FUTURE-PROOFING pMDI DESIGN TO FIT A CHANGING MARKET

In this article, Ross Errington, Head of Drug Product Development at Recipharm, explores how pharmaceutical companies can evolve their pMDI drug products to make them fit for the future considering the several recent regulatory changes that are transforming the landscape of inhalation drugs.

The pulmonary drug delivery market is growing rapidly and forecast to be worth US$76.9 billion (£63.4 billion) by 2027 — up from $57.4 billion in 2022.[1] A significant contributor to this increase is the pressurised metered dose inhaler (pMDI) segment — which was valued at $16 billion in 2022 and is on track to reach $22 billion by 2031.[2]

One of the biggest factors in the rapid rise of the pulmonary market is the global increase in the number of diagnoses of asthma and chronic obstructive pulmonary disease (COPD), as well as other chronic respiratory conditions. A total of 262 million people worldwide were reported to be living with asthma in 2019, with 455,000 deaths attributed to the disease.[3] COPD, meanwhile, was responsible for 3.22 million deaths in 2019.[4] Between 2007 and 2017, the number of people dying from COPD increased by 17.5%,[5] making it one of the three most common causes of death globally.[6]

Thankfully, pMDIs possess key features that make them ideal for use in combination products to transform the lives of the growing number of patients living with these serious conditions:

- **Manufacturing efficiency:** pMDIs are cost-effective to provide to a large number of patients living with chronic conditions.
- **Ease of use:** pMDIs offer breath-independent actuation, reducing the inspiratory flow rates required to achieve adequate drug deposition in the lung.[7] As a result, they can be used to treat both elderly patients and children, delivering a uniform drug dose every time.

A RAPIDLY CHANGING REGULATORY LANDSCAPE

Taking these benefits into account, it is clear why there is a correlation between the global prevalence of chronic pulmonary diseases and the increase in demand for pMDIs. However, the market landscape is changing fast, particularly when it comes to the regulatory environment governing medical devices and the propellants used in pMDIs. Pharmaceutical companies need to understand the most important of these changes and carefully consider both the design of their pMDI devices and their manufacturing processes to ensure that they continue to be compliant.

Introduction of the EU MDR

The EU Medical Device Regulation (MDR) replaces the existing Medical Device Directive (MDD) and the Active Implantable Medical Device Directive (AIMDD). These two directives previously governed the design of all devices used for medical purposes, including inhalation device technology. Under the MDR, all new and existing devices used with medicinal products, including combination products such as pMDIs, must show conformity to the general safety and performance requirements (GSPRs) in Annex I of the MDR. In March 2023, the EU extended the MDR transition periods from May 26, 2024, to May 26, 2026, for Class III implantable custom-made devices, and to December 31, 2027, for Class III and implantable Class IIb devices.[8]

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Post-Kigali Amendment Changes to Propellant Regulations

The Kigali Amendment to the United Nations Montreal Protocol was signed in 2016 to phase down global consumption of hydrofluorocarbons (HFAs) by 80–85% by 2047.[9] Widely used across many industries, HFAs have been the principal pMDI propellants for decades. However, the most common of these gases have a high global warming potential (GWP) and a long atmospheric life.

Following the signing of the Kigali Amendment, key pMDI markets, such as the EU, the UK and the US, have either enacted or begun to consider new legislation requiring existing high-GWP HFAs to be phased out in all applications. It remains uncertain what the timeline will be for this move away from traditional HFA propellants in pMDIs in key global markets, but companies must prepare for the transition to low-GWP alternatives now to minimise disruption of critical medicine supplies to patients.

A Potential EU REACH Ban on PFASs Could Impact the HFA Transition

Germany, the Netherlands, Norway, Sweden and Denmark submitted a joint restriction proposal under the European REACH regulations for polyfluoroalkyl substances (PFASs) in January 2023. This recommends further restrictions or even bans on HFCs and hydrofluoroolefins (HFOs)[10] potentially including gases that are being explored as low-GWP alternatives for current pMDI propellants, such as 1,3,3,3-tetrafluoropropene (HFO-1234ze(E)). Any restrictions on the manufacture and use of these propellants would have negative implications for the industry's efforts to reduce reliance on HFAs in inhalation drug products.

At the time of writing, it is unclear whether the total ban proposed will come into effect — news in recent months suggests it may be subject to revision before it comes before the EU Parliament.[11] Nevertheless, if it does pass, and the ban comes into force in 2025, the industry would have just 18 months from that date to remove any pMDIs containing these gases from the EU market.

DEVELOPING FUTURE-PROOFED pMDIs

Pharmaceutical companies need to take action now to prepare for these changes to the market and ensure the ongoing compliance of their pMDIs. The Kigali Amendment has particularly significant ramifications for the design of the container closure system of pMDI devices and the formulations they administer, due to the need to explore more sustainable alternative propellants. Potential alternatives to current pMDI propellants include both HFO-1234ze(E) and 1,1-difluoroethane (HFA-152a). However, the selection process for new propellants is complex, with many key issues needing to be considered.

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Propellant Compatibility with Formulation and Container Closure System

Compatibility of potential new propellants and container closure systems can be ensured by maintaining seal integrity and valve delivery performance throughout the product's shelf life. Maintaining acceptable levels of extractables and leachables is also key, making comprehensive testing essential. Propellant vapour pressure and molecular weight also need to be considered when determining the propellant leak rate – exposing filled canisters to extreme temperatures and pressures during testing can establish this.

Propellant Physicochemical Properties

These have implications for the formulation to be filled in the pMDI. Two of the leading propellants being explored have similar properties to currently used HFAs in terms of vapour pressure, density and compatibility with surfactants and solvents such as ethanol. This suggests that radical changes to formulation platforms may not be required, but appropriate studies will be needed to confirm this.

Environmental Impact and Safety

The propellant's toxicity must be considered – it is vital that any propellant is safe for human ingestion and that there is no detrimental interaction with the formulation. Flammability is also a concern – ATEX certification of the production line machinery will need to be addressed if there is any explosive risk.

Scalability Concerns

Failure to consider how the manufacture of the new propellant, along with the formulation and device design, can be scaled up could lead to costly delays in commercialisation. These considerations should start at the beginning of the development project to minimise risk. This is true for both new treatments and reformulation of existing pMDI treatments.

COMPLIANCE CONSIDERATIONS

These Kigali Amendment-related issues aren't the only factors to take into consideration when future-proofing pMDI therapies. It is also important to take into account changes to managing regulatory approvals and quality control processes to ensure compliance with the new MDR in the EU. Furthermore, the regulatory landscape continues to evolve – the recent (Oct 11th, 2023) IPAC-RS workshop on "The Transition to Low Global Warming Potential Propellants for Metered Dose Inhalers" showed how that discussion is progressing.

Updates to Quality Management Systems

Design control and GMP protocols need to be updated to meet MDR requirements. New clinical evaluation procedures will be needed to enhance the collection of clinical data, along with a post-market surveillance system to track the performance of the pMDI in the real world after commercialisation.

Changes to Requirements for Supervision of Notified Bodies

Companies must find a notified body to review information regarding the GSPRs under Annex 1 of the MDR to issue an opinion that the product conforms with requirements. Failure to consider this early in development could result in delays in regulatory filing.

PARTNERS ARE KEY TO FUTURE SUCCESS

The regulatory landscape for pMDIs is transforming, and if pharmaceutical companies want to continue to benefit from the convenience and manufacturability

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advantages of these devices, they need to act now. Updating both the design and formulation of pMDI devices, as well as regulatory and commercialisation processes, will be a major undertaking for any pharmaceutical company.

However, there are contract development and manufacturing organisations that can offer expert support throughout the process to ensure that companies continue to comply with new legislation. Such partnerships can help ensure that patients living with chronic pulmonary diseases continue to receive inhalation treatments that are not just effective, but convenient.

ABOUT THE COMPANY

Recipharm is a leading CDMO in the pharmaceutical industry, with almost 9,000 employees. The company offers manufacturing services of pharmaceuticals in various dosage forms, production of clinical trial material and APIs, pharmaceutical product development and development and manufacturing of medical devices. Recipharm manufactures several hundred different products for customers, ranging from big pharma to smaller research and development companies. The company operates development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US, and is headquartered in Stockholm, Sweden.

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