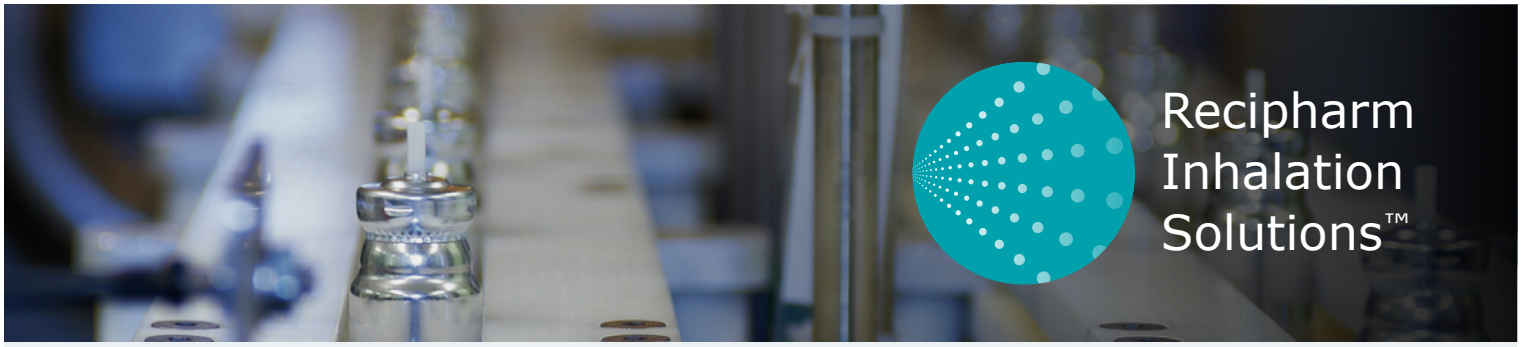


# TACKLING A CHANGING CLIMATE; METERED DOSE INHALERS

## SUMMARY

*Hydrofluoroalkane (HFAs), or F-gases, have been used as propellants in pressurised metered dose inhalers (pMDIs) for many years. They replaced Chlorofluorocarbons (CFCs), which were ozone depleters.*

*However, HFAs have been shown to have a significant negative effect on the global climate, due to their high Global Warming Potential (GWP) and long atmospheric life (AL). With this in mind, the Kigali Amendment to the Montreal Protocol was agreed by the United Nations (UN) countries in 2016. This aims to phase down global HFA consumption by 80–85% by 2047, with the aim of stopping their release into the atmosphere and slowing global warming[1].*

*As other industries phase the gases out completely, there will be a supply shortage of HFAs, requiring pharma companies to seek alternative propellants for pMDIs to ensure there is no disruption to the medication supply.*

*In this white paper, we will explore alternative technologies to HFA propellants, and how the devices and formulations can be optimised to ensure the best possible performance. We will also explore the benefits of working with experts in sustainable device and product development to ensure that your inhalation product complies with sustainability legislation while offering optimum performance for patients.*

## CONTENTS





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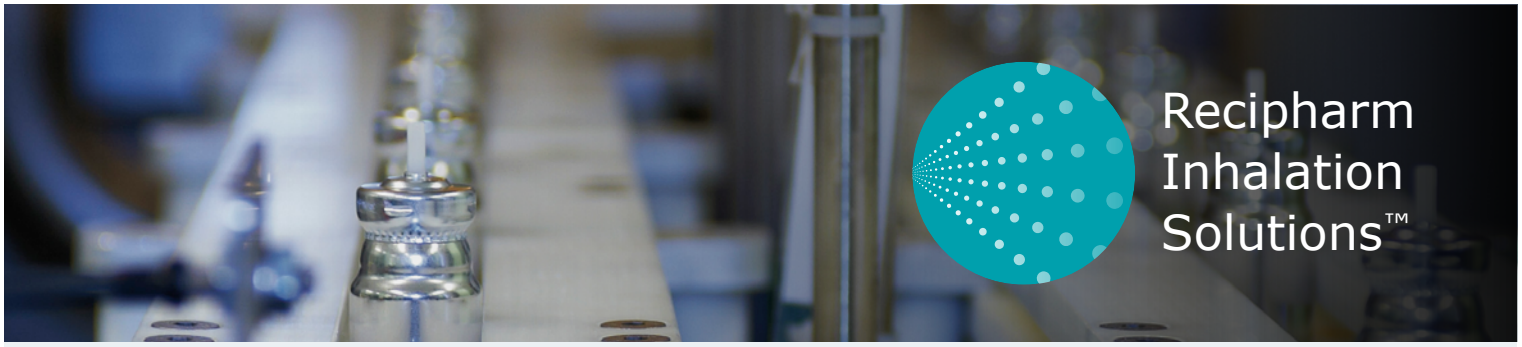


# A BRIEF HISTORY OF THE PROPELLANTS USED IN pMDIs

## THE RISE AND FALL OF CFCs

CFCs were first developed in 1928 as gases for use as refrigerants in refrigerators. Soon after, their special characteristics, combined with their inflammability and non-toxicity to humans, led to them being rolled-out across a range of other applications, including:

- air conditioning systems
- cleaning agents for precision components
- foaming agents for insulating materials
- propellants in aerosol sprays
- propellants in pharmaceutical inhalers and other drug delivery devices

The manufacturing and consumption of CFCs in the pharmaceutical space and elsewhere escalated rapidly from the 1960s onwards. However, in 1974, the potential for the ozone layer to be damaged by CFCs was identified. In 1985, the observation of an ozone hole above the Antarctic provided proof that the ozone layer was being depleted. The ozone layer plays a key role in minimising carcinogenic ultraviolet (UV) radiation from the sun reaching the earth's surface – any thinning therefore would have serious consequences both for the environment and human health.

Recognising the gravity of the situation, world leaders signed the *Montreal Protocol on Substances that Deplete the Ozone Layer* in 1987, as a framework for international cooperation regarding CFC control, leading to the decline in use of CFCs.

Consequently, CFCs were phased out in most economic areas in developed countries by 1996. Pharmaceuticals, however, were exempt from the initial ban, as CFCs still had to be used in many inhalers, due to issues developing alternative propellants for some devices that offered the same performance. It wasn't until 2016 that the last CFC-containing pMDI was produced[2].

## THE ERA OF HFAs

HFAs were introduced from 1987 as an alternative propellant in inhalers. Two HFAs in particular – 1,1,1,2-tetrafluoroethane (HFA-134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA-227ea) are commonly used as propellants to deliver and aerosolise medicines from pMDIs. These offer many of the same benefits as CFCs for many inhalation device applications – high propellant performance and non-toxicity in humans – but also have the advantage of not interacting with the ozone layer. As a result, HFA-containing drug devices have become widespread across the globe.

However, they do have a significant drawback. They have a relatively high GWP[3], meaning that they trap relatively high levels of solar heat in the atmosphere – in doing so, they contribute significantly to climate change.



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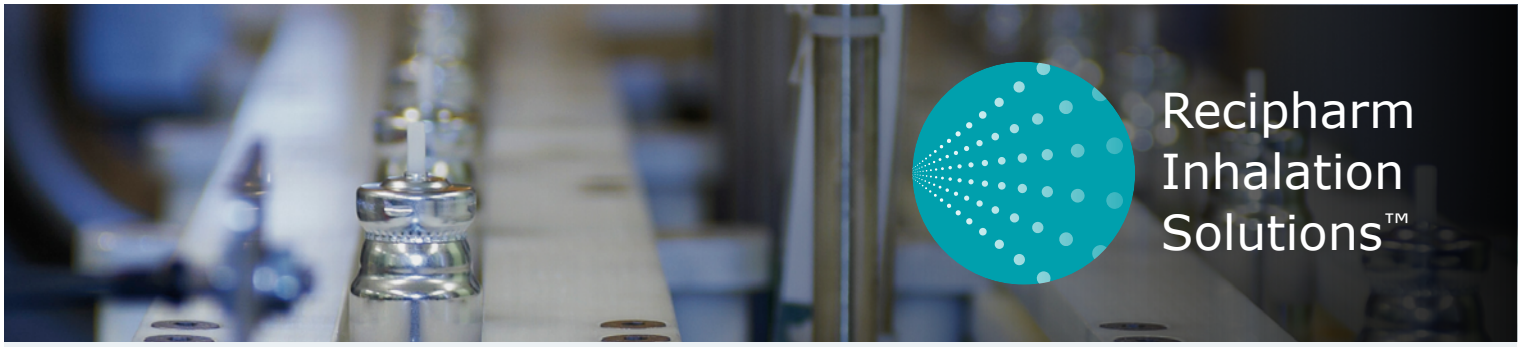



## UNDERSTANDING GWP

Global Warming Potential is the heat absorbed by any greenhouse gas in the atmosphere, as a multiple of the heat that would be absorbed by the same mass of carbon dioxide ($CO_2$).

The GWP of $CO_2$ is 1. For other gases, it depends on the gas and the time frame. The higher the figure, the higher the GWP.

1,1,1,2-Tetrafluoroethane (HFC-134a), a HFA propellant commonly used in pMDIs has a GWP of 1430, meaning it absorbs 1430 times more heat as the same mass of $CO_2$.

As such, global efforts are now being made to phase out HFAs across the wider economy and within the pharmaceutical space – cemented by the Kigali Amendment to the Montreal Protocol agreed in 2016.

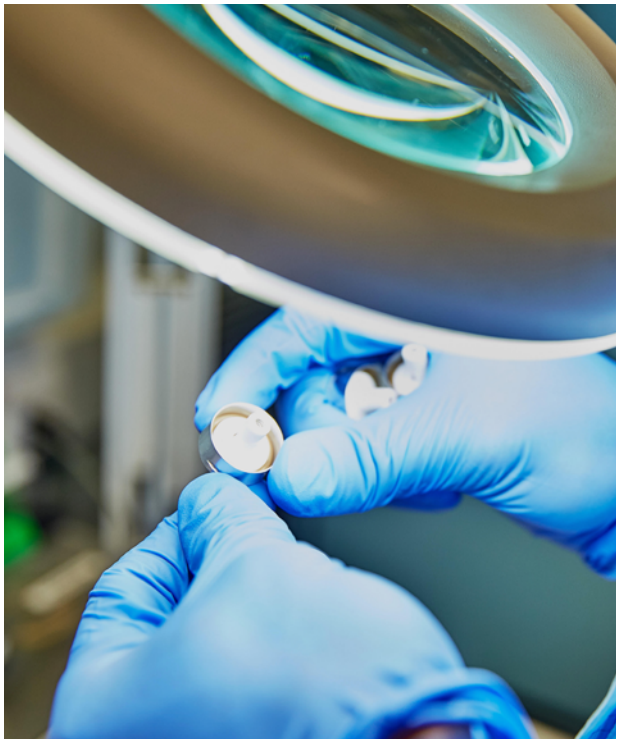
## THE EFFECT ON THE INHALATION DRUG INDUSTRY

The UN decisions on the use of HFAs will have as significant an impact as the ban on CFCs on the inhalation industry and the respiratory healthcare sector. This is due to the widespread use of HFAs as propellants within pMDIs.

In 2017, some 50 million inhalers were dispensed in the UK alone. Of these, 70% were pMDIs. With this in mind, failure to find more sustainable alternative propellants now could mean that patients lose access to vital and effective inhalation drug products in the future.

At the same time, it's important to maintain a reliable supply of older propellants in the short term to ensure that those inhalation devices that require the propellant performance of older HFAs can continue to be produced while alternative devices and gases are developed.

How can pharmaceutical companies achieve both goals?





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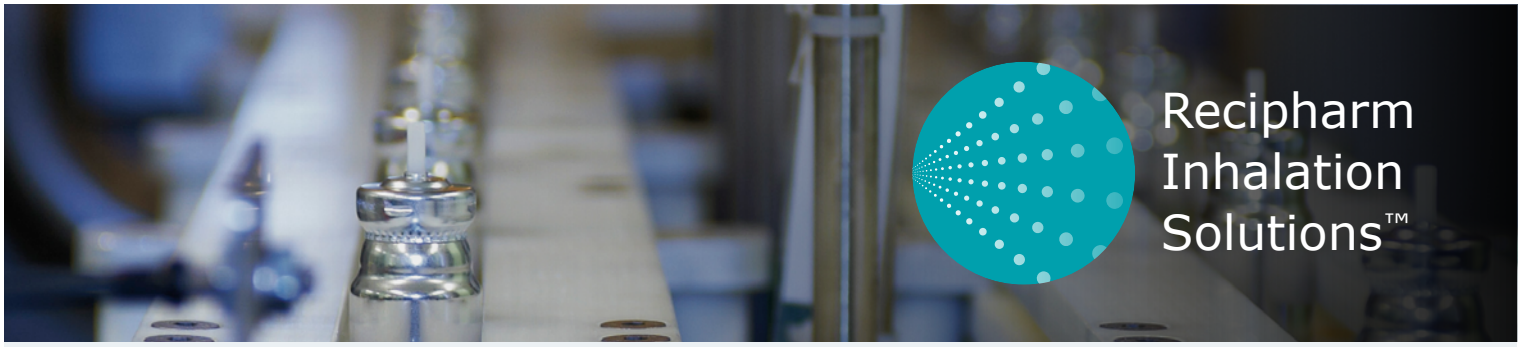


# AN EVOLUTION OF SUSTAINABILITY IN THE PHARMA INDUSTRY

Sustainability is quickly rising up the agenda for the entire pharmaceutical sector, triggered by concerns around global warming due to the consumption of greenhouse gases, like HFAs.

There is growing concern among the consumers and among businesses about reducing their own environmental impact. Increasingly, consumers and businesses are taking measures to reduce their environmental footprint. More and more, businesses want to engage and partner with suppliers that are equally "green".

In addition, there are other pressures on pharmaceutical companies that are making it increasingly urgent to enhance the sustainability of their operations:

- **Compliance with environmental legislation** – there are increasingly stringent environmental safeguards that pharmaceutical companies – and businesses in other sectors – must meet when manufacturing products. Failure to comply could lead to legal action with severe financial penalties that could impact on the company's long-term success
- **Supply instability for traditional materials** – the supply of traditional polluting raw materials, such as HFAs, is forecast to become increasingly unstable as UN protocols banning them begin to take effect. This is because, as more companies abandon them, more suppliers will stop manufacturing them. As a result, they will become harder to source, forcing companies to switch to new sustainable alternatives



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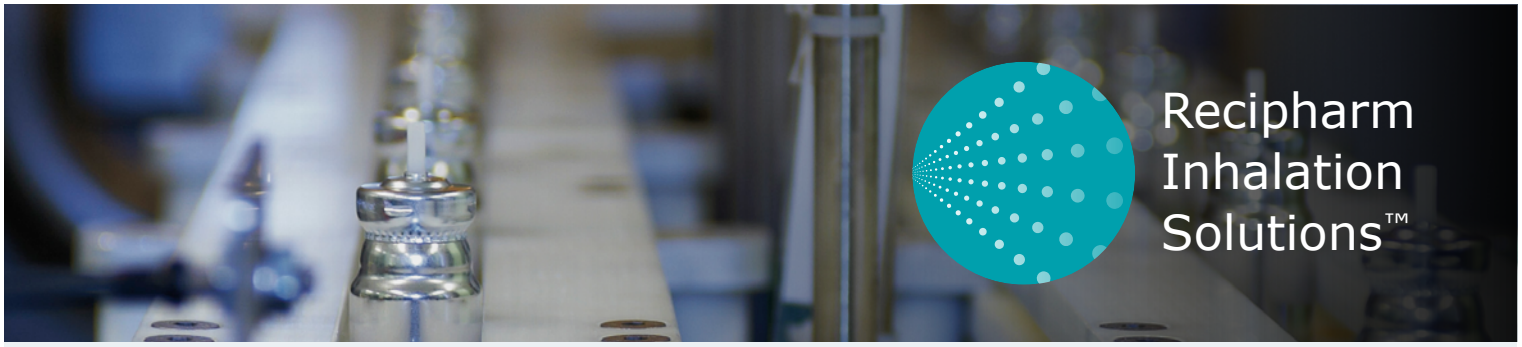



# THE INTRODUCTION OF NEW GREENER PROPELLANTS: SELECTION AND CONSIDERATIONS FOR ADOPTION

With all of this in mind, it is clear that the sooner pharmaceutical companies identify effective and sustainable alternative propellants to HFAs, the more stable their supply chain, and the more secure their business will be.

Time is of the essence when it comes to bringing to market effective pMDIs harnessing alternative propellants that are capable of delivering the same performance as those incorporating HFAs. The sooner the industry does so, the sooner we can ensure supply security for the patients that need such inhalation devices the most.

The pharmaceutical industry has been exploring alternatives to standard propellants for use in inhalation drug delivery devices and other medical devices. The two potential "greener" candidates currently being considered are:

- 1,1-Difluoroethane (HFA-152a)
- 1,3,3,3-Tetrafluoropropene (HFO-1234ze(E))

## ADVANTAGES OF INNOVATIVE PROPELLANTS

These next-generation propellants have a number of key benefits for inhalation drug developers.

They are more environmentally friendly than traditional HFAs, exhibiting a lower GWP. HFA-152a, for example has a GWP of 124 compared with the 1430 for traditional inhaler propellant 1,1,1,2-Tetrafluoroethane (HFC-134a). HFO-1234ze(E), meanwhile has a GWP of less than 1, lower even than $CO_2$.

These GWP figures means that, when in the atmosphere, both HFA-152a and HFO-1234ze(E) do not trap as much heat from the sun, resulting in a less significant global heating effect.

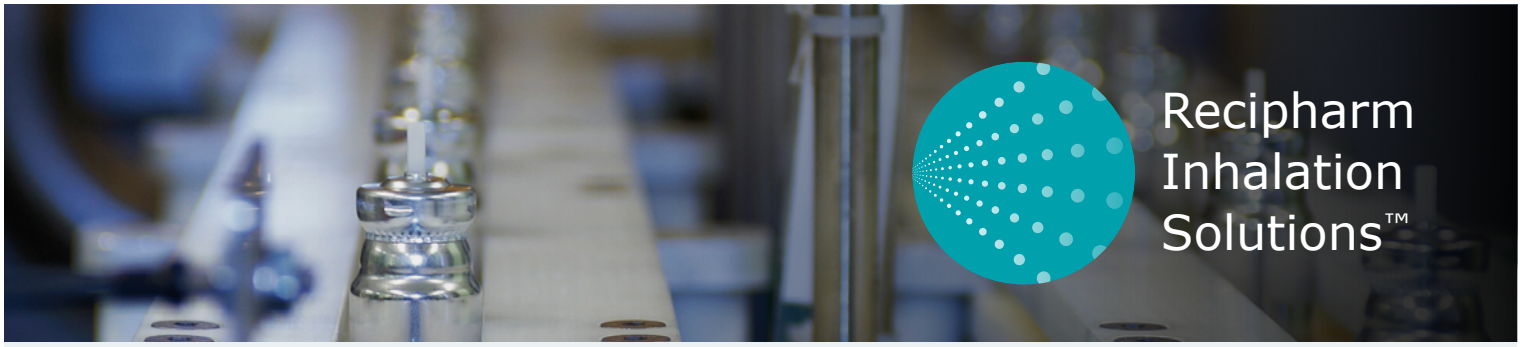
In addition, they have a far shorter atmospheric life (AL) compared with existing propellants. HFA-152a, for example, has an AL of 1.4 years, compared with 14 years for currently used inhaler propellants.

This means that these new-generation propellants remain in the atmosphere for less time than traditional alternatives, further minimising their warming effect and environmental impact.

## THE DRAWBACKS OF NEW CANDIDATES

While they offer important and exciting environmental benefits, the new generation of propellants do have disadvantages that need to be taken into account before they are adopted by the pharmaceutical industry. These include:

- **Untried and untested:** the use of these new propellants is still in its infancy not just in the pharma space, but elsewhere in the economy, and it is too early to say whether they are straightforward and effective replacements for traditional propellants
- **Different properties and performance profiles:** as with other gases, both HFA-152a and HFO-1234ze(E) have their own unique properties that mean that work will have to be done adjusting pMDI device designs in order to create an effective finished product with an adequate shelf life




# CONSIDERATIONS ADOPTING NEW GREENER PROPELLANTS FOR THE pMDI INDUSTRY

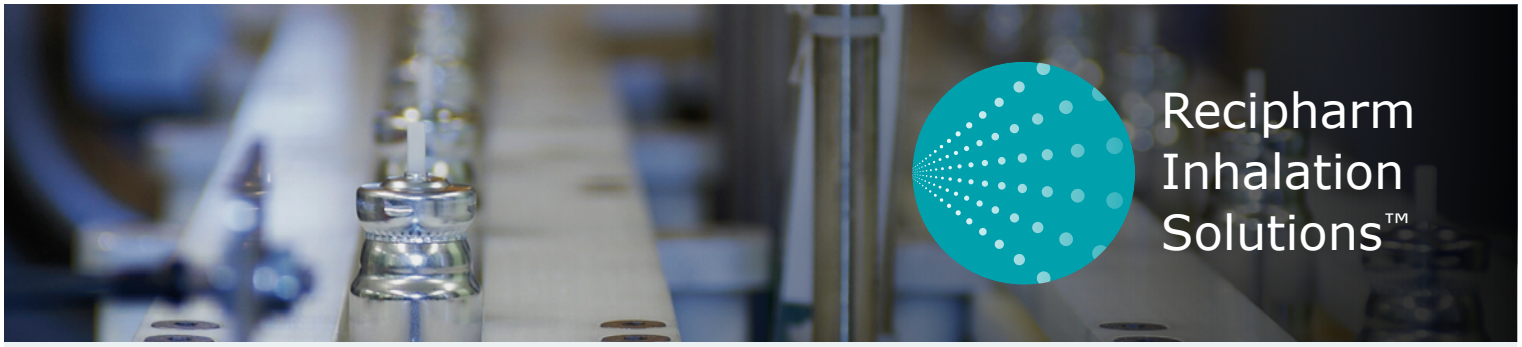
As discussed, every propellant has its own unique chemical properties that impact on a number of areas, from performance to stability to safety.

This means that transitioning to a new "greener" propellant is not as straightforward as simply switching out the old gas for the new.

## FACTORS TO BE ADDRESSED

When considering any new propellant for use in a pMDI, a number of factors have to be explored and addressed. These include:

- **Toxicology** – above all, it is important to determine whether the propellant is safe for human use. The gas will be inhaled by the patient when they administer the drug, so it is vital that it doesn't elicit any negative side effects that can impact on health or affect the effectiveness of the drug
- **Device and formulation** – any new propellant must be able to complement the device to deliver the required aerosol performance for the finished drug formulation to ensure effective delivery of the active pharmaceutical ingredient (API) to the lung. In addition, it must be compatible with the materials that make up the pMDI closure system, i.e. canister and valves. Failure to consider this could impact on the product performance, stability and its long-term shelf life
- **Manufacturing** – propellant must not interact with the materials that make up the equipment on the production line, and there must be careful consideration to the need for special handling or storage requirements
- **Commercial** – any new propellant must be widely available from a range of suppliers, and affordable in order to ensure a ready and cost-effective supply of pMDIs for patients
- **Regulatory registration** – finally, there are regulatory factors that need to be considered. Before developing pMDIs incorporating a new propellant, it is important to determine whether the propellant material has been cleared for patient use by relevant regulatory bodies. The US Food and Drug Administration (FDA) and the EU European Medicines Agency (EMA) carefully regulate the use of propellants within medical devices. Only once they have been approved, can pharma companies begin to harness them in drug and device development




# FORMULATION CONSIDERATIONS: HOW DO THE NEW PROPELLANTS IMPACT FORMULATIONS?

In addition to the above considerations, adopting new propellants has ramifications for the composition and development of the drug formulations intended for delivery via new "greener" pMDIs.

The first major transition away from CFCs to HFAs from 1996 onwards contains important key learnings with regards to inhalation formulation development that can be applied to this new transition period, which we will discuss in this section.

It is crucial to take these into account in order to ensure that we progress from existing HFAs to the new generation of low GWP propellants effectively and efficiently, with minimal disruption to the supply of pMDIs.

## FORMULATION DEVELOPMENT FACTORS TO CONSIDER

Compatibility with APIs, excipients and container closures is a crucial factor to take into account. Every propellant has unique properties that can affect how it interacts with formulations and device components.

Failure to take this into account could lead to stability issues, with the product having a sub-optimal shelf life. It could also lead to problems aerosolising the formulation, impacting on the administration of the drug. Different excipients or closure materials may need to be used, or the physical properties of the API may need to be modified to ensure effective performance.

Above all, it is crucial to consider both the device and the formulation together as a single combination product. The interaction between the formulation and the device will affect the formulation behaviours, closure integrity and ultimately delivery performance and product shelf life.

There is a particular advantage to identifying potential "green" propellants that have similar physico-chemical properties to traditional alternatives. Such similarities are likely to mean the propellant will interact with common device materials and formulation ingredients in a similar manner. They also indicate comparable performance profiles.

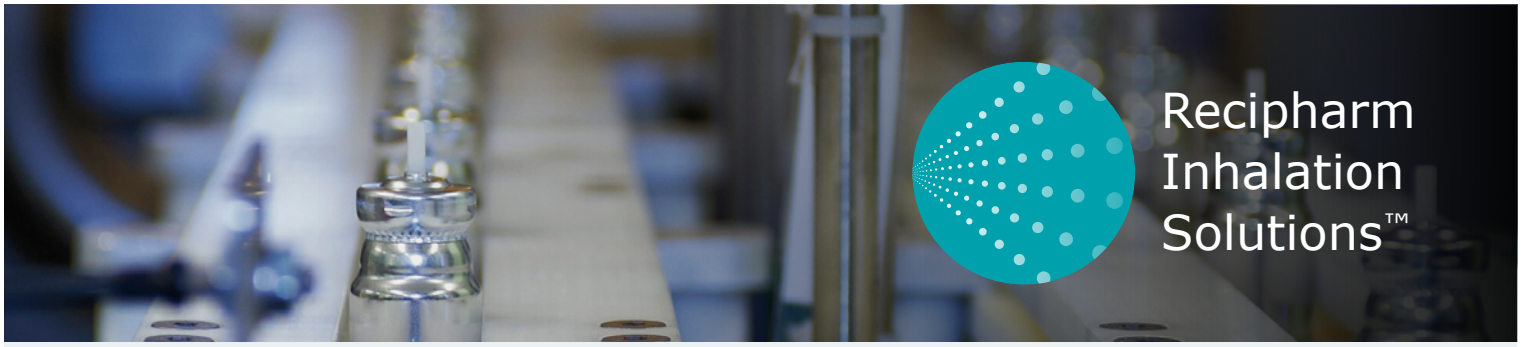
All of this would significantly reduce the amount of redevelopment work required for formulations, as well as delivery devices and manufacturing processes, streamlining the transition process for the new propellant.

## DEVELOPING EFFECTIVE FORMULATION APPROACHES

The first step to developing an effective formulation approach will be to get a thorough understanding of how new-generation propellants differ from the traditional propellants. This knowledge will serve as the basis for knowing what steps need to be taken to get more sustainable pMDIs to market quicker.

Taking a standardised/consistent approach to development, can help streamline the transition process for new-generation propellants, identifying effective methods to adapt quickly and effectively.

Harnessing the Quality by Design (QbD) approach can also help simplify and accelerate development, while also ensuring optimum quality is maintained throughout. QbD is a systematic approach to development that begins with predefined objectives and emphasises understanding and control, based on sound science and quality risk management[4].




By harnessing the concepts of QbD, it is possible to devise effective and repeatable methodologies that can allow us to develop formulations that are compatible with both the device and the new-generation propellant. In doing so, we can ensure we continue to deliver high-performance inhalation drug products for patients.

# THE IMPORTANCE OF FUTURE-PROOFING OPERATIONS

In addition to reducing the environmental footprint of pMDIs, there is another important reason to adopt more environmentally friendly propellants. That is to mitigate against any supply issues that result from the decline in the use of existing options.

As demand for traditional propellants decreases, there will be fewer suppliers offering smaller quantities of the materials. This will make traditional propellants increasingly difficult to source cost-effectively for those companies – such as inhalation drug manufacturers – that still require them.

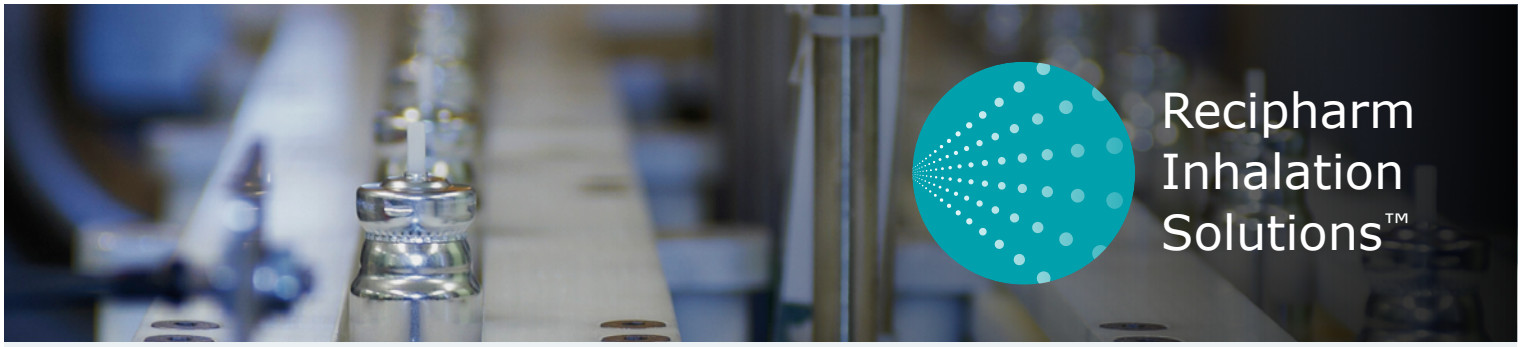
## TIME TO UPGRADE PROCESSES AND DEVICES

Given the effect of the differences in performance profiles and physico-chemical properties of new-generation propellants compared with traditional alternatives, it is crucial to start the process of adapting facilities to handle them effectively. It is also important to begin device and formulation development now to devise effective "greener" pMDI products.

Failure to take steps now could add cost further down the line as demand for new equipment and infrastructure accelerates. Putting measures in place now will future-proof operations, meaning they can continue bringing pMDIs to patients that depend on them.

By starting to work with the potential new propellants and documenting preliminary findings, supply chain partners can begin to establish the next steps to secure supply.

Working with expert device specialists can go a long way towards successfully future-proofing operations. Such a partnership can mean pharma companies can continue to deliver high-quality inhalation drug products to patients as the transition away from HFAs gathers pace.




# HOW RECIPHARM CAN HELP

Recipharm helps companies overcome the challenges they face when finding new propellants to replace HFAs and other gases with high GWP. Recipharm offers an integrated service for inhalation drug products and devices spanning early-stage development to commercial manufacture.

Our dedicated team offers pharmaceutical companies a seamless outsourcing service from early-stage development through to commercial manufacturing for inhalation products, including:

- pMDIs
- Dry powder inhalers (DPIs)
- Nasal solutions, suspensions, powders and sprays
- Soft mist inhalers
- Nebuliser solutions

Through Bespak by Recipharm, the company delivers market leading design, development and manufacture of metered dose inhalers and other inhalation drug delivery devices to the global pharmaceutical market. Bespak by Recipharm also offers support delivering nasal technologies and auto-injectors, as well as development and manufacturing services.

As a result, Recipharm is able to offer specialist support throughout the entire inhalation drug, device and combination drug product development process, streamlining the supply chain for customers and mini-mising time-to-market.

Recipharm sees customers at different stages of the pMDI lifecycle, and understands that propellant change is an important area to them. The company's unique in-depth expertise in developing the new generation of pMDI products means it can contribute to the adoption of newer and greener propellants.

## LEARN MORE

To find out more about how we can support you in making the switch to more environmentally friendly propellants in your inhalation drug delivery products, contact us today: *recipharm.com/contact*



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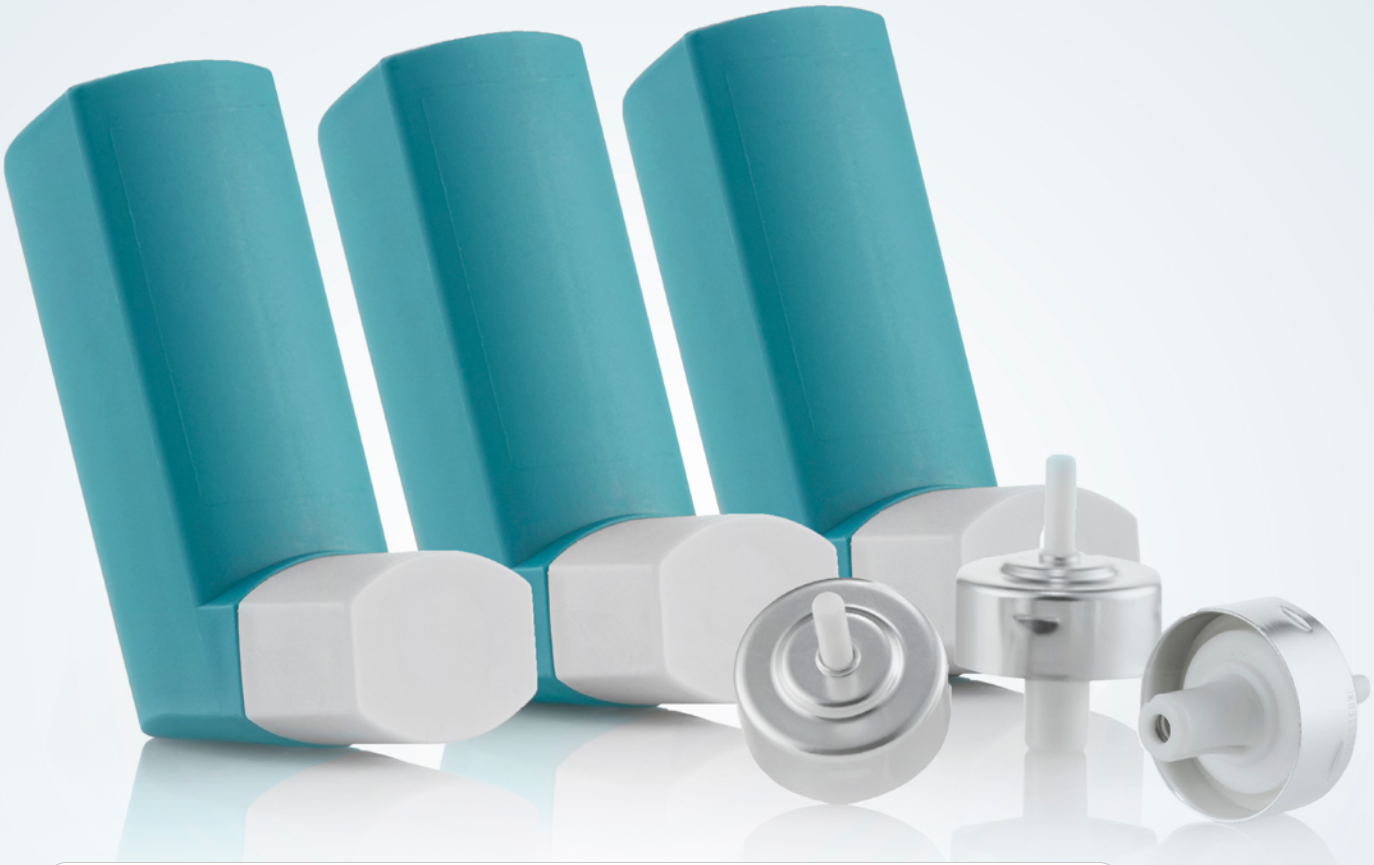

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## RECIPHARM INHALATION SOLUTIONS™

Recipharm is a leading CDMO in the inhalation space, with a long history in inhalation drug product and device development and manufacturing. Recipharm offers an integrated service for inhalation drug products and devices from early stage development through to commercial manufacturing for pMDIs, DPIs and nasal sprays.

Delivering market leading design, development, and the manufacturing of drug delivery devices to the global pharmaceutical market, in conjunction with Bespak by Recipharm, the integrated CDMO can comprehensively cater for, inhaler, nasal and auto-injector projects, as well as providing access to a team of experts with decades of expertise that allows them to manage complexity and accelerate routes to market. These expertise form part of Recipharm's Inhalation Solutions™, an integrated service spanning early phase development to commercial manufacture.

As a global CDMO, Recipharm is at the forefront of global compliance requirements for inhalation products. For more information, please visit: recipharm.com


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