Kindeva
DRUG DELIVERY

NEXT-GENERATION PRESSURISED METERED DOSE INHALERS: A HOLISTIC, PATIENT-CENTRED APPROACH TO SUSTAINABILITY

In this article, Mike Needham, Global Respiratory Product Development Manager, Phil Cocks, Product Design and Optimisation Lead, and Louise Righton, Global Strategic Marketing Leader, all of Kindeva Drug Delivery, discuss how sustainability should be a central theme of future innovation in inhalation drug delivery but must be balanced with the needs of the patient.

Kindeva Drug Delivery has a legacy of advancing the environmental sustainability of inhaled medicines. Formerly 3M Drug Delivery Systems, Kindeva was a founding member of the International Pharmaceutical Aerosol Consortium (IPAC), which was established to represent the industry in navigating the Montreal Protocol in the late 1980s.

Kindeva, a pioneer in hydrofluoroalkane (HFA)-based formulations for pressurised metered dose inhalers (pMDIs), has developed the world's first chlorofluorocarbon (CFC)-free pMDI (launched in 1995) and the first CFC-free nasal pMDI (launched in 2012). These innovations were milestone accomplishments that delivered step-change improvements in the environmental impact of inhaled drugs. There is more work that needs to be done across the pharmaceutical industry, and Kindeva remains at the forefront of environmental progress.

Today, there is renewed energy around the sustainability of inhaled therapies. At its core, this scrutiny is positive and will propel the industry forward. However, much of the debate is narrowly focused on propellants and the comparative global warming potential (GWP) of different devices. As a result, advocacy too often provides blanket recommendations that amount to "device switching" – the notion that propellant-free devices, such as dry powder inhalers (DPIs) and soft mist inhalers (SMIs), are categorically superior to pMDIs, regardless of patient considerations.

Kindeva believes that all inhaler types have a role to play in the management of lung disease and no specific device should be singled out for replacement. It does not support blanket switching based on carbon footprint alone. Kindeva believes in a holistic approach to advancing sustainability in the pharmaceutical industry that offers a longer-term view of environmental and patient impact. This approach involves empowering patient and physician choice to optimise overall disease management, innovation of novel propellants for pMDIs to reduce their carbon impact, and full life-cycle analysis and sustainable improvement of devices. Kindeva's view is that we must simultaneously acknowledge the role of pMDIs as a critical option for patients and seek to alleviate the environmental impact of all inhalation therapies.

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PATIENT-CENTRIC DECISIONS LEADING TO OPTIMISED DISEASE MANAGEMENT

As with any drug delivery development, an innovation that promotes sustainability must consider the needs of the patient. There does not need to be a trade-off between patient needs and sustainability; these twin goals can be complementary. Well-managed, stable patients have lower carbon footprints and less detrimental effects on the environment. They are less likely to be hospitalised and less likely to experience progression of their diseases, impacting their lifetime use of medication and devices. Therefore, a sustainability strategy that depends wholly on broad advocacy for device switching based solely on the relative GWP of different devices is unlikely to satisfy diverse patient needs and may be counterproductive to sustainability goals.

There is no systematic evidence showing that DPIs are categorically more effective than pMDIs.[1] Matching the patient with the right inhaler is a complex decision, which must be judged by the clinician. Guidelines from the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD), as well as current research, emphasise this. If we limit the choice of devices for patients and practitioners, we risk reducing the quality of care. Recent studies demonstrate that pMDIs are clinically equivalent or even significantly more effective than DPIs, indicating that pMDIs are a crucial option for physicians.[2] In short, there's no "one size fits all" inhaler; treatment must be tailored from the plethora of options available and patients should be engaged in the decision.

An essential element of optimised disease management is the training and correct usage of devices.[3] If patients are using their devices incorrectly, the medication will not work as intended. Incorrect usage can be particularly problematic for patients who are prescribed multiple DPIs because it can be challenging to train patients to use various DPI devices – some incorporating reservoirs of powder, others requiring single-use loading with a capsule, for example.

Asthma and chronic obstructive pulmonary disease (COPD) patients with stable disease should have continuity of inhaler device.[4] Suddenly asking the patient to switch from a device that is working for carbon-led reasons, not medical reasons, can have negative consequences. Patients can lose confidence in their medicine; they can lose satisfaction with their treatment; they can even lose trust in their doctor. Learning to handle a new device when the old one was working can lead to exacerbations and even hospitalisations.

Figure 1: The Kindeva Intelligent Control Inhaler.

Novel pMDI device design can also support the overall management of lung disease. The baseline rate of correct use of inhalers is low, with the literature suggesting that up to 94% of DPI users and 74% of pMDI users make mistakes.[5] Beyond correct use, overall adherence to inhaled medicines is low, with 60% of COPD patients and up to 70% of asthma patients non-adherent to their prescribed therapy.[6,7,8]

Kindeva's Intelligent Control Inhaler (Figure 1), which is currently under development and not yet available for commercial sale, may provide a solution to both the correct usage and the adherence challenge. Designed for easy and intuitive use, the Intelligent Control Inhaler provides flow governance designed to optimise inhalation technique, and real-time feedback to aid in proper inhaler technique. It also provides reminders and scoring to promote adherence. The industry should continue to invest in innovation that will transform the way patients engage with their medicine. These solutions will systematically improve the management of respiratory diseases and ultimately lead to lower-cost, more sustainable treatment over the patient's lifetime.

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INNOVATION OF NOVEL PROPELLANTS FOR pMDIS

There is a clear drive towards the use of alternative propellants in pMDIs aligned to the desire to reduce their environmental impact. We need to remember that the use of hydrofluorocarbons (HFCs) in pMDIs represents less than 0.05% of all greenhouse gas emissions. These emissions are a tiny part of the global sustainability challenge. Nevertheless, given the outsized importance of the pMDI as the mainstay treatment for asthma and COPD control, it is sensible to address environmental concerns related to propellants.

It is possible to make a significant change in the carbon footprint of the pMDI. By switching propellant from HFA227 or HFA134a to a lower GWP propellant, such as HFA152a, a considerable reduction in overall device carbon footprint can be achieved (Figure 2). History tells us, however,

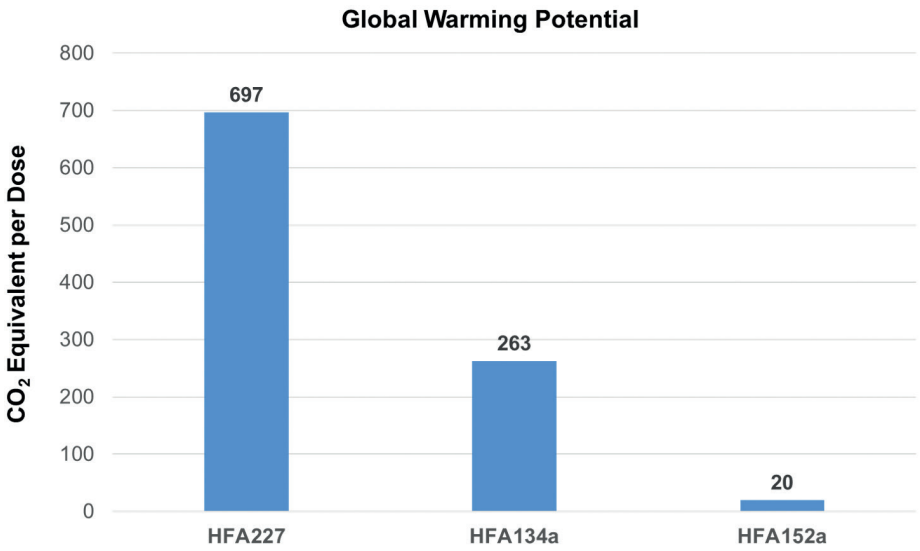

Figure 2: Global warming potential for different propellants.[9]

that it is not entirely straightforward to switch propellants. Kindeva learned this first hand during the transition from CFCs to HFAs following the establishment of the 1987 Montreal Protocol. When considering any alternative, we must think seriously about many factors.

Safety is the primary concern. Any alternative propellant must be safe for patients to use from a toxicology perspective and must be safe to manufacture. The flammability of volatile propellant raises some technological challenges with HFA152a, which must be overcome. Formulation is another concern. A viable propellant must have suitable physical and chemical properties to fully enable solution and suspension pMDI formulations to meet the rigorous pharmaceutical performance and stability standards set for today's inhalation products.

Finally, the cost and quality of any alternative propellant must be acceptable from a supply chain perspective. GMP supplies must be established and made available at an appropriate scale and at an acceptable cost to meet future commercial needs. HFA152a does, however, initially appear to be a highly suitable pMDI propellant candidate. Given the amount of research and investment in this area, commercial manufacturing capabilities are likely to be available soon but a wide range of products in patients' hands is still some years away.

Kindeva has also completed several solubility studies on HFA152a. Pharmaceutical product performance has also been successfully demonstrated on a range of formulations using a typical container-closure system. Following the completion of various flammability and Dangerous Substances and Explosive Atmospheres Regulations (DSEAR) assessments, Kindeva has had small-scale, non-GMP manufacturing equipment installed, giving it the capability to manufacture cold-fill HFA152a safely. This equipment is adequate for most early-stage development projects and enables the company to perform small-scale feasibility assessments and short-term stability studies on future HFA152a opportunities.

There are other developments in novel propellants with negligible carbon impacts that are perhaps even more future-proofed than HFA152a. For example, HFO1234ze is a commercially available propellant that has both technical and consumer applications. With very low GWP, HFO1234ze could offer a sustainability improvement for inhaled medicines.

HOLISTIC DEVICE LIFECYCLE OPTIMISATION

Propellants are only one part of the story. We need a shared understanding of each product's lifecycle and its total environmental impact to expand the discussion from a single focus on propellants and GWP. A holistic approach to sustainability will consider other raw materials used in the drug product or device, how they are sourced, how easily they are recycled, and where they go after the patient has finished using them.

The current carbon-led switching discussion is based on only one element of the environmental issue: global warming. While climate change absolutely should drive policy when it comes to consumption of fluorinated gases, we must not overlook other environmental impacts such as human toxicity, fossil depletion and marine water

quality degradation caused by pollution leading to algae growth and damaging aquatic life. The excessive use of single-use plastics and the resultant burden on landfills are also key considerations in making inhalation therapy more sustainable. While a DPI has the lowest GWP, it is the least environmentally friendly option with respect to eight other impacts.[9] We need to look holistically at sustainability and broaden the avenues that we go down to come up with solutions.

At the forefront of sustainability thinking at Kindeva is a reduction in the parts count of plastic devices. For example, the company is developing a new metal-free dose counter with far fewer parts than has been available previously. This endeavour shows that there does not need to be a trade-off between performance and sustainability. Kindeva believes this new dose counter delivers benefits throughout the value chain – simplicity of assembly, compatibility with a broad range of actuators and valve types, robust reset of dose counting – but also represents a marked sustainability improvement by reducing plastic use. Our industry must recognise that these improvements are possible through the regular cycles of innovation and to continue to challenge ourselves on sustainability.

At one end of the product's lifecycle is the question of sourcing and manufacturing: what materials go into the product? At the other end of the lifecycle is the question of waste management: what happens at the end of patient use? Pharma companies and device makers can and should be influential in promoting the reusability and recyclability of devices. For example, Kindeva is developing new refillable devices that can help lessen the environmental impact of its inhalers. The Intelligent Control Inhaler is designed with a reusable top element with a reduced number of disposable parts. While the significance of propellants cannot be downplayed, the industry must also recognise the vital sustainability implications of materials selection, part counts, manufacturing methods, waste management and recycling.

CONCLUSION

Sustainability should be a central theme of future innovation in inhalation drug delivery but this must be balanced with the needs of the patient. Sustainability strategies that hinge solely on device switching for carbon reduction do not generally serve the patient's best interests. Patients deserve a thoughtful approach to treatment that is designed to optimally treat their conditions. Robust sustainability strategies require a holistic, end-to-end view of the product design, lifecycle and patient impact. By effectively optimising disease management and preserving patient options, innovating low GWP propellants, and sustainably designing devices and components, pMDIs will continue to play a key role in lung disease management.

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ABOUT THE COMPANY

Kindeva Drug Delivery is a contract development and manufacturing organisation offering its partners integrated, end-to-end capabilities spanning formulation, product development, scale-up manufacturing and commercial manufacturing. Its full-service innovation offering covers: inhalation (pMDIs, DPIs, connectivity, nasal delivery); transdermal delivery (drug-in-adhesive systems and gel patches); and intradermal delivery (microneedles based on solid and hollow microstructures). Kindeva Drug Delivery has locations in the US and the UK and employs over 900 people. It was formed in 2020 when 3M's Drug Delivery Systems business was acquired by Altaris Capital Partners for US$650 million (£503 million) and renamed Kindeva.

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