HOW SOFT MIST INHALERS WILL BREATHE NEW LIFE INTO DRUG DEVELOPMENT

This article is based on a whitepaper originally published by GAPLAST GmbH

Kasim Yilginc of **GAPLAST** discusses the expanding importance and influence of the respiratory sector within pharmaceutical pipelines, including the role that soft mist inhalers are poised to play in improving patient outcomes and how the company's AirlessMotion® bag-in-bottle technology can support the development of these inhalation devices.

The prevalence of respiratory diseases is increasing around the world, particularly in high-income regions. According to the Global Burden of Disease Study 2017, 544.9 million people had a chronic respiratory disease in 2017, representing an increase of 39.8% from 1990 and a global prevalence of 7.1%.[1] With key risk factors including smoking, household air pollution and ambient particulate matter, it is no wonder that lung diseases are becoming increasingly widespread.

Chronic obstructive pulmonary disease (COPD), a debilitating and progressive disease characterised by persistent respiratory symptoms and airflow limitation, remains the most prevalent chronic respiratory disease worldwide, accounting for 55.1% of chronic respiratory indications among men and 54.8% among women. Of all countries, the UK has the highest rate of COPD; according to the latest data from the UK Department of Health & Social Care, COPD-related mortality rates recently increased in England from 42.8 people per 100,000 in 2020–2022 to 43.9 per 100,000 in 2021–2023.

Combined with epidemiology figures from GlobalData (London, UK), which forecast the total prevalence of COPD across 16 major pharmaceutical markets to increase from 15% in 2023 to 16% by 2033 in men and from 12% to 13% in women, it is clear that chronic respiratory conditions are becoming an increasingly important global health concern. In fact, according to the WHO, COPD is the third leading cause of death worldwide.

Fortunately, the pharmaceutical industry continues to expand its R&D efforts in novel respiratory therapies, with the US FDA approving 14 non-new molecular entities since 2015, according to GlobalData's drugs database. In 2024 (Figure 1), the industry commenced 1,215 new clinical trials studying respiratory conditions, marking a 36% increase from 2014. As of January 2025, there were 1,823 drug candidates under development for the treatment of respiratory diseases, including 124 products in Phase III trials and 23 in the pre-registration stage.

The respiratory disease pipeline currently reflects a range of therapies and modalities, with a relatively even divide between biologics and small molecules. Most investigative therapies are administered via injection (35.4%), with the other major routes being oral (31.1%) and inhalation (29.8%). Of these, only the inhalation route offers a direct route to the lungs, enabling lower API doses and potentially fewer side effects. Inhalable corticosteroids, for example, have become a mainstay of daily asthma treatment due to their improved safety profile when compared with oral alternatives.

INHALABLE RESPIRATORY THERAPIES – THE CURRENT PIPELINE

According to GlobalData, the majority of inhalable respiratory therapy candidates are in the preclinical stage of development (Figure 2). As of Jan 2025, there was a roughly equal number of candidates in Phase I and II trials (67 and 68, respectively), with less than half of that in Phase III. Within that, the leading indications for inhalable respiratory therapies are COPD and asthma, with a high number of therapies also under development for cystic fibrosis and idiopathic pulmonary fibrosis (Table 1).

Indications	Number of drugs
COPD	88
Asthma	83
Cystic fibrosis	53
Idiopathic pulmonary fibrosis	52
Bronchiectasis	27

Table 1: Inhalable respiratory therapy pipeline by indication (Source: GlobalData, Pharmaceutical Intelligence Center).

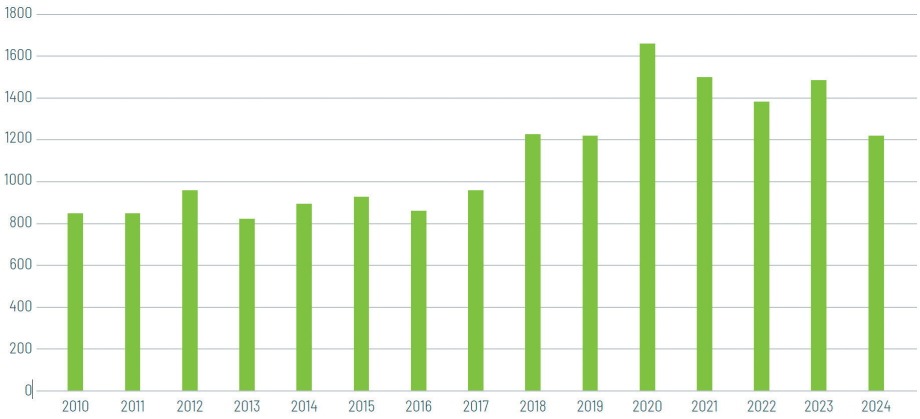

Figure 1: Respiratory clinical trials by start year (Source: GlobalData, Pharmaceutical Intelligence Center).

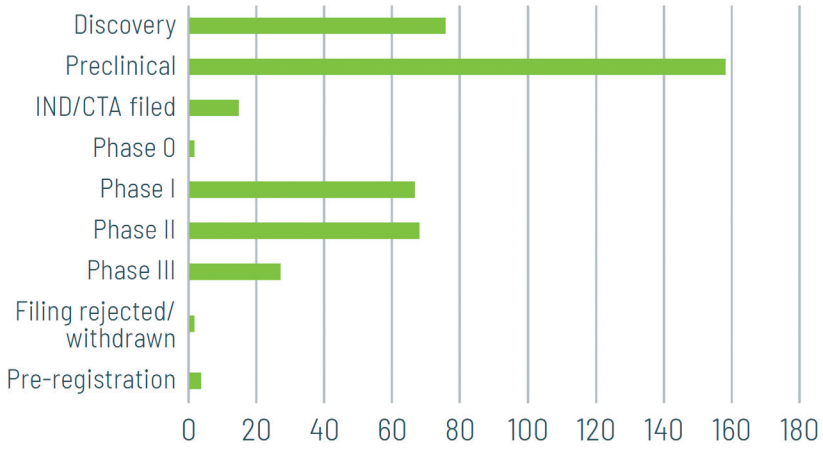

Figure 2: Inhalable respiratory therapy pipeline by development stage (Source: GlobalData, Pharmaceutical Intelligence Center).

While inhalable therapies have traditionally favoured small molecule formulations, such as corticosteroids, a significant proportion is comprised of biologic candidates, representing 41.1% of the total pipeline. Small molecules make up the largest share, at 48.2%, with 30 oligonucleotide products accounting for the remaining 10%. When it comes to mechanisms of action, most of the inhalable therapies are receptor agonists or antagonists, with other common mechanisms being explored, including enzyme inhibitors, ion channel activators, and protein and peptide inhibitors.

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A few examples of inhalable biologics in Phase III trials include an alpha-1 proteinase inhibitor for emphysema (Grifols, Barcelona, Spain), which is prepared from human plasma, and the Broncho-Vaxom vaccine (OM Pharma, Geneva, Switzerland), which is under development for the treatment of recurring wheezing and allergic asthma. Beijing Tri-Prime Genetic Engineering Co (Beijing, China) currently has a Phase III product manufactured using recombinant DNA technology, meanwhile Molgradex (Savara, Langhorne, PA, US), a recombinant protein candidate, is currently undergoing clinical testing for unspecified lung diseases.

THE EVOLUTION OF INHALABLE DEVICES

As the pharmaceutical pipeline evolves, with an increasing number of respiratory biologics under development, there have also been significant advancements in the delivery technology used to administer these medications. Pressurised metered dose inhalers (pMDIs) have been a mainstay of inhalable drug delivery for decades, with well-known products including the Easi-Breathe (Teva) and Autohaler (Teva). More recently, however, dry powder inhalers (DPIs) and soft mist inhalers (SMIs), such as Respimat (Boehringer Ingelheim), have been growing in popularity. Environmental concerns are a key part of the story, as DPIs and SMIs offer the significant advantage of not requiring a propellant, contributing to a significantly more environmentally friendly approach to respiratory treatment.

However, greenhouse gas emissions are not the only reason pharmaceutical manufacturers are showing increasing interest in alternative inhaler technologies. SMIs are frequently considered to be significantly easier to use than traditional inhalers, requiring less co-ordination between actuation and inhalation, supporting improved outcomes in two key ways. Firstly, SMIs offer an easier experience for patients, which can help to solve adherence challenges, ensuring more consistent usage of the product. Secondly, as studies have shown, SMIs can also increase the amount of medication that reaches the lungs per actuation.

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For example, one study that investigated the deposition of fenoterol in the lungs and oropharynx after delivery from three different inhaler devices – an SMI, a pMDI and a pMDI with spacer – found that the SMI device deposited 39.2% of the product in the whole lung, while the pMDIs with and without a spacer deposited just 11% and 9.9%, respectively. For the pMDI, 71.7% of the administered drug deposited in the oropharynx. Inhalational technique errors, which are estimated to occur in approximately 90% of pMDI users, could be playing a key factor in this effect.[2]

The "soft", slow-moving mist achieved with SMIs is also much gentler on the throat than the forceful spray of a pMDI. This factor contributes to less irritation and coughing with the newer technology, indicating that it could be well suited to the delivery of fragile biologic compounds, such as mRNA. Finally, SMIs are small and highly portable, with no requirements for the addition of a spacer or holding chamber.

A CHANGING MARKET

There are currently 67 marketed products in the US, EU and UK that feature inhaler technology, not including generics. In 2023, these products were estimated by GlobalData to generate total global sales of US$9.55 billion (£7 billion), with the highest grossing product – Symbicort Turbohaler (AstraZeneca), a DPI – making $2.36 billion in 2023, accounting for 24.7% of the market. Other blockbusters include Seretide/Advair (GSK), available in both pMDI and DPI devices, which generated $1.41 billion revenue in 2023, and Spiriva (tiotropium bromide) Respimat (Boehringer Ingelheim), an SMI that achieved sales of $1.39 billion the same year. In addition to Spiriva, which received FDA approval in 2001, other key SMI products include Striverdi (olodaterol) Respimat (Boehringer Ingelheim), first approved by the FDA in 2013, and Spiolto/Yanimo (tiotropium bromide/olodaterol) Respimat (Boehringer Ingelheim), approved in 2015 in nine European countries and by the FDA.

According to GlobalData, an average of five patents are expected to expire each year until 2030. In 2025, Aerobec auto-inhaler (Teva), Duaklir Genuair (Covis Pharma, Amsterdam, the Netherlands) and Arnuity Ellipta DPI (GSK) are all expected to expire. When it comes to Boehringer Ingelheim's portfolio of SMI products, expiries are expected in early 2027 for Stirvedi and Spiolto/Yanimo, while the constraining patent expiry of Spiriva in the US is anticipated in 2026.

With this date now just a few years away, several companies are expected to pursue generic formulations; the high costs of the branded products have created a strong demand for generic counterparts. However, there are many challenges involved with replicating both the APIs and the specific inhalation devices. Meanwhile, with dosage form information unavailable for pipeline products, there are currently limited data to support the entry of new molecular entity SMI products into the market.

Nevertheless, with a considerable body of evidence to suggest that SMIs can help formulators optimise drug delivery to the lungs, while also improving the inhaler experience for patients, SMIs are becoming an increasingly appealing technology for drug developers looking to make their product stand out on the market. As such, it is equally likely that companies will look to reformulate existing marketed drugs into SMIs as a method of extending the product's lifecycle before expiry.

FUTURE TRENDS

Future developments and innovations are inevitable in this field, from innovative nozzle designs that enable targeted delivery of specific drugs, such as biologics, to digitalised SMIs that make use of electronic breath actuation and real-time dose verification data. Inhaler technology is expected to be explored far beyond the field of respiratory diseases, particularly as investigation into cannabis-related medications for pain management and mental health conditions increases. Yet, behind all these exciting innovations, is the container closure system at the heart of the system – and without it, even the most advanced SMIs and the innovative drug-device combinations cannot fulfil their promise.

One company that understands the crucial role of the cartridge inside out is GAPLAST, a provider of drug delivery technologies and components and inventor of the AirlessMotion® bag-in-bottle system (Figure 3). The company's AirlessMotion bag-in-bottle technology is a patented drug delivery system that has proven itself in the medical and pharmaceutical industries. It is a packaging system that provides high protection against chemical, physical and microbiological contamination, with options spanning 5–1,250 mL to meet the diverse needs of its customers. Also available as a 5 mL cartridge, this multilayered container closure system can be adapted to the requirements of various SMI devices and formulation compatibilities.

Figure 3: GAPLAST's AirlessMotion cartridge for SMIs with optional cap.

The technology follows the same basic principle that all SMI devices are built around – as the cartridge's flexible inner bag contracts, the internal volume is pushed out and administered via the device's inhalation system as a fine spray mist. The amount of extracted liquid can be defined according to customer requirements, and unique colours and volumes are also possible upon customer request (Figure 4).

Figure 4: The AirlessMotion bag-in-bottle technology can be adapted to the needs of various SMI designs.

One of the most important features of the product is its impressive barrier properties, which play a critical role in maintaining the sterility and stability of the product. Optimised barrier properties are particularly important when it comes to sensitive drugs such as biologics, standing GAPLAST in good stead to support the future wave of inhalable drugs currently in development. GAPLAST has been working with the bag-in-bottle technology for over 35 years, which has enabled the company to create a very strong oxygen and water barrier to protect the product.

Another advantage of the AirlessMotion bag-in-bottle design is that it can achieve very consistent dosages. This is because its inner pouch collapses in a safe and predictable manner that showcases a high repetition rate, so the contained fluid is always kept at the same height as the volume of the inner pouch decreases. This guarantees even dosages throughout the entire device lifecycle up to the last drop, without any propellant.

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Looking ahead, the continued evolution of inhaler technology is set to transform patient outcomes in the respiratory sector and far beyond. Particularly as the development of biologics gathers pace, with ever more manufacturers expected to consider patient-friendly inhaler technologies such as SMIs, the availability of reliable container closure systems with precise dosage control and exceptional barri er properties cannot be underestimated. With decades of experience, proven technologies and a history of innovation, GAPLAST is poised to deliver the cartridge solution these companies need to help their patients breathe easy.

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