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THE pMDI DILEMMA: MANAGING PATIENT NEEDS, HEALTH AND THE PLANET

In this article, Nick Smalley, Vice-President, Regulatory Affairs, at Kindeva, discusses the balancing act involved in meeting patients' therapeutic needs while protecting the planet when it comes to pMDI development.

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Environmentally friendly inhalers have been a topic of discussion for some time. However, the spotlight is on them now more than ever, thanks in part to the proposed phase-down of per- and polyfluoroalkyl substances (PFASs). PFASs are a class of substances comprised of thousands of synthetic chemicals that resist degradation because of their exceptionally strong chemical bonds, making them "forever" chemicals that may have an impact on human health and the environment. Due to their usefulness and consequent ubiquity, any regulatory shifts regarding their usage have the potential to impact a massive range of products across nearly every industry.

The European Chemicals Agency (ECHA) published a PFAS restriction proposal including about 10,00 substances on February 7, 2023.1 The proposal is currently under review by its scientific committees, with a goal of submitting final opinions as expeditiously as possible.

This PFAS restriction proposal adds to concurrent legislation centred around reducing the use of fluorinated gases (F-gases). While the new regulations are aimed at curbing large-scale emissions from refrigeration and industrial usage, they would phase out compounds currently employed as propellants in many inhalers. These proposals have already accelerated shifts within the pharmaceutical sector, where consequences will be felt throughout the drug-device development pathway, including in manufacturing processes and supply chain reliability.

THE BALANCING ACT

Having been a leader in the move from chlorofluorocarbon (CFC) to hydrofluoroalkane (HFA) propellants in the 1990s with the first CFC-free pressurised metered-dose inhaler (pMDI), Kindeva fully understands the challenges that arise from these kinds of transitions. This experience has also cemented within the organisation the importance of formulating and

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developing solutions all potential propellants as part of a proactive plan – something that should be incorporated into every MDI company's long-term strategy.

Some contemporary arguments offer a binary approach to the path ahead for inhalers, suggesting that switching to dry powder inhalers (DPIs) instead of pMDIs is the only answer – but the decision is more nuanced than that. While the transition to a more carbon-neutral and sustainable industry is important, only by thoroughly evaluating the implications for patients, the broader picture of environmental waste and the full scope of available options can that goal be satisfied.

THE PATIENT

As with every transition in the pharma industry, the welfare of patients is paramount. As such, although guidelines may shift to favour DPIs, it is vital that the appropriate path forward for each set of products respects the totality of patient needs. This includes the availability of products that are safe, effective and usable, as well as the maintenance of a healthy environment.

For example, some individuals are unable to generate adequate inspiratory flow to operate a DPI, immediately dispelling the idea that there is a single, one-size-fits-all solution that can satisfy the needs of both patients and the planet. Beyond this unambiguous instance, a tapestry of questions centred on patient welfare must also be addressed, including whether the patient is able to learn to use a new device correctly and whether the change would otherwise negatively impact adherence. The pharma industry exists to improve the lives of those in need, so these decisions must always be made on the basis of what is best for the overall health of the patient.

THE PLANET

The pharmaceutical industry's understanding of the industry's environmental effects must constantly expand, and improvement must be ongoing. While the development of green propellants is an important factor, the evaluation must incorporate the damage caused by chemical components alongside that caused by all other factors, including component materials and recyclability. For example, while much of the current focus is on propellants used in pMDIs, an evaluation of the depletion of fossil resources by the University of Manchester (UK) found DPIs to have the most damaging impact.[2] Taking a wider viewpoint helps provide a more complete understanding of problem areas, from creation to use and disposal, allowing a full accounting of the carbon footprint for each therapy. To provide effective medicines that do as little harm to the planet as possible, it is imperative to move away from siloed thinking and towards holistic solutions.

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THE POSSIBILITIES

To realise a future that satisfies patient needs while also meeting those of the planet and general human health, innovation must be realised across the gamut of effective therapies and devices. Notable exceptions aside, discovery often happens when people are searching. If lines of treatment are abandoned entirely, there is a grave risk of losing consequential innovations – if not in the therapy or device itself, then in an undiscovered manufacturing method or shipping advancement.

Every avenue of improvement begets more opportunities for something transformational to be uncovered. In the current environment for pMDIs, this means investing in the continuous research and development of green propellants, such as HFC-152a (which is a good, but not universal, alternative), for commercial use, as well as HFO-1234ze, which could be restricted through PFAS regulations despite having a 99.9% lower global warming potential (GWP) than HFA-134a – the greenest option in use today.

This ongoing exploration of solutions represents one of the things the industry as a whole does best – find new ways forward in the face of emerging difficulties. Even with the unexpected hurdles common to drug and device development, it can be easy to forget that ideal solutions rarely continue their run with that title intact. As with the transition from CFCs to HFAs decades ago, when the industry is made to grapple with new challenges, novel optimal solutions are needed. Ongoing development across multiple therapies, products and delivery methods is necessary to ensure that patients have an acceptable alternative whenever a newly discovered adjustment needs to be made to an existing therapy.

PROPAGATING PROGRESS

With all of this in mind, what can be done to prepare a combination drug-device product to optimally serve the holistic needs of patients and the planet?

- Stay up to speed on current regulations and what is coming down the pipeline and, guided by developing trends, create an informed strategy that anticipates future issues
- Know the full footprint of a product; identifying all the ways that processes can be optimised can provide a head start when new regulations arise
- Choose an experienced partner with a demonstrated history of adaptability and innovation; between their institutional knowledge and hands-on know-how, the right contract development and manufacturing organisation (CDMO) can help quickly identify the best path forward
- Find the right capabilities for switching faster than the competition, which means making sure to explore how far along a CDMO is in upgrading to green propellants; additionally, look for a partner that can provide manufacturing services with a variety of propellants, so that a project is covered no matter what legislation comes next.

As the ECHA, the European Commission and the entire drug delivery industry take a long hard look at what propellants and materials are safe for the planet, it can be easy to miss the larger picture and even lose patients in the conversation altogether. Given that inhalers and similar medical devices exist specifically to assist them, it is vital that patients are central to the conversation. Meeting their therapeutic

needs while protecting the planet as a whole, however, requires a wide-lens view.

The most ideal therapy for a patient is one that is safe, effective, affordable and promotes easy adherence – at times, that will not be the greenest therapy. However, it could likely be greener.

Evaluating the full footprint of every therapy allows the industry to truly address its environmental impact and meet every patient's needs with more environmentally sound treatments. This big-picture approach puts patients at the forefront while proactively moving the industry on the path to a more sustainable future. To continually improve therapies while safeguarding the array of options that best meet tailored patient treatment plans, the search for greener solutions must be developed with the holistic well-being of patients, now and in the future, at the forefront.

ABOUT THE AUTHOR

Nick Smalley, Vice-President, Regulatory Affairs, has more than 25 years' experience in pharmaceuticals and contract manufacturing and now leads Kindeva's advanced drug delivery regulatory affairs function. After starting his career in inhalation research and development working on both pMDIs and DPIs, Mr Smalley moved into regulatory affairs in 1999 and has worked globally across multiple different product areas, including complex generics, biologics, consumer healthcare, medical devices and ethical pharmaceuticals. He is also the Vice-Chair of the board of directors of the International Pharmaceutical Aerosol Consortium, a coalition of eight multinational pharmaceutical companies that strives to ensure global environmental policies that are relevant to inhaled therapies are patient-centric and appropriately balance patient care and sustainability efforts. Mr Smalley hasa BSc in Chemistry from Loughborough University (UK).

ABOUT THE COMPANY

Kindeva Drug Delivery is a global CDMO focused on drug-device combination products. The company develops and manufactures products across a broad range of drug-delivery formats, including pulmonary and nasal, injectable and transdermal. Its service offerings span early-stage feasibility through to commercial-scale drug product fill-finish, container closure system manufacturing and drug-device product assembly. Kindeva serves a global client base from its state-of-the-art manufacturing, research and development facilities located across the US and UK.

REFERENCES

1. *"ECHA publishes PFAS restriction proposal". Press Release, ECHA, Feb 7, 2023.*
2. *Jeswani HK, Azapagic A, "Life cycle environmental impacts of inhalers". J Clean Prod, 2019, Vol 237, article 117733.*

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