Meeting Challenges in Inhaled Drug Delivery

Pharma must reduce the environmental impact of respiratory drugs delivered in pressurised metered-dose inhalers with agile development solutions helping to bring new alternatives to market

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The commercial outlook for metered-dose inhalers (MDIs) has been estimated at a compound annual growth rate (CAGR) of 4.3% for 2022-2032. The market is predicted to reach $40,140m by 2032.[1] This growth is fuelled by a variety of factors, including a growing prevalence of pulmonary disease and an ageing global population.

Pressurised metered-dose inhalers (pMDIs) are the preferred and most cost-effective respiratory drug delivery system. They comprise a metering valve, canister and actuator that aid delivery of the contained formulation.[2] A key part of this formulation (other than the drug and excipients) is the propellant, which drives the atomisation of the mixture into medication-containing droplets for delivery to the lungs.[3]

Inhaled delivery of medicines for asthma and chronic obstructive pulmonary disease (COPD) began in the 1950s, using chlorofluorocarbons (CFCs) as the propellant. Following concerns about the environmental impact of CFCs, pharma companies began switching to hydrofluorocarbons (HFCs) in the 1990s.

Today, those HFCs are being replaced by alternative HFCs with lower environmental impact, starting the redevelopment cycle again. Hydrofluoroalkane (HFA)-134a and HFA-227a, the most common of the original HFA propellants, are 1,300 times and 3,300 times, respectively, more potent as global warming agents than carbon dioxide.[4] This has necessitated a move towards low global warming potential (GWP) propellants such as HFA-152a and HFO-1234ze, which boast an over 90% reduced GWP when compared with HFA-134a. However, these low GWP alternatives also exhibit different physiochemical properties from their predecessors, which may impact the stability and spray formation associated with the formulation, as well as overall pMDI performance.[5]

As a result, products need to be reformulated, device design needs to be reconsidered, manufacturing processes and controls may need to be modified, and clinical trials redone to support any new regulatory filing application required. In this scenario, a pharma company is looking to:

- Minimise the impact on the existing product
- Carefully manage development times and costs of change
- Complete trials and regulatory processes as soon as possible
- Understand any effect on the cost of the new medicine and how this could impact prescribing habits and revenue.

In the risk-averse world of pharma this represents an onerous task.

Clinical Need For pMDIs Remains

In the face of such pressures, why not simply reformulate to take advantage of

other, non-pressurised formats, like dry powder inhalers (DPIs)?

For some applications, this would be a sound decision, but there is a general consensus that pMDIs remain essential in certain situations, such as in 'relief' inhalers, where a patient is struggling to breathe and may be unable to deliver the necessary pressure by inhalation to receive the required dose from a DPI device.

GSK published a policy statement in 2021 noting that all 'latest generation' products were developed and launched in DPI devices and that they were working to reduce the environmental impact of their remaining 'rescue' pMDI products.[6]

Understanding the New Challenges

Low GWP propellants are likely to impact formulations, container closure systems and manufacturing processes. Other crucial considerations include:

- Their physical properties
- Compatibility with current hardware and filling equipment
- The miscibility and solubility of the molecules
- Drug loading
- Delivery efficiency
- The physical and chemical stability of the formulation
- Manufacturing
- Regulations and toxicology
- Alignment with good manufacturing practices (GMP).

Manufacturing processes are a leading concern for pharma companies considering the development of low GWP MDI products, as any change involves updates to equipment, established ways of working and company knowledge.

Companies must also consider the many factors that dictate the clinical efficacy and delivery of the formulations contained in a pMDI during development. One important factor is the aerodynamic particle size distribution (PSD). This metric describes the size of drug-containing particles released by the inhaler and plays a vital role in determining drug deposition and efficacy. Particles of between 0.5 and 5µm have the highest probability of depositing in the lungs and smaller particles have a greater probability of penetrating more deeply.

The intrinsic PSD of ethanol-based HFA MDIs is consistent at the point of atomisation and dependent on propellant choice, but independent of the formulation composition, metering valve chamber size, or the actuator's atomisation orifice.[7] This performance quality allows rapid formulation success with alternative propellants. Then there is the residual PSD, which is dependent on the non-volatile content of the MDI formulation.

Choices regarding the formulation and propellant are essential for maximising drug delivery and are a major consideration. In the case of solution MDIs (in which the active ingredient is dissolved in a pure propellant or mixture of propellants), the robustness of drug delivery can help formulators to understand how formulation, propellant and hardware choices affect the potentially respirable residual PSD.

A Matter of Design

The canister, actuator and metering valve can all impact drug delivery when using different propellants. Promising results have been obtained for HFA-152a, which demonstrates dose delivery within European pharmacopoeia guidelines from nought to 12 months in plasma-treated canisters.[8]

There are still improvements to be made when it comes to inhaler design for low GWP propellants. In the case of HFA-152a, actuator geometries require optimisation to perform at the same level as existing HFA-134a products; spray patterns also require further evaluation and investigation is needed beyond 12 months to determine a suitable shelf life.

Clearly, conducting studies into the impact of inhaler design on drug delivery with propellants represents another cost burden for pharmaceutical companies, but these cannot be avoided. This is emphasised by the fact that manipulation of the orifice diameter and length can be used to alter the near-orifice spray structure for both HFA-152a and HFO-1234ze.[9] In the HFA-152a study

described, an increase in the actuator orifice diameter from 0.4 to 0.5 mm more than doubled the relative standard deviation of the mean drug delivered. In real-world conditions, this could translate to sizeable differences in the amounts of medication inhaled per dose.

Outsourcing the manufacturing of inhaler components offers access to specialised equipment and the ability to scale production without committing to costly purchases.

Inhaled Delivery for Systemic Drugs

In addition to local delivery of drugs for respiratory diseases, the lure of pulmonary delivery of systemic drugs for other conditions is strong. It is a potentially advantageous alternative drug delivery route for those usually administered by injection, tablet or capsule.

Recent initiatives and publications highlight developments such as treatments for viral and bacterial infections and the use of lipid nanoparticle (LPN) delivery systems.[10,11] A recent review paper outlined the past, present and future of inhaled medicines.[12]

Unlike the reformulation of an existing pMDI product, companies progressing drug development in this space face the usual pressures of timescales of ten years or more for drug discovery and commercialisation.

'Fast-track' Collaboration

Working with specialists who can provide integrated and agile development solutions is helping to meet demand and bring new pMDIs to market more quickly.

Integrating expertise in formulating pMDIs, the identification and manufacture of appropriate device components for that formulation, plus expertise in GMP manufacture of products for clinical trials and knowledge of rapid clinical trial management, offers considerable advantages.

This approach means a pharma company can rely on existing infrastructure and expertise from external sources, rather than having to develop them in-house. For example, the first company provides formulation and stability data for a second to design or modify a device. Then a third company combines these elements and oversees manufacture in accordance with GMP licences to produce product in blinded packaging for use in human studies.

Inter-company collaborations also allow each company to leverage the advantages of one another's geographical locations. For example, Australia represents a promising location for GMP manufacture and conducting early clinical trials, as well as having a faster route to the clinic than most countries. This is partly because it has a publicly funded healthcare system, clinical trials ecosystem, the availability of many phase 1 study units and potential government tax incentives.

Collaboration can encompass full R&D and chemistry, manufacturing and controls management, intellectual property (IP) generation, technology transfer and GMP manufacturing for initial in-human and early-phase clinical trials.

Collaboration in Action

This example illustrates how a collaborative approach can accelerate bringing inhalation products to clinical trial.

A pharma company needed support to develop its drug-device combination for the delivery of a potential treatment for neuralgia through the inhalation route. The product was for the relief of trigeminal neuralgia, a sporadic, sudden, facial pain, and used a rapid-delivery, inhaled formulation of an undisclosed phytocannabinoid mixture. The medicine would have designated orphan status and be delivered via an inhaler, which could mean faster onset of pain relief when compared to other routes.

The team worked to shape and accelerate the pharma firm's development plan, using their decades of experience in the inhalation field to meet quality and timeline goals. This resulted in a high quality product to take through the preclinical stage, clinical development, as well as giving them valuable IP.

Looking Ahead

When CFCs in pMDI products had to be replaced, the industry stepped up. Now, as 'first-generation' HFAs must be changed for newer ones with lower impact, the industry must again accommodate change.

The year 2025 is the date set by many governments, NGOs and companies to achieve significant reductions in environmental impact.

With pharma's extended development timescales and an aversion to risk that can slow progress, the industry must leverage all expertise and learn the lessons of collaboration, to reach its goals.

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