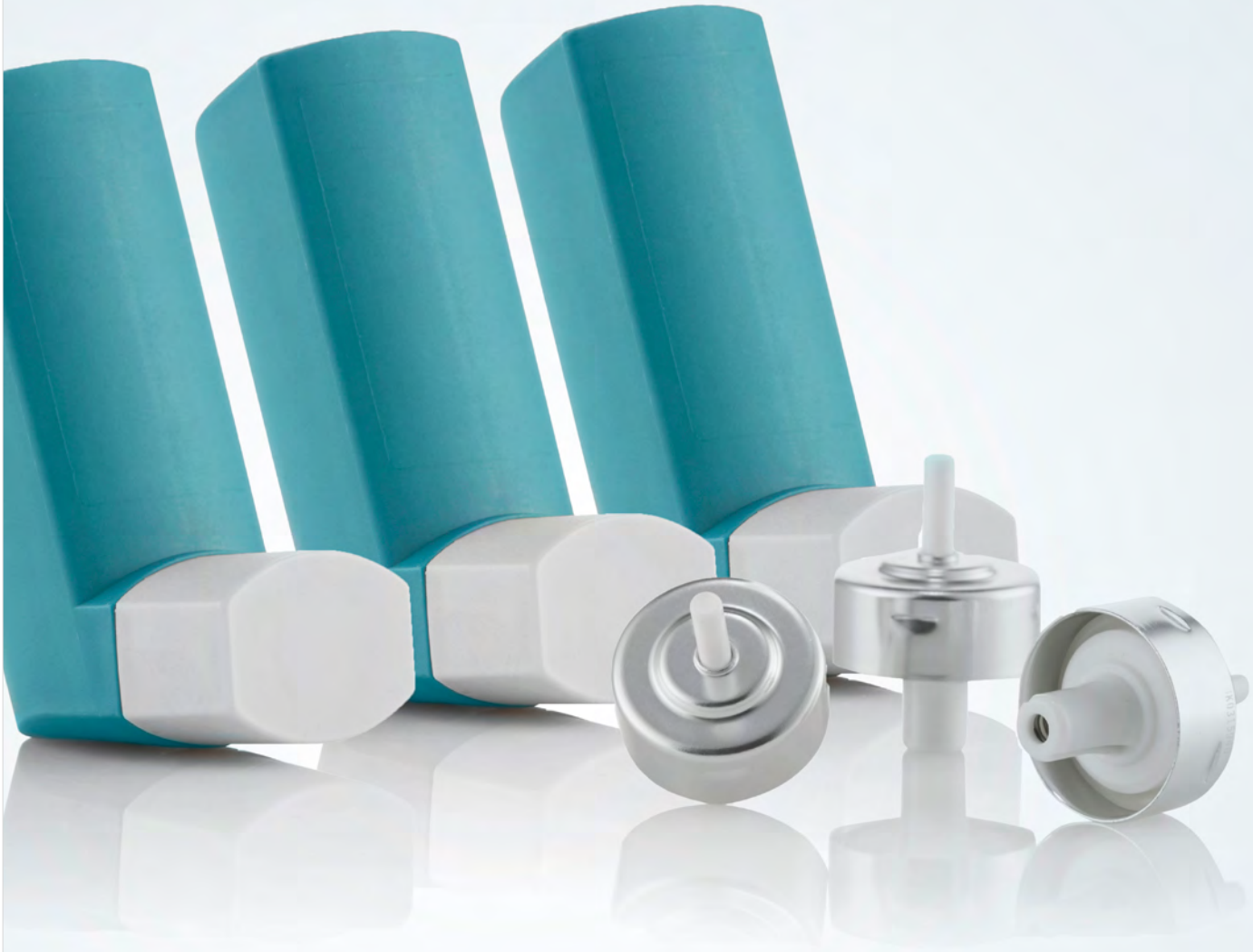

ABOUT RECIPHARM INHALATION SOLUTIONS™ AND BESPAK BY RECIPHARM

Bespak by Recipharm delivers market leading design, development and manufacture of drug delivery devices to the global pharmaceutical market. This includes inhaler, nasal technologies and autoinjectors as well as development and manufacturing services.

Recipharm is at the leading edge of drug delivery device innovation. Driven by customer and patient demand, our innovations have the potential to create new treatments and opportunities across the globe as well as accelerating routes to market.

Bespak by Recipharm's inhaler and nasal technologies expertise forms part of Recipharm Inhalation Solutions™, an end-to-end solution spanning early phase development to commercial manufacture of both inhalation drug product and device.

For more information about Bespak by Recipharm visit: *bespak.com*

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