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SMART SCALING FOR SUCCESSFUL CAPSULE-BASED DRY POWDER INHALER FILLING USING DRUM TECHNOLOGIES

In this article, Carolyn Berg, Vice-President, Business Development, William Chin, PhD, Manager, Global Scientific Affairs, and Patrick Goncalves, Account Executive, Business Development, all at Catalent, discuss the considerations for filling capsules for dry powder inhalers across the various stages of clinical trials and commercialisation, and how to tackle the challenges of scaling up filling processes.

Over the past two decades, the field of respiratory medicine has undergone significant growth and evolution. What was once a focus on developing drugs to treat asthma and chronic obstructive pulmonary disease (COPD) has expanded to include a range of therapy areas, including the respiratory, anti-infective, neurological and cardiovascular sectors, among others (Figure 1). According to industry clinical trial databases, nearly 100 molecules for respiratory delivery are currently in the clinical development pipeline, spanning from preclinical to Phase III stages, for both pulmonary and non-pulmonary indications.[1]

The growing interest in targeting the lungs as a viable drug delivery route reflects the potential of this approach to improve the treatment of a wide range of diseases.

By targeting the lungs directly, the pulmonary route of administration can minimise the systemic side effects often associated with other delivery methods. Traditionally, large doses of inhaled drugs have been administered by nebulisers. However, these devices are inconvenient for patients, as they are bulky, noisy, require a power source and have a longer administration time than other inhalation devices.[2] On the other hand, dry powder

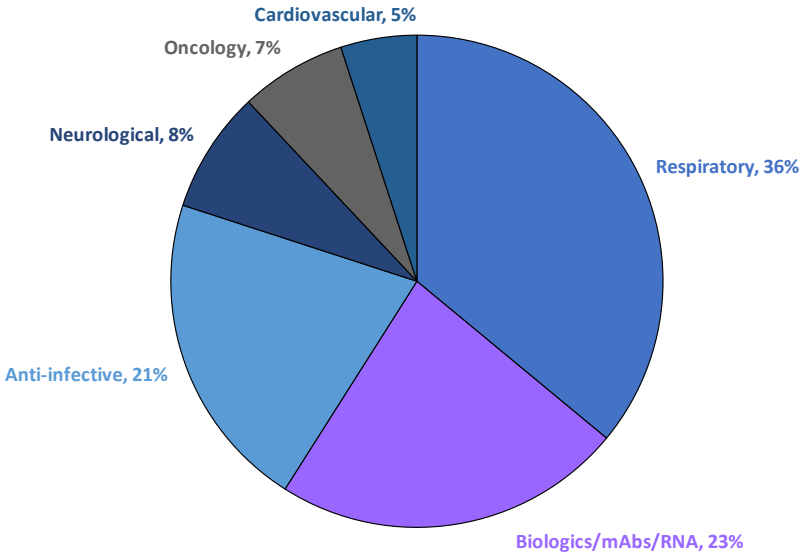

Figure 1: Pulmonary drug delivery sector by therapy area. Pulmonary delivery is a growing field with the potential to revolutionise the treatment of a wide range of diseases. (Source: Catalent's internal research on PharmaProjects database, 2022.)

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inhalers (DPIs) are easy to use and their propellant-free design makes them a safe and convenient choice for individuals across age groups. DPIs are based on the concept of a dose metering system that delivers a determined dose to the patient.

Various dose metering systems, such as single-dose capsule-based DPIs (sDPIs), blister-based devices and reservoir-based devices, each offer unique advantages and challenges.[3] Furthermore, they provide a good delivery method by offering targeted lung delivery with reduced side effects.[4] While blister- and reservoir-based systems offer advantages for specific applications and patient needs, sDPIs are generally considered to be the most versatile and user-friendly type of DPI due to two important factors:

1. Different-sized capsules, ranging from Size 00 to Size 3, can be used.
2. Different fill weights per capsule can be achieved, depending on the manufacturing technique of the powder and the variability of the fill weight per capsule.

Typically, sDPIs devices use a capsule containing the drug product, which is punctured to release the drug upon inhalation. Most inhalable drugs in development use hydroxypropyl methylcellulose (HPMC) capsules due to their high moisture barrier and lower risk of breakage upon puncture, thereby ensuring effective drug release.

However, manufacturing sDPIs presents its own set of challenges, including meticulous control over capsule materials and dimensions, as well as powder characteristics. The capsule's design must facilitate puncturing with a specific force and ensure uniform powder release. The performance also depends on the capsule's material, the inhaler design and the powder formulation contained within. This last point is the most crucial, as the flow characteristics of the powder can vary depending on the type of powder formulation. Each type of powder, whether it be a blended, carrier-based product with micronised drug or an engineered particle obtained through spray drying, has a unique set of rheological properties that can have a significant impact on the downstream manufacturing processes involved in capsule filling.[5]

Feature	Drum Filling	Dosator-based Filling
Principle	• A rotating drum with dosing cavities is filled with powder and then rotated to transfer the powder into the capsules • A vacuum can be used to draw powder into the dosing cavities	• A dosator, which is a precision metering device, is used to dispense powder into the capsules
Dosing range	• 1–50 mg	• 10–600 mg
Accuracy	• Very high with low variability; usual RSD < 3%	• Not as high as drum filling, influenced by high concentration of fines
Flexibility	• Can fill low doses; depends on dosing bore and vacuum • Fill weight can be slightly adjusted by vacuum setting to overcome batch-to-batch variations	• Can compact and retain powder in the pin for transfer • Fill weight can be adjusted by compaction force and pre-positioning of compaction pin
Powder characteristics	• Better for flowable powders • Arching in hopper can occur • Suitable for extremely cohesive powders • Particle size from 1 µm upwards with Carr's Index of 30% and higher	• Can handle hydrophilic powders with increased cohesiveness • Challenging when filling large particles with excellent flow behaviour • Plug formation issues • For powders with a Carr's index between 15 and 25% • Particle size ideally in the range of 50–150 µm
Equipment complexity	• Requires vacuum and specific dosing bore; typically higher equipment cost	• Requires plug formation and compaction in the pin; medium equipment cost
Residual volume	• Less, approximately 50 mL	• Higher than drum filling, approximately 200 mL

Table 1: Comparison of drum filling and dosator-based filling for sDPIs.

FACTORS TO CONSIDER WHEN SELECTING CAPSULE-FILLING TECHNOLOGY FOR DPIs

When it comes to filling capsules for DPIs, there are two primary methods to choose from – drum filling and dosator-based filling. It is important to determine which dosing system is most suitable for the given powder formulation as early as possible during product development so as to reduce the risk of needing to change the manufacturing process during clinical trials and commercialisation.

Drum filling is a method that uses a rotating drum to transfer powder into the capsules, with a vacuum capability to draw in the powder. On the other hand, dosator-based capsule filling uses a precise metering device called a dosator to dispense the powder into the capsules. Both filling methods are highly accurate, but drum filling has an edge over dosator-based filling due to its superior accuracy. Drum filling has also proved to be very robust across a range of powder properties,[6] making it a reliable option for precise dosing, especially for high-dose formulations. Additionally, drum filling is suitable for low-potency, high-dose drugs.[7] Both methods can fill a wide range of capsule sizes and formulations, but dosator-based filling has some limitations compared with drum filling (Table 1).

Molecule	Product	Company	Technology		
			Manufacturing	Filling	Device
Insulin	Exubera®*[2]	Nektar	Spray dried	Drum	Unit dose blisters Proprietary inhaler
Insulin	Afrezza®	Mannkind	Freeze-dried Technosphere®	Drum	Cartridge Dreamboat®
Treprostinil	Tyvaso DPI®	United Therapeutics & Mannkind	Spray dried	Drum***	Single-dose cartridge Dreamboat®
Levodopa	Inbrija®***[9]	Acorda	Spray dried	Drum (inferred)	Capsule Proprietary inhaler (pen device)
Tobramycin	Tobi®[10]	Novartis	Spray dried	Drum	Capsules Podhaler®

Withdrawn in 2007 for commercial reasons
**Original patents suggest dosator technology, but manufacturing facility supports drum technology*
****Uses same device and technology as Afrezza*

Table 2: Commercialised spray-dried inhalable powders.

Choosing between a dosator or a drum system for filling capsule-based DPIs with spray-dried powder depends on specific project needs and requirements. One key factor to consider is the flowability of the powder, as it determines which filling system is most suitable. Powders with a flow function coefficient (FFC) of less than four can be filled using a dosator system, while those with an FFC greater than four are more compatible with a drum system.[8] Another important consideration is the strength of the vacuum in the drum system, which has a significant effect on the fill weight. If there is a need to fill many capsules quickly and efficiently, vacuum-based drum filling is a good option. According to the data presented in Table 2, it can be observed that, in the case of most approved spray-dried products available in the market, drum-based filling is the prevalent technology used for capsule filling.

ADVANCED DOSING SYSTEMS FOR CAPSULE-BASED DPIs

Catalent's state-of-the-art facility is equipped with two advanced compact benchtop dosing devices – the Drum TT and Drum Lab – both of which are capsule-filling machines leveraging the latest drum dosing technology from Harro Höfliger (Allmersbach im Tal, Germany). The Drum TT, a compact manual filling machine, can be conveniently placed on any tabletop. It can precisely measure and fill as little as 0.5 mg of material into capsules within a short period of time. Additionally, it features a sophisticated pneumatic control system to regulate vacuum and compressed air. In the initial stages of clinical development, the Drum TT can be used to prepare galenic formulations for capsule-based DPIs. It is particularly useful for testing different powder formulations and optimising them for batch manufacturing.

The Drum Lab system is designed to semi-automatically dose small quantities of powder into capsules. This equipment is suitable for small-batch production, making it an ideal option for scaling up to a pilot scale. Additionally, this system also has an integrated check weighing system that ensures that the filled capsules meet the required weight criteria, resulting in more accurate dosing. Dose accuracy and weight checks are crucial from both a quality and operator standpoint.

From a quality perspective, it is vital to ensure that each capsule contains the correct amount of medication. Even a small variation in dose can significantly impact the medication's efficacy and safety. From an operator's perspective, dose accuracy and weight checks can help to reduce the time spent in manufacturing. By ensuring that each capsule meets the required weight criteria, operators can avoid having to rework or reject capsules.

Historically, contract development and manufacturing organisations (CDMOs) have had to send powders and capsules to external labs for testing, which could be a time-consuming process, taking several days or even weeks to receive results. However, with Drum Lab, CDMOs can perform dose accuracy and weight checks in-house, significantly reducing the time required to develop and launch new products.

The Drum TT and Drum Lab are highly versatile systems that can fill capsules, as well as other customised containers or cartridges, for use in proprietary devices that may be in development. Both systems are capable of dosing blended and spray-dried powders with ease. The Drum TT and Drum Lab systems can be used in various scenarios, such as preparing small batches of a blended powder formulation for clinical trials or dosing spray-dried powder formulations for commercial production.

The Catalent facility also includes a Harro Höfliger Omnidose powder-filling machine, a versatile semi-automatic machine that can fill capsules with high precision. It is ideal for pharmaceutical companies working on DPI formulations, whether for new developments or scaling existing products. The Omnidose can be easily adjusted to handle different types of powders, making it an excellent tool for prototyping and developing new DPIs, while ensuring accurate powder filling in each capsule, which is crucial for the safety and efficacy of DPIs.

Furthermore, the design of the machine is scalable to meet the production-level demands of pharmaceutical companies. For larger quantities of powders, the Harro Höfliger Modu-C MS high-speed filling machine is capable of manufacturing up to

"One of the significant challenges in the process is scaling up capsule filling for clinical trials, which requires comprehensive planning and execution."

100,000 capsules per hour. This advanced equipment can encapsulate a wide range of powders at kilogram scale, is capable of filling doses as low as 0.5 mg and is particularly useful for highly cohesive products, such as spray-dried formulations. The Modu-C MS also includes the inline capsule de-duster, 100% net weighing via a capacitive advanced mass measurement sensor for minimal quantities dosing and containment systems. The high-speed and high-volume capabilities of Modu-C MS can provide an efficient pathway to commercial production.

INTEGRATED SCALE-UP PATH

Developing sDPIs is a complex process that demands careful consideration and execution. One of the significant challenges in the process is scaling up capsule filling for clinical trials, which requires comprehensive planning and execution. During different phases of clinical trials, the number of capsules needed may vary significantly. It has been proven that scaling up drum filling is feasible, and the sDPI development process can be easily scaled up from Drum TT, Drum Lab and Omnidose to Modu-C MS. The Modu-C MS is designed to be compatible with the same dosing and filling systems used on the Omnidose, ensuring that the scale-up process is as seamless as possible. This makes it quick and simple to transfer the existing process parameters. This integrated scale-up path can help pharmaceutical companies accelerate the development and launch of new sDPI products while maintaining the highest quality and consistency at all production scales (Figure 2).

CONCLUSION

The development and manufacture of sDPIs present a multifaceted challenge that spans material selection, device design, powder formulation and filling technologies. Drum filling emerges as a superior method for capsule filling, offering high accuracy and speed, particularly beneficial for high-dose formulations. Catalent's advanced dosing systems, including the Drum TT, Drum Lab, Omnidose and Modu-C MS, provide an integrated and scalable solution for sDPI development, from early-stage clinical trials to commercial production. To overcome the challenges associated with scaling up capsule filling, pharmaceutical companies can partner with a CDMO, such as Catalent, that has the necessary equipment and expertise to manage complexities, ensure quality and navigate regulatory requirements. By gaining access to this specialised knowledge and experience, pharmaceutical companies can de-risk the scale-up process and maximise the chances of commercial success. Partnering with a CDMO can mitigate the risks associated with scaling up and expedite time to market, ensuring both quality and commercial viability.

ABOUT THE COMPANY

Catalent (NYSE: CTLT) is a global leader in enabling pharma, biotech and consumer health partners to optimise product development, launch and full lifecycle supply for patients around the world. With broad and deep scale and expertise in development sciences, delivery technologies and multi-modality manufacturing, Catalent is a preferred industry partner for personalised medicines, consumer health brand extensions and blockbuster drugs. Catalent helps accelerate over 1,500 partner programmes and launch over 150 new products every year. Its flexible manufacturing platforms at over 50 global sites supply approximately 70 billion doses of nearly 8,000 products annually. Catalent's expert workforce of nearly 18,000 includes more than 3,000 scientists and techncians. Headquartered in Somerset, New Jersey, the company generated nearly US$4.3 billion (£3.5 billion) in revenue in its 2023 fiscal year.

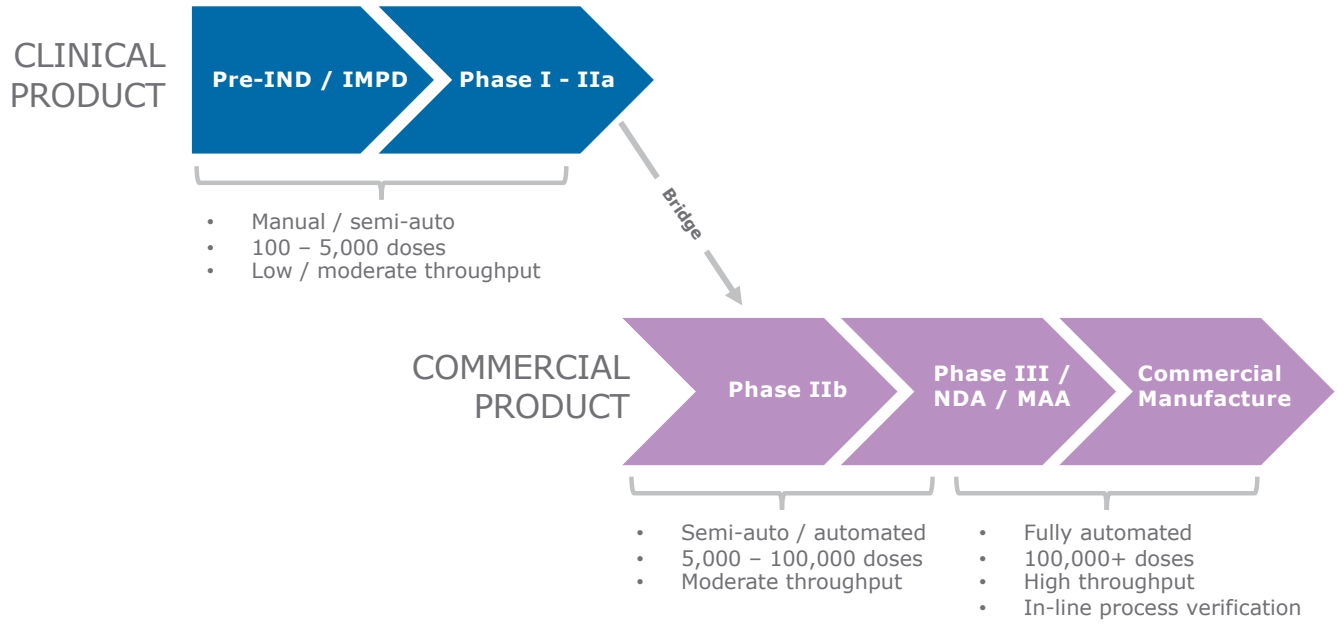

Figure 2: A seamless scale-up path for the development and manufacturing of an sDPI.

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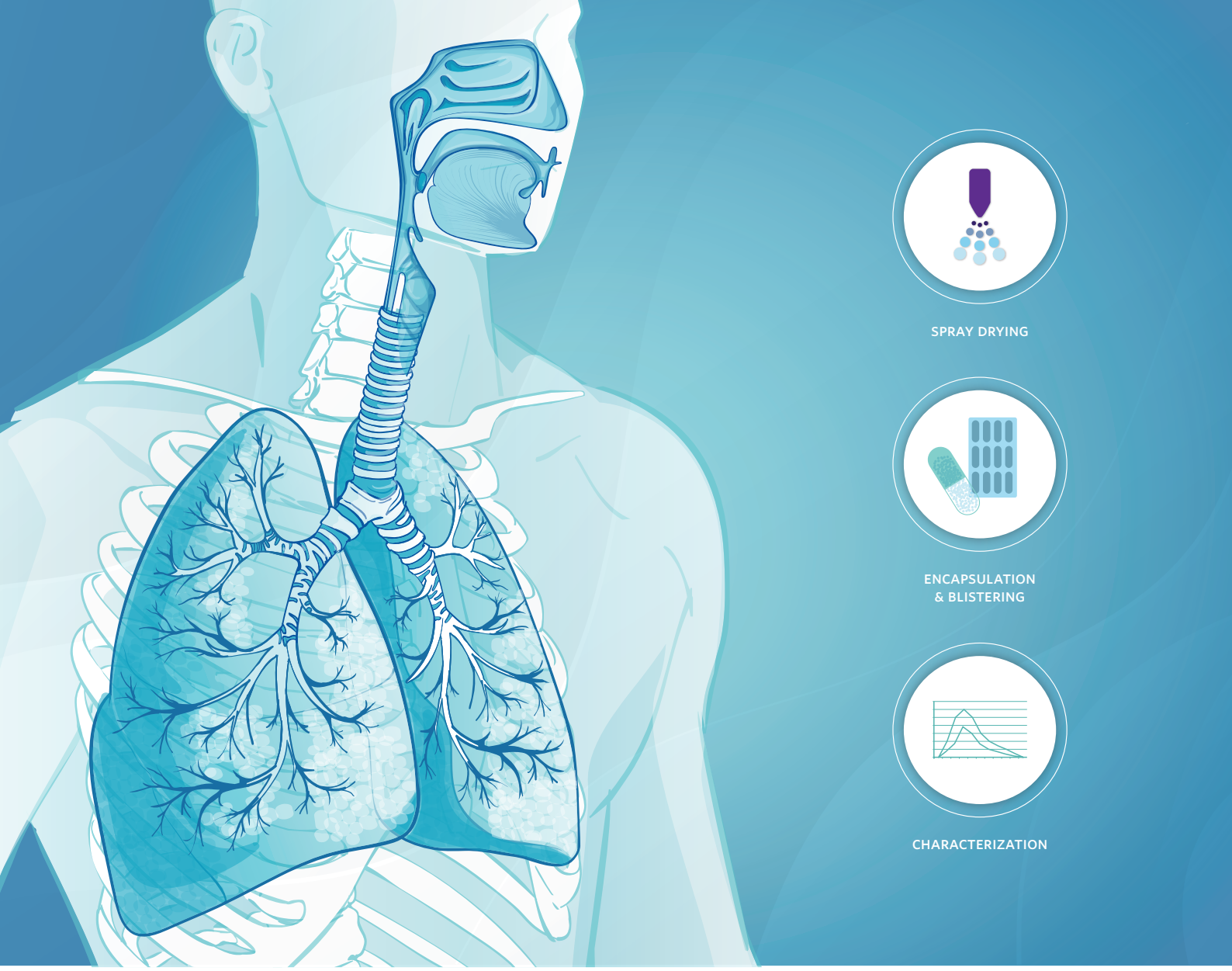
ABOUT THE AUTHORS

Carolyn Berg is Vice-President, Business Development at Catalent and has over 25 years of experience in pharmaceutical sales, marketing and business development. She is currently Vice-President, Business Development for Catalent's inhaled drug delivery solutions, where she is responsible for growing the inhalation business in North America and Europe. Prior to Catalent, Ms Berg held various leadership roles within Cipla, Teva Respiratory and Merck, and owned her own consulting practice for pharmaceutical and healthcare clients. Ms Berg holds a Bachelor's degree in Journalism in Public Relations and another in French from the University of Texas at Austin (TX, US), as well as an MBA from the University of South Carolina (SC, US).

Dr William Chin is Manager, Global Scientific Affairs at Catalent and holds a Bachelor's degree in Biotechnology and a PhD in Biomedical and Pharmaceutical Sciences. With a background in both academia and industry, he has extensive experience in *in vitro* and *in vivo* evaluation of pharmaceuticals formulations and drug delivery systems. He joined Catalent in 2017, initially as a Technical Specialist in Germany, before transitioning to Scientific Affairs. Currently, he heads Catalent's Scientific Affairs department in the US and EU, focusing on ensuring technical accuracy in key messaging and driving scientific leadership.

Patrick Goncalves is Account Executive, Business Development at Catalent. He has worked in the pharmaceutical industry since 2014, amassing extensive expertise in dry powder inhalation. In his current role, he is responsible for growing Catalent's inhalation business in Europe. Mr Goncalves joined Catalent from Harro Höfliger, where he held various sales and project management roles, most recently as a senior sales manager for inhalation technologies, overseeing all dry powder inhalation projects. He holds a Bachelor's degree in Industrial Engineering from the University of Esslingen (Germany) and an MBA in sales engineering from the University of Kaiserslautern (Germany).



expertise & proven success in pulmonary delivery

Catalent is your preferred CDMO for pulmonary delivery, with over 30 years of dry powder inhalation expertise. Our capabilities in drug development, scale-up and commercial manufacturing for spray dried and carrier-based powders can accelerate the time to market of your inhaled therapy.

Our state-of-the-art facility in Boston, MA has the largest capacity worldwide, supporting manufacturing, encapsulation and blistering of dry powders from clinical supplies through commercial scale.

- DPI FORMULATION DEVELOPMENT
- SPRAY DRYING EXPERTISE FOR SMALL & LARGE MOLECULES
- SCALES FROM LABORATORY TO PSD-1, PSD-4 & PSD-7
- CLINICAL TO COMMERCIAL SCALE CAPSULE FILLING & BLISTER PACKAGING
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