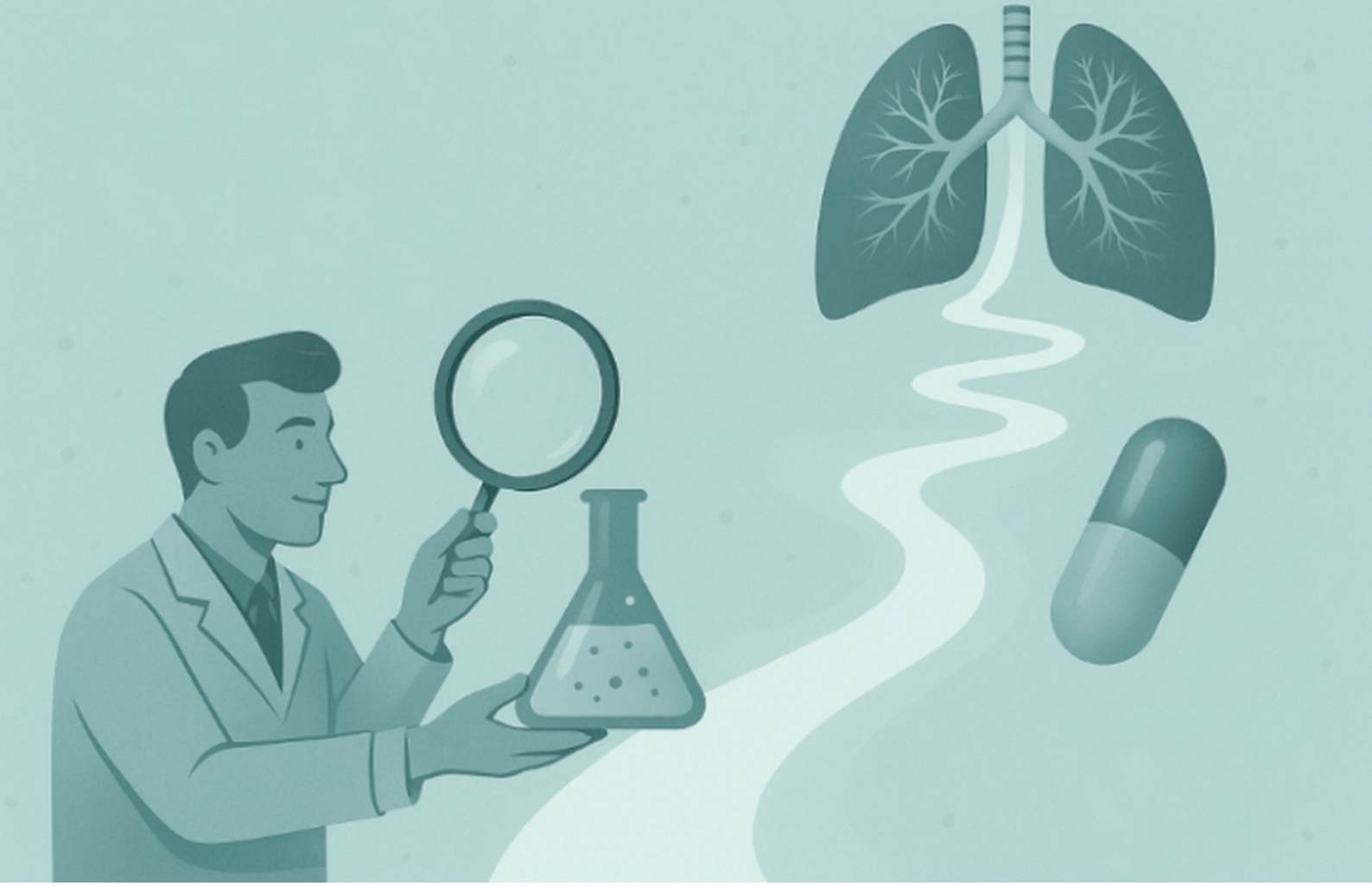

CHARTING THE COURSE FOR PULMONARY DRUG DEVELOPMENT

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Carolyn Berg and **Dr Alan Watts** of **Catalent** examine strategy considerations that can help emerging biotech companies navigate early-stage pulmonary drug development, providing practical guidance for addressing challenges of respiratory delivery and avoiding common pitfalls that can derail development programmes.

The pulmonary drug delivery landscape has evolved over the past quarter century. Once a specialised field focused almost solely on asthma and chronic obstructive pulmonary disease therapeutics, the sector has now expanded to encompass 440 active development programmes worldwide, 60% of which are in preclinical or Phase I stages (according to data from Pharmaprojects). This growth reflects both technological advancement and a reconsideration of the respiratory tract as a delivery route for a diverse range of therapeutic applications.

Notably, over 70% of pulmonary development programmes now come from emerging biotech companies. However, these organisations are often inexperienced in the development of inhalation products and face challenges navigating the complexities and regulatory requirements specific to this delivery route. The pipeline has also shifted from traditional respiratory indications to novel therapeutic areas, with large molecules now making up 40% of development candidates, introducing additional formulation and delivery challenges.

For emerging companies entering this specialised field, the development pathway presents critical decision points with far-reaching implications. Unlike oral solid-dose products, pulmonary delivery requires early commitment to both formulation platform and device technology. These decisions, made with limited clinical data, establish constraints that impact manufacturing scalability, regulatory strategy and commercial viability.

CHALLENGES OF EARLY-STAGE PULMONARY DRUG DEVELOPMENT

Early-stage pulmonary drug development presents distinct technical and strategic challenges that differentiate this field from other administration routes. Unlike conventional oral formulations, inhalation products require consideration of multiple interdependent variables:

- The API's physicochemical properties
- Formulation approach
- Aerosol delivery system
- Human factors.

These elements must function synergistically to achieve consistent, reproducible delivery to the targeted respiratory tract region.

For emerging biotech companies, development is further complicated by resource constraints and the need to make critical platform decisions with limited data. The traditional pharmaceutical development paradigm, where formulation decisions can often be deferred until Phase II, is not applicable to pulmonary delivery. Early choices regarding particle engineering approach, excipient composition and device platform create cascading effects throughout the development timeline. As development programmes advance, resistance to change rapidly increases with both time and invested capital, making formulation or device pivots progressively more difficult and costly to implement.

The target product profile (TPP) is an essential strategic framework for managing this complexity. Rather than allowing available technical capabilities to drive product design decisions, successful development programmes begin with the end in mind, visualising the final product in the patient's hands and working backwards to define development requirements. This approach enables teams to balance patient needs against molecular constraints while maintaining focus on commercial viability and manufacturability.

The material requirements for early development introduce another dimension of complexity. While many emerging companies possess the capabilities and budget for producing small-scale API batches (≈50 g), which is sufficient for initial feasibility studies, progression to good laboratory practice inhalation toxicology studies demands 0.5–2.0 kg of material. This represents not merely a scale-up challenge but a major financial inflection point that many companies underestimate. Development teams are often surprised when they first realise the magnitude of material required for regulatory-enabling studies, which typically exceeds their combined Phase I and II trial requirements.

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Investment in chemistry, manufacturing and controls (CMC) development warrants particular emphasis in early-stage planning. While financial pressures often drive companies to defer CMC investments until clinical proof-of-concept is established, early CMC investment can lead to a more straightforward approach in later development stages. Establishing robust analytical methods, identifying critical quality attributes, justifying and optimising excipient levels, and understanding manufacturing constraints early can help to prevent costly delays and reformulation further down the line.

CRITICAL DECISION POINTS IN PULMONARY DRUG DEVELOPMENT

The progression through early-stage pulmonary drug development is characterised by several critical decision points that can fundamentally alter the trajectory of a development programme. Understanding when these inflection points occur – and their downstream implications – can enable development teams to allocate resources effectively and mitigate development risks.

The initial feasibility assessment represents the first major decision point, where developers must evaluate whether their molecule's intrinsic properties align with pulmonary delivery requirements. This evaluation extends beyond basic solubility and stability parameters to encompass the broader question of dose quantity and their compatibility with inhalation constraints. With patient comfort and device capabilities generally limiting single inhalation doses to approximately 50 mg of powder or 10 mL of liquid, high-dose compounds may face insurmountable delivery challenges regardless of formulation sophistication or device performance.

Device platform selection constitutes perhaps the most consequential early decision, as it influences virtually every subsequent development activity from formulation approach to clinical trial design. The selection between device types, such as dry powder inhalers, nebulisers or metered dose inhalers, must balance multiple factors:

- Anticipated dose range
- Target patient population characteristics
- Stability requirements
- Manufacturing complexity.

Each device platform presents distinct advantages and limitations that must be carefully evaluated against the specific requirements of the development programme and TPP.

Formulation strategy decisions carry particular significance in pulmonary development due to the limited list of excipients in approved products and the stringent safety requirements for respiratory delivery. Formulation should be kept as simple as possible while achieving the desired performance and stability. Any changes become progressively more difficult to implement as development programmes advance through clinical phases.

The timing of technology transfer and scale-up activities is also important. While maintaining internal control over

early development offers maximum flexibility, the specialised equipment and expertise required for inhalation product manufacturing often necessitates external partnerships. Determining when to engage a CDMO, and which capabilities to transfer to them, requires careful consideration of both immediate development needs and long-term strategic objectives.

Analytical methods used during clinical development should be phase-appropriate – they should be qualified for early clinical work and will require full ICH validation in later stages. The unique performance requirements for inhalation products demand resource-intensive methods to determine aerodynamic particle size distribution and delivered dose uniformity – and should follow compendial requirements. These methods are used to characterise the ability of the API to target the lungs effectively and are used not only to support formulation development but also to allow for meaningful comparisons across batches and manufacturing scales.

Unlike clinical trials for oral products, where dose escalation can be achieved by simply administering additional tablets or capsules, inhalation products may require reformulation or device modifications to accommodate different dose levels. This reality necessitates careful planning of Phase I studies to generate sufficient dose-ranging data while minimising the need for subsequent formulation changes.

The commitment to specific manufacturing processes and equipment represents a particularly important inflection point with long-term implications. While laboratory-scale processes may use equipment and techniques that do not scale efficiently, early commitment to scalable technologies can obviate the need for costly process redesigns later in development. This consideration becomes especially critical for the specialised manufacturing approaches common in pulmonary product development, such as spray drying, jet milling and coarse lactose blending.

THE DOSE DILEMMA: MANAGING UNCERTAINTY IN PULMONARY DRUG DEVELOPMENT

The challenge of dose determination in pulmonary drug delivery represents one of the most significant paradoxes in pharmaceutical development. This fundamental uncertainty – dose ranges can span a 10–100-fold range in early development – creates cascading complications throughout the development process that require strategic management.

Unlike systemic delivery routes, where pharmacokinetic modelling can provide reasonable dose predictions, pulmonary delivery introduces multiple variables that confound traditional approaches. The site of action – whether topical within the lung, systemic via pulmonary absorption or targeted to specific lung regions – dramatically influences dose requirements. Local delivery for respiratory conditions may achieve therapeutic effects with microgram quantities, while systemic delivery through the lung might require doses approaching tens of milligrams or more, pushing the boundaries of what can be practically delivered via inhalation.

The relationship between nominal dose, lung deposition and therapeutic effect adds layers of complexity unique to inhalation products. Device efficiency, patient inspiratory patterns and formulation properties collectively determine what fraction of the nominal dose actually reaches the target site. A formulation delivering 20% of the nominal dose to the lung might be acceptable by historical industry standards; however, such a five-fold difference between nominal and delivered dose must be accounted for in all development activities from analytical method development to manufacturing scale considerations. On the other hand, particle engineering approaches or advanced breath-synchronised devices are capable of delivering upwards of 60% of the nominal dose to the lungs.

Early-stage companies face particular challenges in generating the data necessary for informed dose selection. Traditional pharmacology studies in animal models are often poor predictors of human pulmonary delivery due to significant anatomical and physiological differences in respiratory tract architecture and breathing patterns. The expense and complexity of conducting early in-human studies with inhalation products, which require specialised clinical facilities and equipment, may delay acquisition of critical dose-ranging data until significant investment has already been committed to specific formulation and device approaches.

The manufacturing implications of dose uncertainty extend beyond simple batch size calculations to impact fundamental process design decisions. Analytical method sensitivity, content uniformity requirements and process control strategies all depend on the target dose. A product delivering 10 µg per actuation demands different analytical sensitivity and extraction approaches than one delivering 10 mg. Early investment in analytical methods spanning the potential dose range can help to avoid delays when clinical data clarify actual requirements.

The interplay between dose and formulation strategy creates additional complexity that must be addressed early in development. Low-dose products often require carrier particles or other bulking agents to ensure consistent delivery and handling properties. High-dose products, on the other hand, may push the limits of what patients can comfortably inhale, necessitating careful optimisation of powder properties to minimise the inhaled volume while maximising delivery efficiency. The practical limit of approximately 50 mg for a single inhalation creates hard constraints that must be considered even in early feasibility assessments.

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Regulatory expectations for dose justification in pulmonary products adds another dimension to the challenge. While systemic products might support dose selection through pharmacokinetic and pharmacodynamic modelling, inhalation products often require direct clinical evidence of dose-response relationships. This expectation creates pressure to explore multiple doses in early clinical studies, multiplying formulation development requirements and extending timelines.

PRACTICAL GUIDANCE FOR EMERGING BIOTECH COMPANIES

For emerging biotechnology firms entering the field of pulmonary drug development, achieving success necessitates not only technical proficiency but also strategic decision-making and prudent resource management. Based on Catalent's experience supporting numerous development programmes from concept through commercialisation, it can offer the following practical guidance for navigating this challenging but rewarding field.

Build Strategic Partnerships

Recognise that pulmonary product development requires specialised expertise and infrastructure that few emerging companies can efficiently maintain internally. Therefore, it is important to identify partners with proven track records in inhalation product development and manufacturing. Look for organisations that understand the unique challenges of respiratory delivery and can provide guidance beyond simple contract services. Structure agreements to maintain flexibility as clinical data emerge, allowing for technology changes if findings demand adjustments to the development approach.

Understand Regulatory Expectations

Pulmonary products face unique regulatory requirements that differ from other delivery routes. Early engagement with regulatory authorities and experts in inhalation product development can help to clarify expectations and avoid costly missteps. Consider that demonstration of local delivery may require different approaches than for systemic delivery, and plan studies accordingly. Regulatory agencies typically expect direct clinical evidence of dose-response relationships for inhalation products, creating pressure to explore multiple dose sizes in early clinical studies.

Manage Investor Expectations

Educate investors about the unique challenges and timelines associated with pulmonary development. The need for early device selection and formulation commitment differs from oral product development patterns. Help stakeholders understand that apparent delays for technology development actually reduce overall programme risk and development time. Be transparent about the material requirements for toxicology studies and the financial implications of scale-up activities required before clinical proof of concept.

Learn from Others' Mistakes

There are numerous examples of development programmes within the pulmonary field that failed due to preventable errors. Study these cases to understand common pitfalls. Development programmes typically struggle when they underestimate material requirements, overcommit to narrow technology choices or assume that pulmonary delivery follows oral development paradigms. The combination of a new molecule, new device and new manufacturing process can add unnecessarily high levels of risk. Developers should look to incorporate novel approaches only when it is necessary to enable the product.

CONCLUSION

The pulmonary route provides unique benefits for emerging biotech companies, allowing for targeted delivery of therapeutics or a means to rapidly deliver drugs systemically avoiding first-pass metabolism without the use of needles. Successful development requires careful navigation of technical challenges, strategic resource allocation and thoughtful partnership decisions. By understanding the unique requirements of respiratory delivery and avoiding common pitfalls, emerging companies can efficiently advance promising therapies that address significant unmet medical needs.

Carolyn Berg

Carolyn Berg, Vice-President of Business Development for Catalent's inhaled drug delivery solutions, has more than 25 years of experience in pharmaceutical sales, marketing and business development. Since 2021, she has been responsible for all commercial, strategic and sales efforts to develop and grow Catalent's inhalation business globally. Throughout her career, Ms Berg has produced a solid record of meeting sales and business targets through individual and team efforts.

T: +1 786 606 4276
E: carolyn.berg@catalent.com

Dr Alan Watts

Alan Watts, PhD, is Director of Technology & Innovation for Pulmonary and Nasal Products at Catalent. He has nearly 15 years' experience in the development of inhalation products in industrial and academic settings. Prior to Catalent, Dr Watts was Associate Director of Pharmaceutical Development for Savara Pharmaceuticals, leading combination product development, and Research Assistant Professor at the University of Texas at Austin (TX, US), where he oversaw an aerosol research lab, taught pharmacy courses and co-invented a novel dry powder inhaler platform. Dr Watts has a PhD in Pharmaceutics from the University of Texas at Austin and a BS in Biomedical Engineering from Louisiana Tech University (LA, US).

T: +1 512 689 2982
E: alan.watts1@catalent.com

Catalent Pharma Solutions
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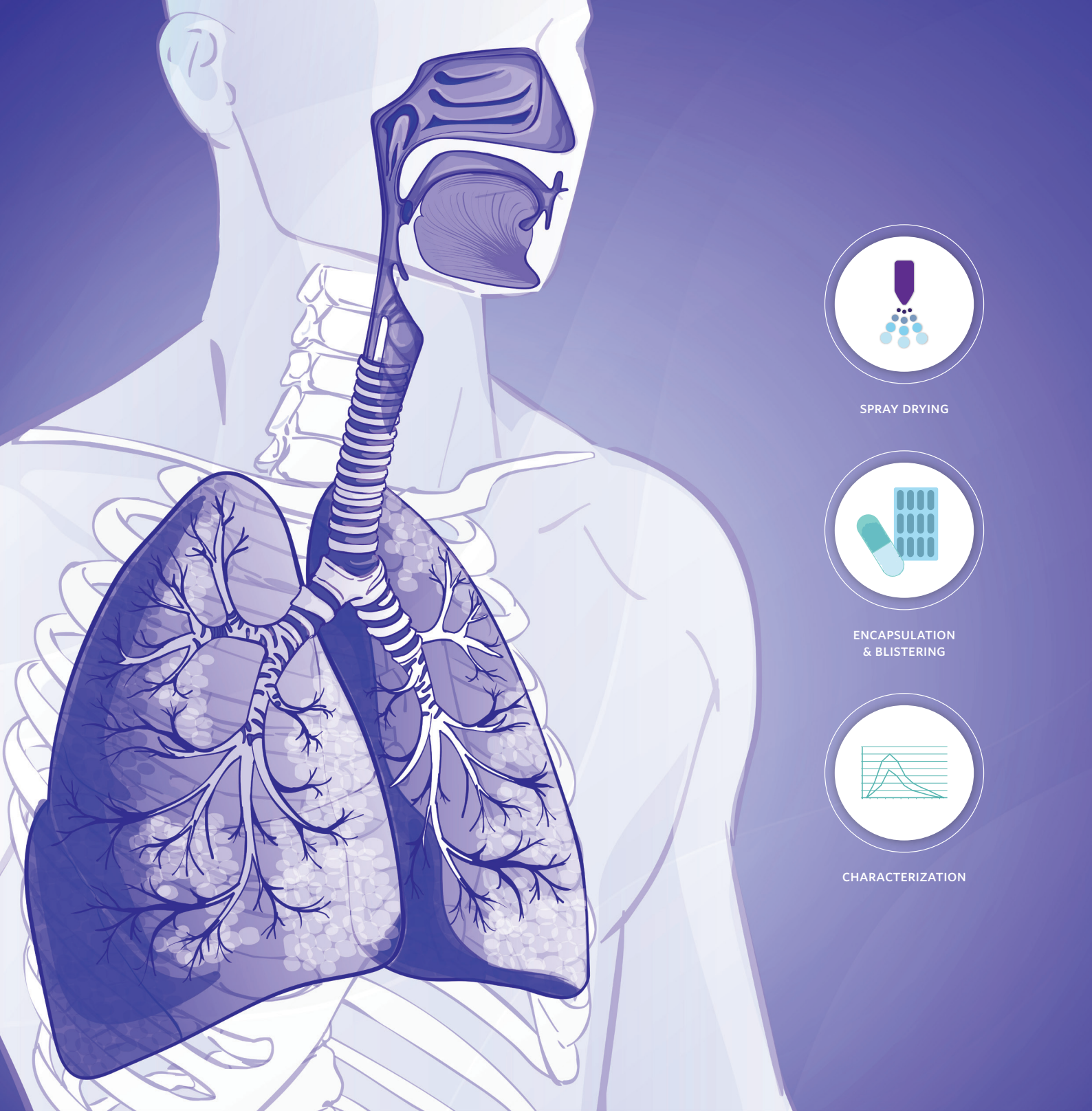
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