

Soft Mist Inhalers: Enabling the Next Generation of Complex Inhaled Therapies

The inhaled medicines pipeline is changing, expanding from conventional small molecules towards proteins, peptides, nucleic acids and other complex therapeutics.

Pulmonary delivery could broaden the opportunities for complex therapeutics, supporting both local treatment in the lung and systemic delivery.

New therapeutics require new approaches to delivery. Preserving drug integrity through storage, aerosolisation and administration is becoming as important as generating the right aerosol and achieving efficient lung delivery.

Delivery technology is therefore becoming an early strategic development choice. Soft mist inhalers are particularly well positioned to address these emerging requirements and potentially enable the next generation of complex inhaled therapies.

Emerging Opportunity for Pulmonary Delivery of Biologics

Pulmonary delivery of biologics is moving beyond recombinant proteins towards a broader range of therapeutic modalities with five biologics currently approved for direct airway delivery.¹ Specifically, inhaled genetic medicines is emerging with multiple programmes exploring mRNA and viral-vector approaches for cystic fibrosis (CF) and primary ciliary dyskinesia (PCD).²

While growth in biologic therapies remains dominated by injectable products, pulmonary delivery offers an attractive alternative for selected biologics, enabling both direct treatment of the respiratory tract and systemic delivery. The lung's large surface area, thin epithelial barrier and extensive vascular network can support rapid absorption while bypassing gastrointestinal degradation and first-pass hepatic metabolism. As the broader biologics pipeline is predominantly formulated as liquids, liquid inhalation appears to be a natural route, also reflected by in 79% of current inhaled biologic programmes using nebulised delivery.^{2,3}

Yet pulmonary administration brings its own challenges. Formulation stability, aerosol generation, device compatibility, dose delivery and regional deposition are closely interconnected, and a biologic stable in its primary container may not retain its integrity during aerosolisation. For advanced biologics, the delivery system should therefore be considered an integral part of therapeutic development rather than a downstream device or packaging decision.

New Therapeutics Demand New Delivery Technologies

Biologics place specific demands on delivery: proteins are susceptible to aggregation, denaturation and degradation, while mRNA-LNP formulations require preservation of both the nucleic acid payload and nanoparticle structure.^{3,4} The choice of formulation and delivery technology is therefore closely linked. Dry-powder approaches may improve stability but introduce mechanical and thermal stresses during processing, while liquid delivery avoids some of these steps but requires careful control of stability, sterility and aerosolisation compatibility.

Device selection consequently becomes part of the formulation strategy. The challenge is not simply to generate a respirable aerosol, but to do so while preserving integrity and biological function. For complex biologics, delivery technology is an early development choice with consequences for formulation, CMC and programme progression.

Low-Shear Aerosolisation Becomes a Critical Quality Attribute

For sensitive mRNA-LNP and other nano-

particle formulations, aerosolisation must generate a respirable aerosol while minimising mechanical and interfacial stresses that can disrupt the carrier and compromise the encapsulated payload.⁵ Soft mist inhalers offer an attractive alternative to conventional nebulisation, with the aerosol-generation mechanism playing an important role in preserving formulation integrity. Colliding-jet systems such as Respimat® form droplets through impinging liquid jets, whereas Rayleigh-based systems such as the Resyca PFSI® exploit the natural instability of micron-scale liquid jets to generate the aerosol.^{5,6}

These fundamentally different aerosol-generation mechanisms also differ in the energy and mechanical stress imparted to the formulation. High aerosolisation energy has been associated with increased lipid-carrier disruption, loss of encapsulated material and mRNA degradation, while low aerosolisation energy such as for Rayleigh breakup has shown improved preservation of nanoparticle size, encapsulation, mRNA integrity and biological functionality compared with the other nebuliser and SMI technologies (Figure 1).⁷⁻⁹

Current evidence remains predominantly *in vitro* and formulation-specific, but as payloads become more complex and sensitive, aerosolisation stress should be considered. Device performance must therefore extend beyond aerosol characteristics: the relevant question is not only whether a device produces the required aerosol, but whether it preserves and delivers the functional therapeutic. Low-energy Rayleigh breakup offers a promising approach where biologic and nanoparticle integrity is critical.

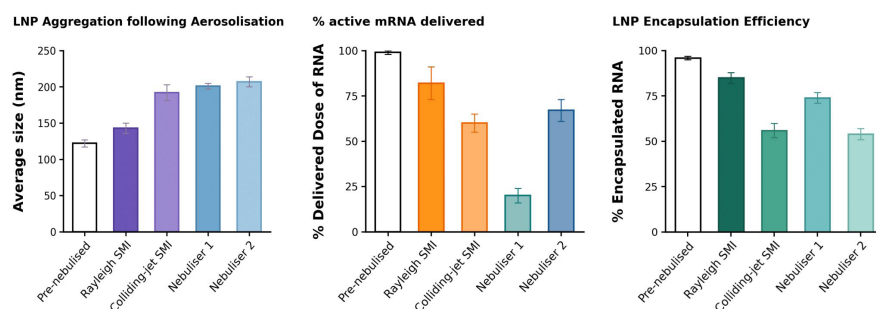


Figure 1: Impact of aerosol-generation mechanism on the integrity and biological functionality of sensitive mRNA-LNP formulations. Comparison of LNP aggregation, mRNA delivery and encapsulation efficiency following aerosolisation using Rayleigh- and colliding-jet SMIs and nebuliser technologies. Adapted from.⁷

Sterile Primary Packaging and Drug Product Compatibility

Preserving biologic integrity extends beyond aerosolisation to storage and administration, making primary packaging an integral part of the delivery-system strategy. Biologics typically require sterile, well-characterised container-closure systems and are often preservative-free, with established formats such as vials and prefilled syringes (PFS) supported by extensive development experience and supply chains. Transferring these products into a dedicated inhalation reservoir can introduce additional compatibility, stability and fill-finish requirements.

One approach is to integrate an established sterile primary container directly into the inhaler, serving as both primary container and drug reservoir. In a PFS-based SMI, a sterilised prefilled syringe can connect directly to the aerosol-generation system through a closed fluid path designed to maintain container-closure integrity (CCI). This minimises product transfer between fill-finish, storage and administration, while supporting refrigerated and frozen supply chains commonly used for biologics.

While this approach can simplify the drug-product pathway, product-specific stability, container-closure compatibility and extractables and leachables assessments remain essential. Building the SMI around established biologics packaging can avoid a bespoke inhalation reservoir and potentially reduce packaging-related development risk and complexity.

Manufacturing Scalability

Beyond simplifying drug-product architecture, primary packaging has important implications for manufacturing scalability.

Functional mRNA Delivery

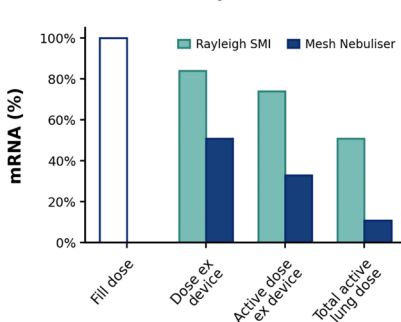


Figure 2: From fill dose to functional mRNA lung delivery. Illustration of how device output, mRNA integrity following aerosolisation and pulmonary deposition collectively determine the predicted functional mRNA dose delivered to the lung for Rayleigh SMI and mesh nebuliser technologies. Adapted from.¹¹

Emerging inhaled biologics often progress through early development with uncertain future demand, making investment in dedicated filling infrastructure, proprietary cartridges and inhalation-specific manufacturing processes a significant development and commercial risk.

A PFS-based SMI offers a different pathway by leveraging existing infrastructure. Prefilled syringes are widely established across the biologics industry, supported by global fill-finish networks, mature processes and scalable supply chains. Using the PFS as both primary container and inhaler reservoir allows drug-product manufacture and aseptic filling to remain within this infrastructure.

This allows the same primary packaging and manufacturing strategy to be maintained from early clinical development through commercial supply, preserving flexibility while avoiding unnecessary technology transfer or premature investment in inhalation-specific filling infrastructure. By leveraging proven biologics manufacturing infrastructure, developers can limit upfront investment, reduce scale-up risk and potentially shorten the path to commercial supply.

Platform Strategy: Balancing Standardisation and Adaptability

A successful device platform strategy balances standardisation with product-specific adaptation. While a common delivery platform can simplify development and manufacturing, different biologics require the delivery system to match the formulation, therapeutic target and deposition profile.

A configurable inhaler platform needs control beyond aerosol generation. Nozzle geometry and pore size should be tailored to droplet formation, while metered volume and spray duration should be adaptable to the required dose. Equally important is the interaction between aerosol and patient. Built-in airflow resistance can passively guide patients towards a more consistent, slow and deep inhalation, reducing patient-to-patient variability and supporting high lung deposition, as demonstrated in studies with different SMI flow resistances.¹⁰

When these parameters are optimally configured, delivery efficiency becomes more than the fraction of drug leaving the device. For complex biologics, the relevant measure is the functional drug reaching the intended lung region. mRNA modelling illustrates this principle, showing how device output, post-aerosolisation integrity and lung

deposition together determine the predicted functional lung dose (Figure 2).¹¹ Optimising this functional lung dose, rather than aerosol performance in isolation, should therefore be a central consideration in developing delivery systems for complex inhaled biologics.

Patient-Centricity and Real-World Use

Optimising functional lung delivery is only valuable if patients can reproduce it in everyday use. Poor inhaler technique, including insufficient inspiratory effort, actuation-inhalation coordination and inconsistent handling, remains an important source of dosing variability, particularly among elderly and paediatric patients and those with respiratory impairment. This is especially relevant for complex biologics, which are often high-value products and may require relatively high delivered doses, making it important to minimise losses and reliably deliver functional drug to the lung.

SMIs are well suited to these challenges. They are compact, portable devices that generate aerosol mechanically rather than relying on inspiratory energy or external power. Their slow-moving, long-lasting aerosol cloud reduces the need for precise actuation-inhalation coordination. Combined with passive flow guidance, these characteristics can reduce dependence on patient technique to support more reproducible lung delivery. These characteristics can also support broader patient-centric design, combining convenient handling and efficient drug use with options such as reusable devices and replaceable drug cartridges to reduce material consumption. For next-generation inhaled therapies, patient-centricity should therefore encompass not only consistent administration, but also portability, efficient use of valuable drug product, affordability and environmental impact.

Regulatory Perspective

Taken together, these interactions between drug product, delivery technology and patient use make the delivery platform an important development and regulatory decision for complex inhaled biologics. Developers may need to demonstrate not only consistent aerosol performance and dose delivery, but also that formulation, primary packaging and aerosolisation preserve critical quality attributes and biological functionality throughout storage and administration, without changes that could affect safety or immunogenicity.

This makes early integration of the biologic and delivery system important. Formulation,

primary packaging and device performance need to be developed together, with attention to stability, sterility, compatibility and preservation during aerosolisation. Identifying these requirements early can reduce the risk of later changes that trigger additional development, manufacturing or regulatory work.

A platform-based SMI approach can help manage this complexity. Established sterile primary packaging, low-energy aerosol generation and a configurable device architecture can provide a common technical foundation across biologic products. Using the same platform from clinical development through commercial supply can reduce the need for changes in primary packaging or delivery technology as a programme progresses. While product-specific regulatory evidence remains necessary, established platform knowledge and manufacturing processes may be leveraged across programmes, reducing technical risk and unnecessary redevelopment.

Looking Ahead

The next generation of inhaled therapies will place different demands on delivery technology. As pulmonary development expands from small molecules towards biologic therapeutics, success will increasingly depend on preserving the drug product while providing efficient, reproducible and patient-friendly administration.

This changes the role of the inhaler. the delivery platform becomes an integral part of the therapeutic product and should be considered from the outset. Soft mist inhalers are well positioned in this landscape. Their compatibility with liquid formulations, mechanically generated aerosols and compact handheld delivery provides a strong foundation for complex therapeutics. Platforms combining these characteristics with low-energy aerosolisation, established sterile primary packaging and adaptable delivery parameters can extend the range of biologics suitable for pulmonary administration (Figure 3).

Ultimately, the opportunity is not simply to develop a better inhaler, but to enable therapies that would otherwise be difficult to deliver effectively through the lung.

REFERENCES

- Giri N et al., Pulmonary delivery of biologics: a literature review. *Drugs*. 2026; 86:1187-1229.
- Shaibie NA et al., Inhaled biologics for

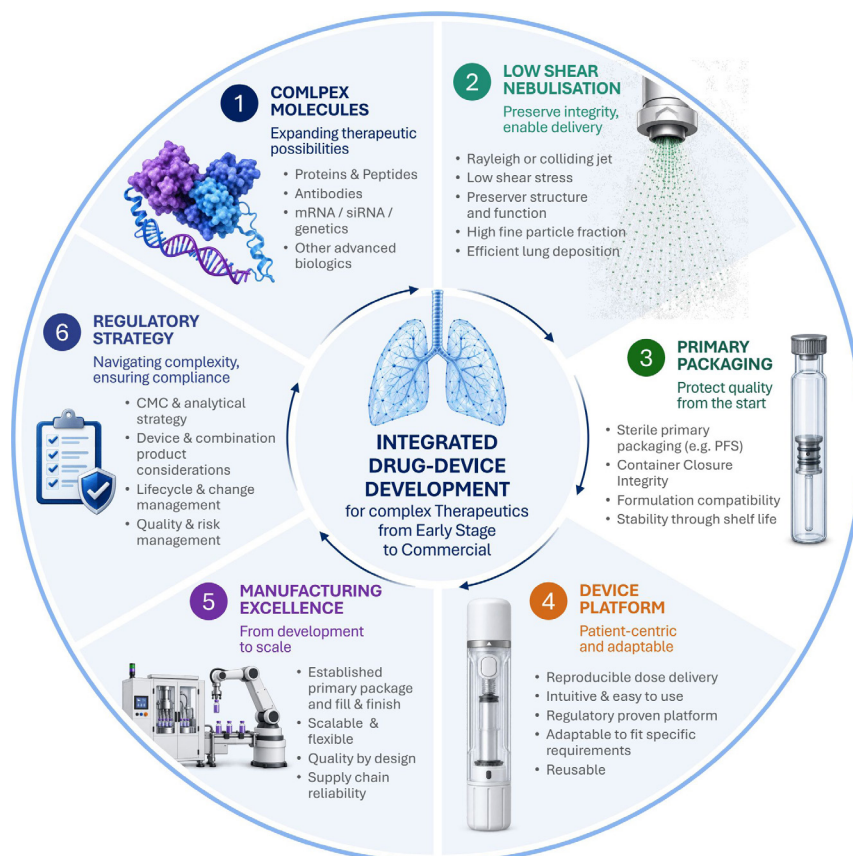


Figure 3: Integrated drug-device development for complex inhaled therapeutics. Bringing molecule, aerosolisation, packaging, device, manufacturing and regulatory strategy together from early development to commercialisation.

respiratory diseases: clinical potential and emerging technologies. *Drug Deliv Transl Res*. 2025;15:4098-4114.

- Cipolla D et al., Inhalable and Nasal Biologics: Analytical, Formulation, Development, and Regulatory Considerations. *J Aerosol Med Pulm Drug Deliv*. 2025;38(5):284-303.
- Matthews AA et al., Developing inhaled protein therapeutics for lung diseases. *Molecular Biomedicine*. 2020; 1(11).
- van Rijn CJM et al., Low energy nebulization preserves integrity of SARS-CoV-2 mRNA vaccines for respiratory delivery. *Scientific Reports*. 2023;13:8851.
- Komalla et al., Advances in soft mist inhalers, Expert Opinion on Drug Delivery. 2023; 20(8).
- He P et al., Rayleigh-based soft mist inhalers preserve mRNA-LNP integrity for pulmonary delivery. *J. Drug Delivery Science and Technology*. 2026; 115.
- Biesel A et al., Soft mist inhaler nebulization by Rayleigh-breakup largely preserves functional integrity of liposomal mRNA in respirable aerosols. *European J. Pharmaceutical Sciences*. 2025;214.
- Klein et al., Degradation of lipid based drug delivery formulations during nebulization. *Chemical Physics*. 2021;547.
- Buchmann NA et al., Influence of device flow resistance on inhalation manoeuvre and predicted lung deposition using a soft mist inhaler. *Respiratory Drug Delivery (RDD)*. 2024.
- Sibum I et al., A device screening method

for predicting delivery of inhaled mRNA via a nebuliser. *Drug Delivery to the Lungs (DDL)*. 2023; 34:170-173



Dr. Nicolas Buchmann

Nicolas Buchmann is Chief Technology Officer at Resyca B.V., where he leads the development and commercialisation of advanced technologies for inhaled and nasal therapies. With a background in aerosol physics and pulmonary drug delivery, his work focuses on translating innovative aerosol-generation and device technologies into practical drug-device combination products, with particular expertise in soft mist technologies, inhalation systems and complex-molecule delivery. He has held senior technology and development roles at Vectura, PARI and Resyca and has authored more than 60 scientific publications spanning inhalation science, aerosol delivery and fluid dynamics.