

# PULMONARY & NASAL DRUG DELIVERY:

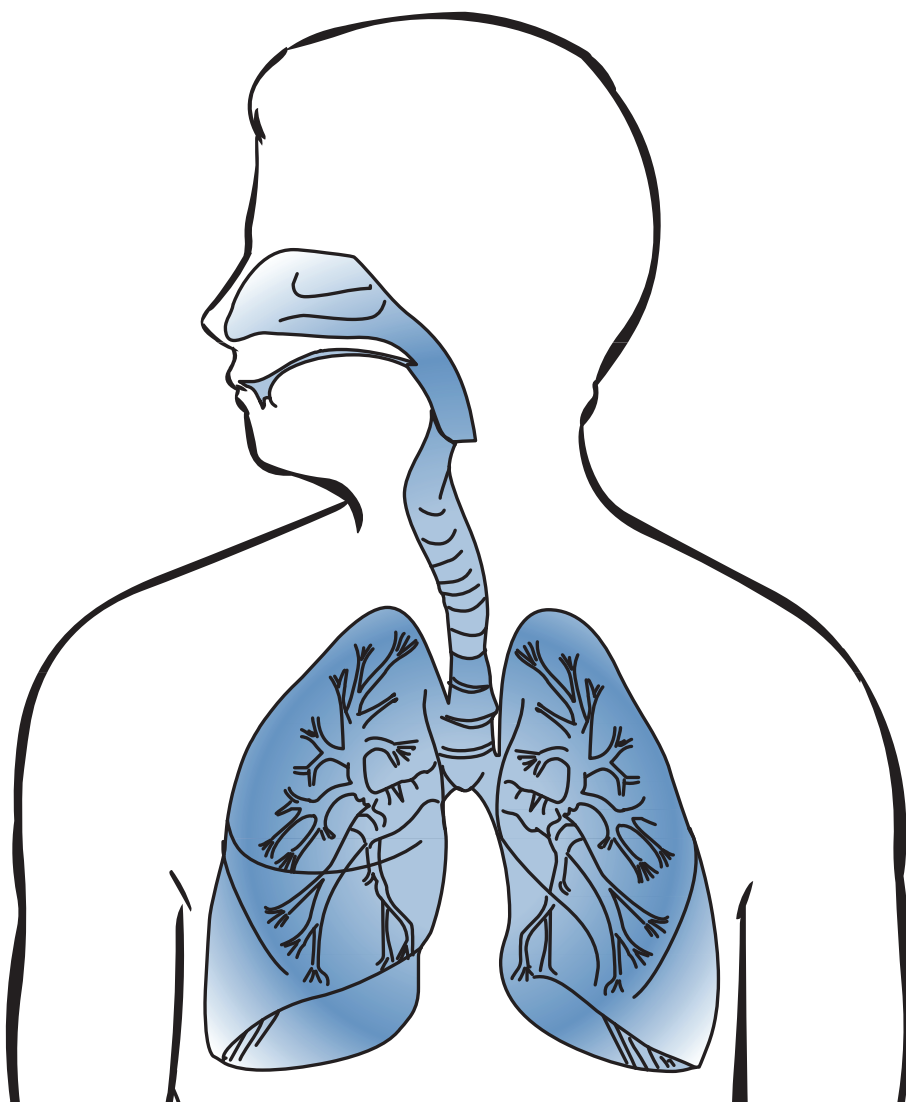
## FOCUS ON PATIENTS, AND EMERGING MARKETS



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Focus on Patients, and Emerging Markets"**

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Nov: Pulmonary & Nasal Drug Delivery  
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ENABLING YOUR SUCCESS





## MOVING TOWARD PATIENT-PREFERRED NASAL DRUG DELIVERY SYSTEMS

Today's patients are increasingly better informed and more opinionated about their treatment options and product preferences. With 400 million people worldwide suffering from allergic rhinitis, which includes hay fever and allergies to things such as mould, plants, dust and animal dander, demand for alternatives to aqueous sprays is growing. Here, Louise Righton, MSc, Global Market Development Manager, and Les Harrison, PhD, Preclinical & Clinical Manager, both of 3M Drug Delivery Systems Division, describe how providing patients with new, more preferred inhalation drug delivery devices is one way that pharmaceutical companies can improve compliance and increase success in this changing arena. They also review recent research highlighting patient preferences in device design and user experience for a nasal MDI.

With an estimated 400 million allergic rhinitis sufferers worldwide, the market for topical nasal sprays to treat this condition is significant.<sup>1</sup> The market for nasal corticosteroids, the leading therapy type, is worth some US\$2.5 billion (£1.6 billion), with the leading brands achieving blockbuster status.<sup>2</sup>

However, these sales figures do not necessarily indicate satisfied customers. Since CFC

propellants were phased out in the 1990s, aqueous pump sprays have been the primary delivery mechanism for nasal corticosteroids (Figure 1), and patients report that using these sprays can be unpleasant, and inconvenient. For example, drug formulation frequently drips down the back of the throat (post-nasal drip), not only causing an uncomfortable sensation, but also a bad aftertaste. Additionally, the



**Figure 1: A selection of currently marketed aqueous pump sprays.**

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liquid can run back out of the nose, embarrassing patients and reducing the retained dose. The sales figures for this category, therefore, should be viewed as a testament to the effect of allergic rhinitis on quality-of-life, meaning that sufferers' desire for treatment is so strong that they will tolerate uncomfortable products in the name of relief.<sup>3</sup>

Insights like this highlight the need for pharmaceutical companies to develop new, better solutions for allergic rhinitis. In a competitive marketplace, major opportunities exist for those who can improve the user experience with an innovative drug delivery device. Indeed, pharmaceutical leaders are increasingly focusing on and considering the user experience, as a patient-driven marketplace demands increased attention to these factors. Over the coming years, companies must develop solutions for drug delivery that are efficient and user friendly in order to build patient preference.

In the allergic rhinitis market, a nasal pressurised Metered Dose Inhaler (pMDI) device (Figure 2) represents one helpful solution to the problems associated with aqueous sprays. This device allows the medication to be administered as a quickly evaporating, no-drip spray. Furthermore, patient-friendly features such as dose counters and ergonomic designs can help further differentiate a product from competitors. In this patient-driven environment, the addition of features like these can help build patient preference and assist in the regulatory process. This article will review research recently conducted that highlights patient preferences in device design and user experience for a nasal MDI.

## UNDERSTANDING KEY DIFFERENTIATORS FOR PATIENTS

In an effort to understand the needs of allergic rhinitis sufferers better, 3M Drug Delivery Systems recently conducted a clinical research study comparing a new nasal MDI device with existing aqueous pump spray devices. The patient acceptance research was conducted with adult users of nasal spray devices. Study participants used the new nasal MDI device, and compared it with their experiences of using currently available pump spray devices. Their responses were collected in interviews designed to highlight the holistic patient experience of using nasal devices, and to gauge what considerations are most important to patients when considering their choices in nasal sprays.

To gain these insights, an open-label study in fifty participants was conducted in which responses to written questions were used to evaluate subject preference for a new nasal

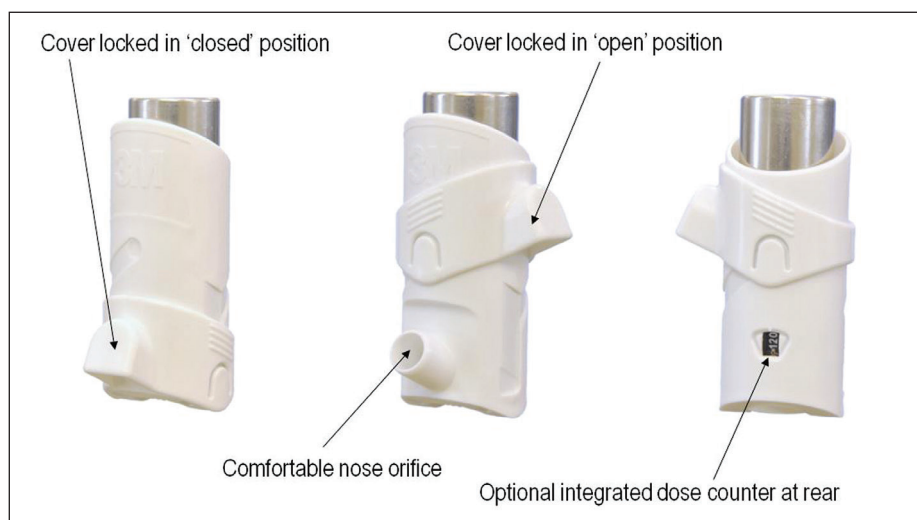


Figure 2: The 3M Nasal MDI from 3M Drug Delivery Systems.

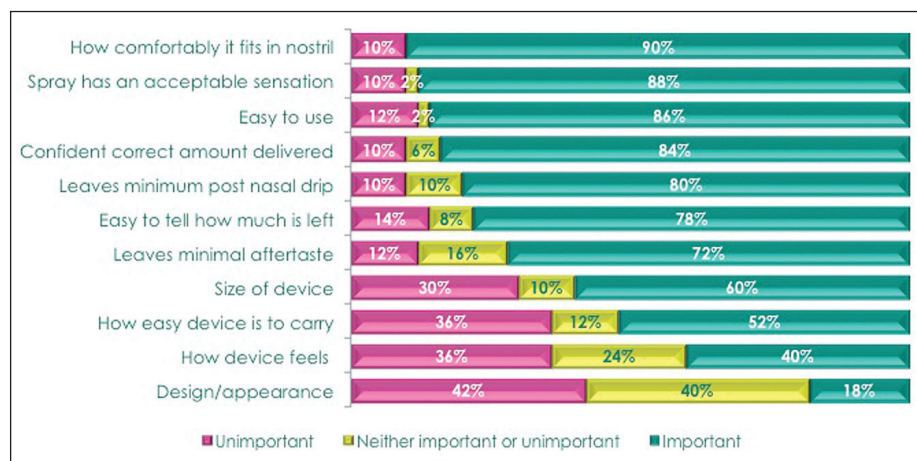


Figure 3: Ranking of importance of characteristics when using a nasal spray.<sup>4</sup>

aerosol device. In parts one and two of the study, researchers first asked subjects for their initial impressions of the new MDI design in a questionnaire format. In the third part of the study, subjects were asked to read application instructions for the inhaler and apply one

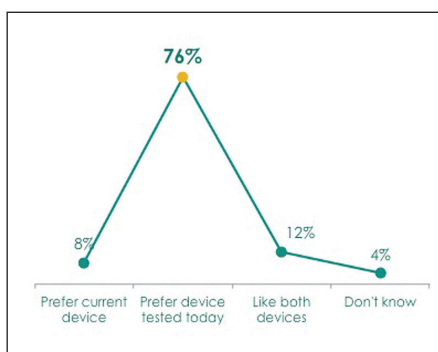
with conventional nasal pump sprays. With this data, researchers gathered a picture of subjects' overall perceptions of the nasal MDI device; their experiences in administering the aerosol up the nose; the device's ergonomics, size, feel and fit; and their overall evaluation of the device

**"INSIGHTS LIKE THIS HIGHLIGHT THE NEED FOR PHARMACEUTICAL COMPANIES TO DEVELOP NEW, BETTER SOLUTIONS FOR ALLERGIC RHINITIS. IN A COMPETITIVE MARKETPLACE, MAJOR OPPORTUNITIES EXIST FOR THOSE WHO CAN IMPROVE THE USER EXPERIENCE WITH AN INNOVATIVE DRUG DELIVERY DEVICE"**

placebo aerosol spray from a prototype nasal aerosol device to one nostril, and a second placebo aerosol spray from the same device to the other nostril. Participants then completed a questionnaire comparing the prototype device

in comparison with their current aqueous pump spray device. In the final part, to put these opinions into perspective, researchers also gathered data on the importance users placed on various attributes of a nasal device.





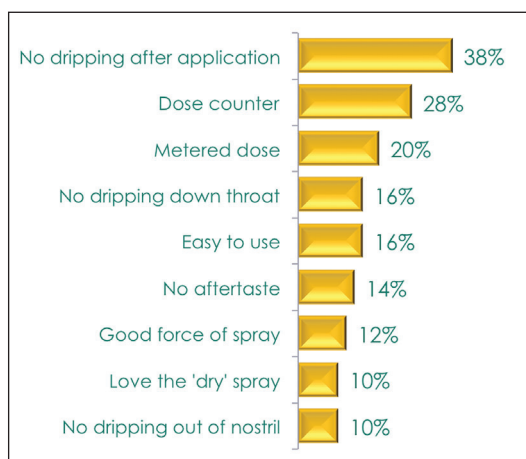
**Figure 4: More than three quarters of subjects preferred the Nasal MDI over their current pump spray device.<sup>4</sup>**

### EMPHASIS ON COMFORT

The study found that comfort (a halo of attributes including comfort in nose and spray sensation) is the most important consideration when buying and using a nasal spray. 90% of subjects stated that how comfortably a device fits in the nostril was a key factor, and 88% stated an acceptable spray sensation was most important (see Figure 3).<sup>4</sup>

Following closely in importance after comfort were factors related to the user experience, including ease of use, confidence in the amount of drug delivered, minimisation of post-nasal drip, and how easy it is to tell how much medication is left in the device.

Lower-ranked factors included size and portability concerns, as well as factors related to a device's appearance and feel. Whilst subjects may not have ranked these concerns as highly as those related to comfort, ease of use, and good delivery, it is important to keep in mind that



**Figure 5: Reasons for preferring the 3M Nasal MDI over aqueous pump sprays.<sup>4</sup>**

minutes to handle the device before use. Initial responses to the inhaler at this time were positive, with participants giving unprompted responses praising the secure, attached cap, the convenient dose counter and the fit of the device in the hand.

Following their initial handling assessment of the device, subjects were given instructions for use of the device containing placebo formulation. Upon use, subjects rated the device highly with a mean score of 8.1 on a scale of one to 10. This rating was attributed to the pleasant and comfortable experience of using the inhaler, with participants citing its ease of use, lack of dripping after application and metered dose as top reasons for their ratings. When asked to rate how easy the device was to use on a scale of one to 10, participants gave the inhaler a mean score of nine.

nasal MDI assigned a mean importance of 8.8 on a scale of one to 10 for the fact that the inhaler delivered one set dose per spray, regardless of how hard they pressed the button, compared with a force-dependent aqueous pump spray, for which the dosage can vary significantly (Figure 5).<sup>4</sup>

As noted above, the nasal MDI used in this research also incorporated a dose counter, which was similarly well received by users (Figure 6). By looking at the dose counter before and after using the device, patients receive a visual confirmation that the dose has been delivered, and they no longer have to wonder about how much medication is left in the device or whether they should replace it. Benefits like this help patients feel more secure using a device, as reflected by the high score this feature was given in the research.

Among these subjects, the dose counter and metered dose features were cited as top reasons for preferring the device versus their current nasal pump spray, along with the fact that the MDI delivers a no-drip spray, which does not run back out from the nose or drip down the back of the throat after application (Figure 5).

### ARE YOU PROVIDING YOUR CUSTOMERS WITH EVERYTHING THEY NEED TO "BUY IN"?

In today's digital world, patients have ready access to product information, reviews and forums, and those who are dissatisfied with the products they depend on often research alternatives independently before meeting with their health care professional. In this environment, pharmaceutical companies must be more mindful than ever before to develop treatments that keep user-friendliness at the forefront. Products that disregard these factors, or that do not offer useful differentiation from the field of competitors, are easily overlooked in a patient-influenced prescribing process.

The research summarised in this article details the top issues of concern for users of nasal treatments for allergic rhinitis, and clearly demonstrates the opportunity for a more patient-friendly solution than those that are currently being marketed, with over three quarters of patients preferring the 3M Nasal MDI compared with their current aqueous pump spray.<sup>4</sup> With a treatment solution that addresses patients' needs and wants—for ease of use, comfort, convenience and efficacy, pharmaceutical companies can gain buy-in from patients who are eager for new alternatives.

## "IN AN EFFORT TO UNDERSTAND THE NEEDS OF ALLERGIC RHINITIS SUFFERERS BETTER, 3M DRUG DELIVERY SYSTEMS RECENTLY CONDUCTED A CLINICAL RESEARCH STUDY COMPARING A NEW NASAL MDI DEVICE WITH EXISTING AQUEOUS PUMP SPRAY DEVICES"

they remain key considerations given that allergic rhinitis devices are often used outside of the home—or would be if patients felt comfortable doing so. Any device intended to treat a condition triggered by pollen or pollution should be designed with portability in mind to encourage patients to keep it with them outdoors.

### IMPRESSIONS UPON HANDLING AND USE

In the evaluation of impressions of the prototype nasal MDI, subjects were given several

Following completion of the device test, when asked to state a preference for either their current nasal pump spray device or the new nasal MDI, more than three quarters of subjects stated a preference for the new nasal MDI (see Figure 4).<sup>4</sup>

### INNOVATIONS FOR PATIENT CONFIDENCE

An important advantage of a nasal MDI over an aqueous pump spray is the inherent metered dose. In the research, subjects who used the

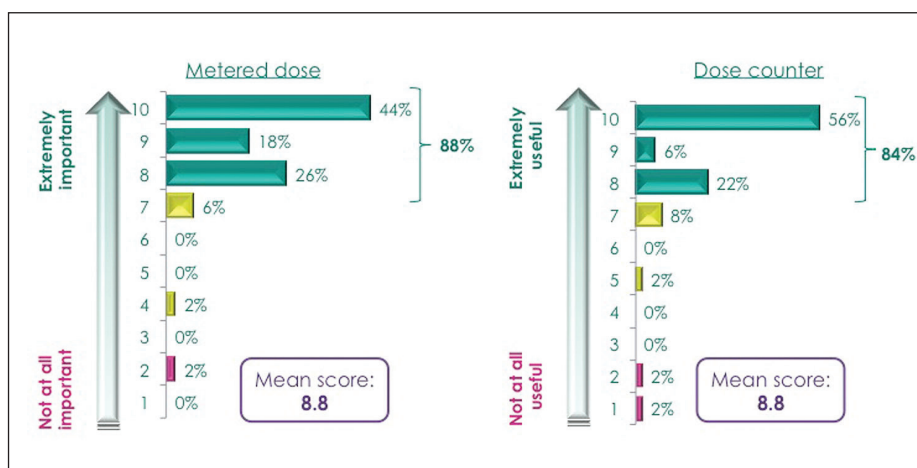


Figure 6: Assessment of metered-dose and dose-counting features of a nasal MDI.<sup>4</sup>

## GETTING STARTED

Identifying what makes a device stand out for patients is not always a simple task. In efforts to develop new solutions, pharmaceutical companies should seek out technology development and manufacturing partners who are committed to understanding patients' needs and incorporating their voices into developing future technologies. With the development of

any new drug product, especially a new delivery system, pharmaceutical companies must also always keep the practicalities of manufacturing in mind. By working with a partner that is committed to ensuring an efficient and cost-effective development and manufacturing process, while at the same time innovating to deliver patient-preferred solutions, companies can maximise the chances of success for their new nasal MDI product.

"AMONG THESE SUBJECTS, THE DOSE COUNTER AND METERED-DOSE FEATURES WERE CITED AS TOP REASONS FOR PREFERRING THE DEVICE VERSUS THEIR CURRENT NASAL PUMP SPRAY"

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October 2013	Prefilled Syringes	September 2nd
November 2013	Pulmonary & Nasal Drug Delivery (OINDP)	October 7th
December 2013	Delivering Biotherapeutics	November 4th
January 2014	Ophthalmic Drug Delivery	December 9th
February 2014	Prefilled Syringes	January 13th
March 2014	Transdermal Patches, Microneedles & Needle-Free Injection	February 10th
April 2014	Pulmonary & Nasal Drug Delivery	March 10th



# PRESSPART

## MODIFYING MDI CANISTER SURFACES TO IMPROVE DRUG STABILITY & DELIVERY

Hydrofluoroalkane (HFA)-based propellants are widely used in modern metered-dose inhalers (MDIs), due to their lack of hazardous and environmentally-damaging effects. However, an HFA's active pharmaceutical ingredient can interact with the canister substrate, causing deposition of the drug to the canister walls, or interact with the solution, causing degradation and resulting in increased impurity levels. Over the past few years, a number of surface coatings have been developed that can be applied to MDI canisters and valve components, to protect the contents from deposition and degradation. More recently, plasma processes have been developed to modify and improve the surface energy performance of a MDI canister. This approach has a number of advantages to alternative coatings but requires careful optimisation to ensure the highest quality finish and MDI performance. Richard Turner, Business Development Director, Presspart Manufacturing Ltd, explains.

MDIs are commonly used to deliver drugs for treating respiratory and nasal disorders. The drugs are administered by aerosol, in suspension or solution, with a liquefied gas propellant. For more than 50 years, chlorofluorocarbons

chemically inert, making them ideal candidates for use in medical products. However, some properties of these compounds are substantially different from those of the CFCs traditionally used in MDIs.

**"WHEN HFA-MDI DRUG FORMULATIONS ARE IN SUSPENSION, INTERACTIONS WITH THE CANISTER SUBSTRATE CAN CAUSE DEPOSITION OF THE DRUG ON THE CANISTER WALLS OR ON EXPOSED SURFACES OF THE VALVE COMPONENTS"**

(CFCs) were the propellants of choice, but these have now largely been phased out, in line with the Montreal Protocol.<sup>1</sup>

Replacement propellants have been developed over the past two decades based on hydrofluoroalkanes (HFAs), specifically HFA 227 and HFA 134a. These substances are not ozone-depleting, and they are non-flammable and

The surface properties of a device can have an important effect on the device's interactions with its most immediate environment and substances with which it comes into contact. As a result, the device's surface chemistry has a vital role on the surface functionality and, therefore, overall performance of the device and drug.

When HFA-MDI drug formulations are in suspension, interactions with the canister substrate can cause deposition of the drug on the canister walls or on exposed surfaces of the valve components. Interactions with solutions more commonly cause degradation, resulting in increased impurity levels. In both cases the interaction leads to a reduction in the drug content in the formulation, resulting in the patient receiving less than the prescribed dose.



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## RANGE OF COATINGS

Applying a suitable surface coating to the MDI components improves the stability of the formulation as well as the product performance, and helps to extend the product's shelf life. A range of coatings have been developed that can be applied to both the canister and valve components to protect the contents from deposition and degradation.

Commonly used coatings include barrier coatings, such as anodisation of the canister, to change the surface characteristics and ultimately act as a protective barrier for sensitive formulations. Various low-surface energy coatings are available for suspension formulations. For example, a surface treatment has been specially developed for deep-drawn 5052 aluminium canisters (Figure 1) and is suitable for budesonide HFA, and new coating compounds have been developed that prevent certain HFA-containing drug formulations (for example, salbutamol) from interacting with the MDI and adhering to canister walls.

Fluorocarbon polymers are commonly used to coat the interior canister surfaces to eliminate adhesion or deposition of albuterol on canister walls; albuterol is widely used with MDI drugs, particularly beclomethasone dipropionate. Fluorocarbon polymers used in coatings are commonly made from multiples of one or more of a variety of monomers. Particularly preferred coatings tend to be pure perfluoroalkoxyethylene (PFA), and blends of polytetrafluoroethylene (PTFE) and polyethersulphone (PES), due to their relatively high ratios of fluorine to carbon. In addition, coatings that combine fluorocarbon polymers with non-fluorocarbon polymers (such as polyamides) are used for certain formulations to improve adhesion of the coating to the canister walls; other coating types include epoxy-phenol resins.

## COATING TECHNIQUES

Standard metal-coating techniques can be used to pre-coat the metal substrate and cure it, prior to shaping the metal into the components (for example, through deep-drawing or extrusion). This pre-coating method has the advantage of being well suited to high-volume production.

Other coating techniques include: spraying the insides of preformed cans; dipping; or electrostatic dry-powder coating, followed by curing. Many of these processes require high temperatures (up to 400°C when curing), which can create additional costs and complications. Furthermore, only the most robust canisters (that is, those produced through deep-drawing) should be subjected to such high temperatures, as less robust canisters can become unrolled or suffer other morphological changes under these conditions.



**Figure 1: Deep-drawn aluminium MDI canisters.**

**“PLASMA TREATMENTS HAVE BEEN TRIED IN THE PAST ... BUT THESE HAVE FAILED TO PENETRATE THE MARKET DUE TO POOR SCALABILITY AND COST VIABILITY. HOWEVER, ALTERNATIVE DEVELOPMENTS HAVE BECOME AVAILABLE THAT MAKE PLASMA A REAL CHOICE FOR MDI CANS”**

## PLASMA PROCESSING TECHNOLOGIES

More recently, gas plasma-based processes have been developed to modify and improve the surface energy performance of an MDI canister. Gas plasma processing is an industrial technique that is carried out in a vacuum to coat a wide range of substrate materials. The process involves constant or pulsed excitation of gas by either a radio frequency (RF) or microwave field to produce an energetic plasma.

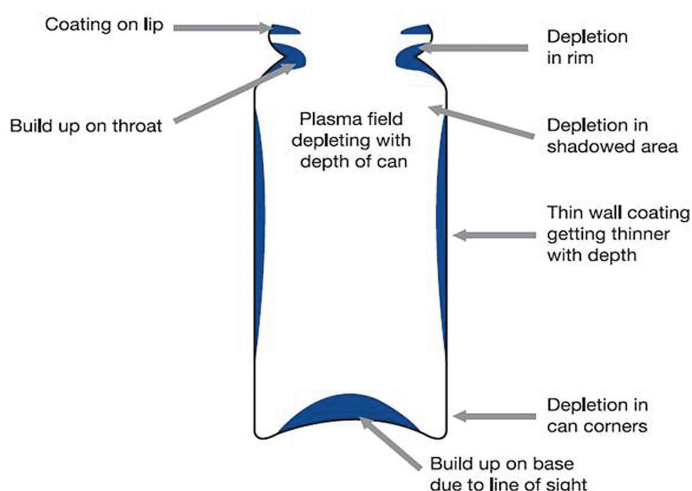
The process creates an ultra-thin layer that protects against degradation, deposition and corrosion. It is a low-temperature process (<75°C for metallic substrates and <45°C for polymeric substrates), and is ideal for uniform treatments of components with complex shapes, including small components in large volumes. The coating adheres well to the component substrate, because the plasma process cleans the component surface while in the vacuum, resulting in an ultra-clean substrate-coating interface.

Using gas plasma to tailor the surface chemistry has the advantage of providing uniform surface treatment without changing the properties of the bulk material. The process can be used to change the outermost layers of the material only, without polymerising a coating, resulting in modifications to the functional chemistry. These modifications can be used “stand-alone” or with the addition of a subsequent surface coating through a single process cycle, depending on the application and desired properties.

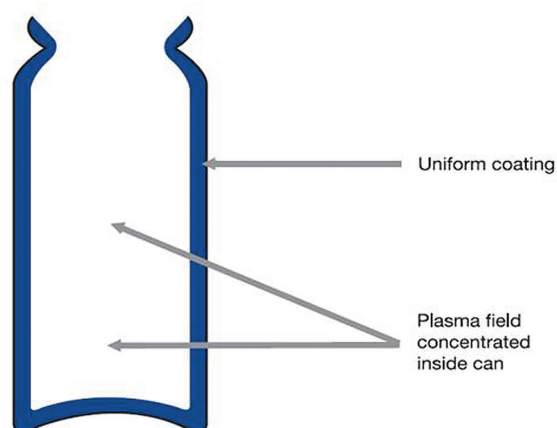
## OPTIMISING THE PLASMA PROCESS

Plasma processing of MDI canisters can bring multiple benefits to the MDI performance, helping to reduce drug deposition and also to improve the stability of formulations where interactions with the aluminium substrate would lead to product degradation and reduced shelf life. However, plasma processing for MDI canisters needs to be highly controlled to

a) CAN COATED BY TRADITIONAL PLASMA PROCESS



b) CAN COATED BY NEW PLASMA PROCESS.



**Figure 2: a) Traditional plasma processing does not ensure a uniform coating to internal wall of the canister. b) The new plasma process gives a uniform coating to canisters.**

ensure complete consistency of treatment and uniformity of coating to the internal walls of the canisters.

Plasma chemistry is critical to the performance of the coated canisters – the right choice of precursor chemistry enables a robust process with excellent performance. A variety of plasma treatments have been tried in the past, including single- and dual-layer technologies with a range of monomers, but these have failed to penetrate the market due to poor scalability and cost viability. However, alternative developments have become available that make plasma a real choice for MDI cans.

A cost-effective process has been established using an optimised plasma chemistry consisting of an intrinsically robust monomer, highly ionised to form a high crosslink density. The ultra-pure gases and monomers do not contain any solvents, so do not produce any waste by-products. The result is a coating technology without the extractable issues potentially encountered with some polymer systems.

It is critical that plasma processing achieves complete and consistent coating across the entire surface of the inside of the canister. Traditional plasma processes, RF or micro-

wave, are particularly difficult to control when internal surfaces are to be treated. Poor penetration of plasma ions with low energy results in non-uniform, thin or porous coatings with poor performance. Increased ion energy to aid depth of can penetration gives rise to ion etching at the can neck and a more “line-of-sight” process.

This partial “line-of-sight” process leads to non-uniformity/thickness variation in such geometries (see Figure 2a). For thin nanometre coatings on MDI cans this is observed as striations in colour or colour bands down the can. With the best compromise the coating builds up around the canister lip, throat and base, with depletion at the rim, shoulders and can corners.

More recently, an improved process has been developed that eliminates the issues associated with typical plasma system designs. Using proprietary gas/monomer delivery configurations and electric field control (designed specifically for can coating geometry), uniform coatings can be deposited (Figure 2b).

Dedicated system design configurations mean constant, high deposition rates with extreme reproducibility in terms of coverage, chemical speciation and product performance. The unique combination of process equipment

design and precursor monomer means the technology is now scalable to handle the throughput and commercial demands of the MDI world market.

This process has been used to develop several different plasma coating options that successfully prevent drug deposition on the can walls, and prevent drug degradation in solution or suspension. Examples include surface treatments for budesonide, formoterol, fluticasone propionate and beclomethane dipropionate, amongst others.

## CONCLUSIONS

Gas plasma processing offers considerable advantages in the coating and treating of MDI canisters for improving the stability of the formulation and extending product shelf life. In addition, the ability to plasma-process high volumes of the canisters fulfils the high-volume demand from the MDI market.

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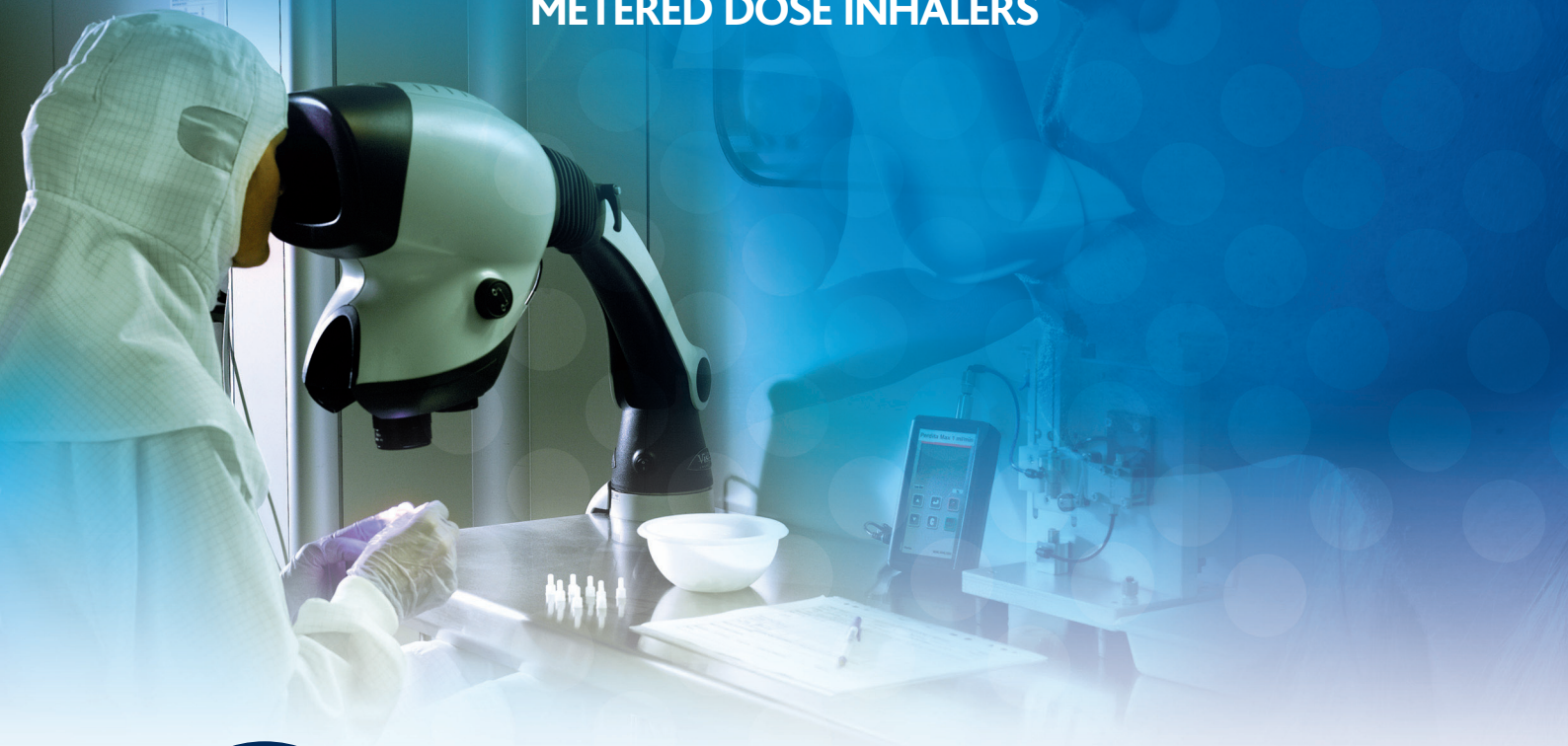
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## TWISTER®, A VERSATILE DPI FOR ASIA, SOUTH AMERICA AND OTHER FAST-GROWING MARKETS

In this piece, Aptar Pharma analyses the dynamics between the use of DPIs and MDIs for asthma and COPD in the US and Europe compared with the fast-growing Asian and South American markets. The company's Twister DPI has been specifically designed in anticipation of the trend for take-up of DPIs to spread to fast-growing markets, where currently pMDIs are still often preferred because they are considered more cost effective.

It is estimated by the WHO that, worldwide, some 300 million people suffer from asthma and 240 million people suffer from chronic obstructive pulmonary disease (COPD). The cost of these diseases to the US healthcare system is estimated at \$50.2 billion (£33 billion) for asthma, and \$32.1 billion (£21 billion) for COPD. The majority of asthma and COPD treatment sales in the US and Europe come from drugs delivered by Dry Powder Inhalers

(DPIs). However, in the fast-growing markets of Asia and Latin America, asthma has been treated predominantly with pMDIs, which in many countries are still considered to be more cost-effective than DPIs.

DPIs represent 50% of the total asthma/COPD market by value worldwide, with most growth seen historically in the US and Europe. Aptar Pharma is anticipating that this DPI growth trend will spread to fast-growing markets, driven

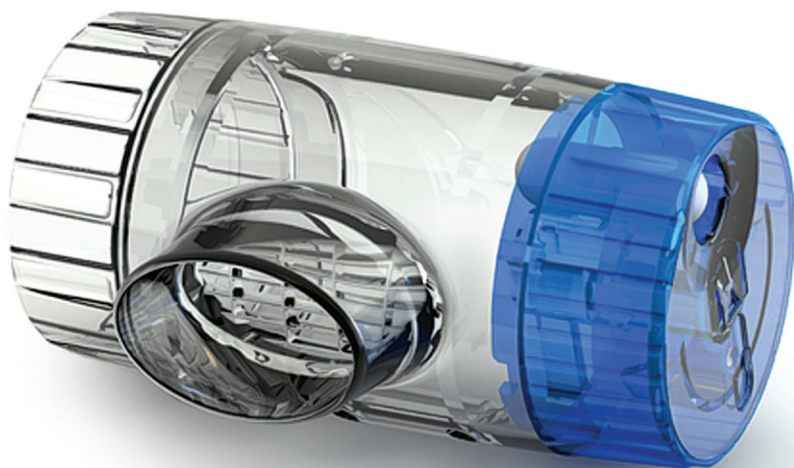


Figure 1: Aptar Pharma's Twister®, an affordable, versatile, off-the-shelf DPI.

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by the healthcare reforms that are making asthma and COPD diagnosis and medication more available to patients.

The latest patient-focused studies using DPIs, carried out for Aptar Pharma in China, indicated that the expectations of patients and pneumologists regarding DPIs in fast-growing markets have evolved. They are now increasingly focusing on convenience and ease of use, favouring a compact and simple design. The studies highlighted the fact that DPIs should be of good quality to ensure a long life, and be recyclable when they need to be replaced.

#### KEY BENEFITS OF TWISTER®

Twister® is a new capsule-based DPI, designed specifically to address unmet medical needs in fast-growing markets (see Figures 1 and 2). During its development by a dedicated Aptar Pharma multi-disciplinary technical team, Twister® was tested and validated with a number of different dry-powder drug formulations. It has a simple and robust design with few components, making it cost-attractive for asthma and COPD treatments in fast-growing markets.

Twister® is designed to be patient-friendly and easy to use, allowing patients easy access to their medication in three simple steps: Insert, Twist and Inhale. To help improve patient compliance with the prescribed treatment, Twister® is transparent, allowing the capsule and powder to be seen in the device as they are processed. In addition to these visual cues, the patient is also guided by audible feedback during inhalation.

#### TO MEET DEMAND IN FAST-GROWING MARKETS

Development of Twister® by an international Aptar Pharma project team started in France and continued in China, where industrial manufacturing now takes place. Twister®, which is regis-

**“THE LATEST PATIENT-FOCUSED STUDIES USING DPIs ... INDICATED THAT THE EXPECTATIONS OF PATIENTS & PNEUMOLOGISTS REGARDING DPIs IN FAST-GROWING MARKETS HAVE EVOLVED. THEY ARE NOW INCREASINGLY FOCUSING ON CONVENIENCE AND EASE OF USE”**

tered as a medical device by the Chinese sFDA, is moulded and assembled in a ISO class 7 cleanroom at Aptar Pharma's state-of-the-art production facility in Suzhou, China.

Aptar Pharma was one of the pioneers of local drug delivery systems manufacturing in China, and was the first company licensed

to manufacture spray and aerosol drug delivery devices for this market. Aptar Pharma Suzhou was opened in 1996 and produces pMDI metering valves and spray pumps for the Asian market. Manufacturing Twister® at the Suzhou facility is another step forward in Aptar Pharma's global expansion and commitment to

provide world class quality products, promoting better healthcare access worldwide.

Adam Shain, Associate Director Business Development, Aptar Pharma Prescription Division, commented: “This device is designed to fulfill regional needs for a simpler and cost-effective solution to deliver dry powder to the lungs.”

#### ABOUT APTAR PHARMA

Aptar Pharma – part of the Aptargroup family of companies along with Aptar Beauty + Home and Aptar Food + Beverage – creates innovative drug delivery systems that meet the evolving needs of biotechnology, healthcare and pharmaceutical companies around the world. The company provides its customers with a wide range of delivery technologies and analytical services backed by decades of proven expertise.

Aptar's main focus is on metering valves for pressurised metered-dose inhalers (MDIs), and dry-powder inhalers (DPIs); and multidose pumps, single-dose devices and metering valves for nasal and sub-lingual drug delivery.

The company offers a full set of associated services to support customer speed-to-market and provide global support to branded and generic customers in all geographies and in both developed and emerging markets.

Aptargroup (NYSE: ATR) is headquartered in the US and has manufacturing sites in North America, Europe, Asia and South America.



**Figure 2: Twister® has a simple and robust design with few components, making it cost-attractive for asthma and COPD treatments in fast-growing markets.**

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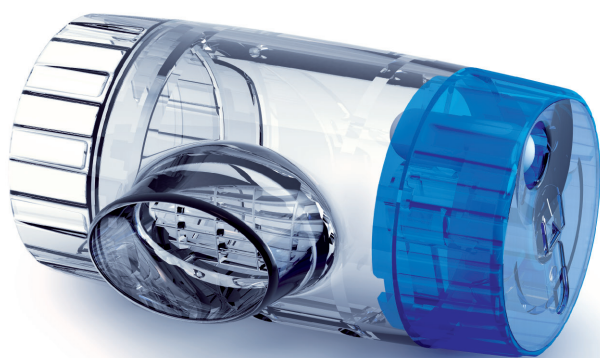
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## AEROSOLISATION PROPERTIES OF QUALI-V®-I VERSUS GELATIN CAPSULES: AN IMPROVEMENT IN INHALATION DRUG DELIVERY

In this article, Imran Saalem, PhD, Senior Lecturer, Pharmaceutical Technology, Pharmacy & Biomolecular Sciences, Liverpool JMU, Liverpool, UK, Fernando Díez, Business Development Manager, Qualicaps Europe, and Brian Jones, Scientific Advisor to Qualicaps Europe, report the results of a study comparing aerosolisation properties of dry-powder formulations delivered from Quali-V®-I capsules with those of dry-powder formulations delivered from gelatin capsules.

### INTRODUCTION

There has been an increase in respiratory disease in the last decade: chronic obstructive pulmonary disease (COPD) affects an estimated 210 million people worldwide and is predicted to be the

third leading cause of death by 2020. Pulmonary delivery is being investigated as a route for delivering actives that cannot be given by the standard oral route and as an improved alternative to administration by the parenteral route.

The use of hard capsules in dry powder inhalers (DPI) to deliver formulations to the lung has been in use since 1970.<sup>1</sup> Pharmaceutical companies subsequently started to manufacture more complex delivery systems, such as powder depot devices or powder dispensed from blisters, but their complexity tended to make them less patient friendly. Lately there has been an interest in returning to capsule-based systems because they are simple to formulate, cheap to manufacture and patient friendly. They are easy

to use and the patient can see when the dose has been taken.

The original inhalation-grade hard capsules were made from gelatin, which becomes brittle when exposed to low humidities. Inhalation-grade hypromellose capsules have been developed in the last few years to overcome this problem because water does not act as a plasticizer in their structure. Little has been published that compares the properties of the two types of capsules, except for studies that have measured their puncturing in DPI, which showed that hypromellose capsules had better performance.<sup>2</sup> In this investigation the effects of capsule properties on the aerosolisation of powders from DPIs were compared.<sup>3</sup>

### KEY PARAMETERS FOR INHALATION DELIVERY

Inhaled drug delivery systems can be divided into three principal categories: metered-dose inhalers (MDI), dry-powder inhalers (DPI) and nebulizers, each class with its unique strengths and weaknesses.

DPIs are typically formulated as one phase, solid particle blends, they have advantages from stability and processing standpoint, dry powders are at a lower energy state, which reduces the rate of chemical degradation and the likelihood



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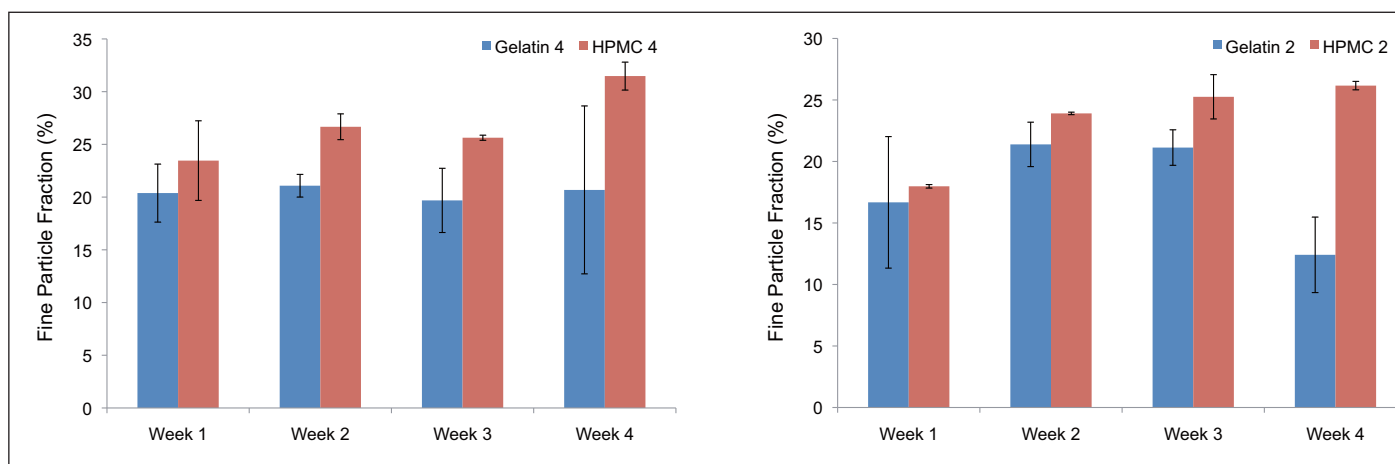
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**Figure 1: FPF% for gelatin and Quali-V®-I capsules. (The numbers “2” and “4” refer to the different inhalers used.)**

of reaction with contact surfaces. In addition, DPIs are activated by the patient’s inspiratory airflow and subsequently require little or no co-ordination of actuation and inhalation compared with MDIs.<sup>4</sup>

Particle size is the most important design variable of a DPI formulation. Methods for determining particle size and distribution use various geometric features or physicochemical properties. Aerodynamic diameter is the most appropriate measure of aerosol particle size, because it relates to the particles’ dynamic behaviour and describes the main mechanism of aerosol deposition; gravitational, sedimentation settling and inertial impaction depending on the aerodynamic dynamic diameter. This is defined as the diameter of an equivalent volume sphere of unit density with the same terminal settling velocity as the actual particle

To reach the peripheral airways, where the drug is most efficiently absorbed, particles need to be in the 1-5 µm aerodynamic diameter range. Particles larger than 5 µm usually deposit in the oral cavity or pharynx, from which they are easily cleared. In contrast, particles smaller than 0.5 µm may not deposit at all, since they move

by Brownian motion and settle very slowly. The optimal size for delivery is always in the 1-5µm range. The fine particle fraction (FPF) is the percentage of emitted dose with particles in the fine particle range (<5µm)

### EXPERIMENTAL STUDY: MEASUREMENT OF AEROSOLISATION PROPERTIES FOR GELATIN AND QUALI-V®-I (HPMC) CAPSULES

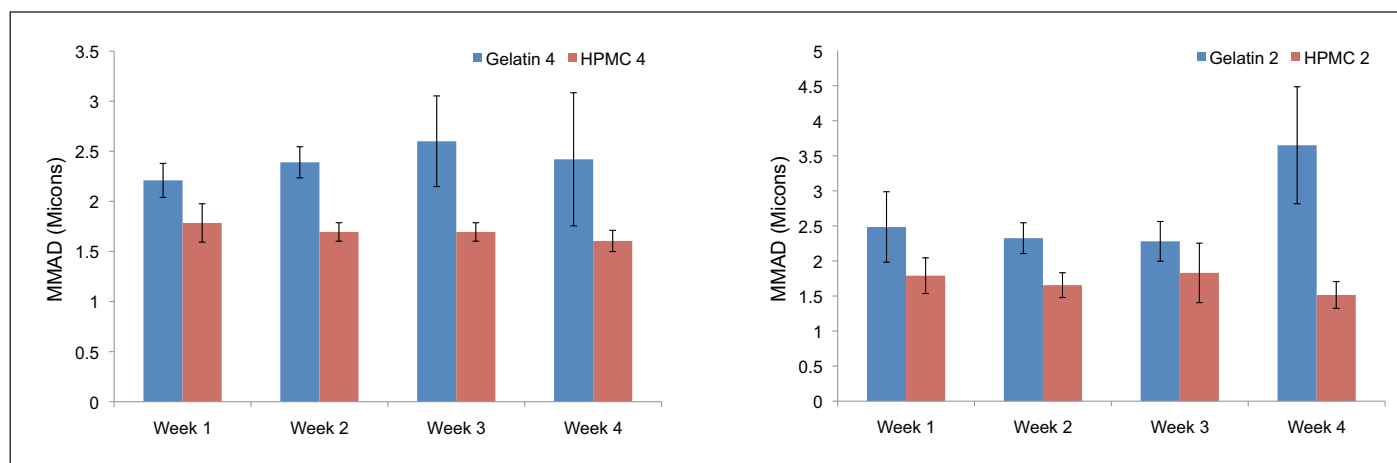
The aim of this study was to compare the aerosolisation properties, (FPF% and the mass median aerodynamic diameter (MMAD)) of a typical powder formulation (binary mixture of salbutamol sulphate and lactose) from two different types of inhalation capsules (gelatin and hypromellose) using two different DPI devices.

Inhalation-grade lactose (Respitose® (DFE Pharma, Goch, Germany, obtained from Laboratoires SMB, Belgium)) was fractionated to give particles of 90-125 µm and blended (Turbula® orbital mixer (Glen Mills, Clifton, NJ, US) for 30 min at 46 rpm with micronised salbutamol in a ratio of 50:1 (w/w). 20 ± 1 mg

of this blend was filled in to inhalation-grade capsules, size three, gelatin and Quali-V®-I hypromellose previously stored in a humidity chamber (Sanyo Atmos Chamber) at 22°C 40% RH for 4 weeks. Samples were taken at weekly intervals and tested in two inhalers with either two or eight puncturing pins (Plastiape SpA, Italy) and then attached to a next generation cascade impactor (NGI) operated at a flow rate of 60 L.min<sup>-1</sup> for four seconds. Salbutamol deposition on the various parts of the NGI, capsule and inhaler device was measured using HPLC. The FPF% and MMAD were calculated from the data: FPF% was the ratio of the drug mass depositing in the NGI (aerodynamic diameter <4.46 µm) over the emitted dose and the MMAD was calculated by subjecting the inertial impaction data to log-probability analysis.

### RESULTS AND CONCLUSIONS

The fine particle fraction (FPF %) values for Quali-V®-I capsules (HPMC) are always higher than gelatin, with a significant difference noted as test time increased, during weeks 2-4 (see Figure 1).



**Figure 2: MMAD for gelatin and Quali-V®-I capsules. (The numbers “2” and “4” refer to the different inhalers used.)**

The results for MMAD for both capsules, shown in Figure 2, confirm a lower MMAD value for Quali-V®-I compared with gelatin capsules, and agrees with the higher FPF% shown in Figure 1.

the capsules: for gelatin capsules it is between 13.0% and 16.0% and for Quali-V®-I it is 4.5-6.5%. This would lead to differences in relative humidity (RH) inside the capsules. The strength of the interaction between the drug and the

of particles surfaces resulting in fused particles and, therefore, larger particles size, leading to aggregation and particles that may not be of a respirable size.<sup>5</sup>

## "QUALI-V® I HYPROMELLOSE CAPSULES HAVE BETTER PROPERTIES THAN GELATIN CAPSULES FOR USE IN PUNCTURING DPIS BECAUSE OF THEIR BETTER AEROSOLISATION PROPERTIES"

This demonstrates that Quali-V®-I hypromellose capsules have better properties than gelatin capsules for use in puncturing DPis because of their better aerosolisation properties (FPF% and MMAD). The data also indicates the importance of device, capsule and storage conditions in obtaining an optimum therapeutic delivery, which could effect to patients over the course of their treatment.

One of the reasons for this behaviour may be the moisture content difference between

excipient carrier or the propensity for particles to detach is dependent on the forces between the particles (van der Waals, electrostatic and capillary forces) and can be influenced by relative humidity (RH). At lower RH, the adhesion force is mainly comprised of the van der Waals and electrostatic forces and as the RH increases capillary forces become prominent and a thin layer of water will appear on the surface of the drug and carrier particles creating a liquid bridge. These bridges may cause solidification

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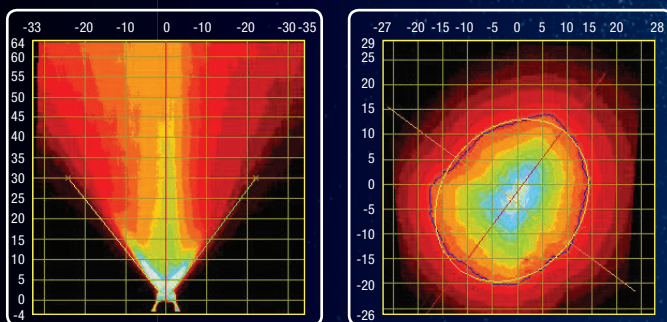
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## THE POWER OF DRUG-DEVICE COMPANY COLLABORATION

In this article, Phillips-Medisize describes how drug-device combination development involves tough challenges for pharmaceutical and biotechnology companies, yet brings with it significant benefits. The advantages of involving a specialist supplier that undertakes device design and manufacturing functions are also highlighted.

During the development phases, drug and device companies alike encounter obstacles in complying with both the US FDA's drug and medical device regulations, as well as other global regulations, that determine which current good manufacturing practices (cGMPs) and quality system regulations apply for product manufacturing. Add to these challenges the need to manage complicated supply chain logistics, from design, testing and development through low-volume clinical trial manufacturing and scale-up into higher-volume production for commercialisation. The most minor detail can derail a successful product development effort, resulting in time and resources lost and

leveraging their suppliers' existing, proven, regulatory-compliant manufacturing processes and infrastructure. Tapping into the expertise of device companies also helps pharma/biotech companies poise their product project for success. Early collaboration, from initial design concept phase, allows the device company partner to help anticipate potentially problematic areas that can occur during pilot production, clinical trials and eventual high-volume manufacturing.

Project success, and the ability to control the many variables in product development, depends upon the ability of drug companies to select the right device manufacturing partner, with the right mix of development support and commercial manufacturing service offerings, to help guide the project. Frequently, project complications and delays can arise as a result of collaboration among disparate organisations. For example, a design firm might not understand, first hand, all that can be achieved in injection moulding processes. Further, designs may not be optimised for manufacturing or assembly.

Similarly, critical tolerances may not be fully understood. When a design partner is also the manufacturer, or when the pharma/biotech company engages its manufacturer early on in the development process, the need to perform knowledge and technology transfer is eliminat-

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crucial deadlines missed – potentially causing the product development or regulatory submission to stall before it ever reaches the market.

When product launch success depends upon speed-to-market, drug and device companies benefit by joining forces. Such partnerships can free pharmaceutical and biotech companies to focus on their core competencies, while

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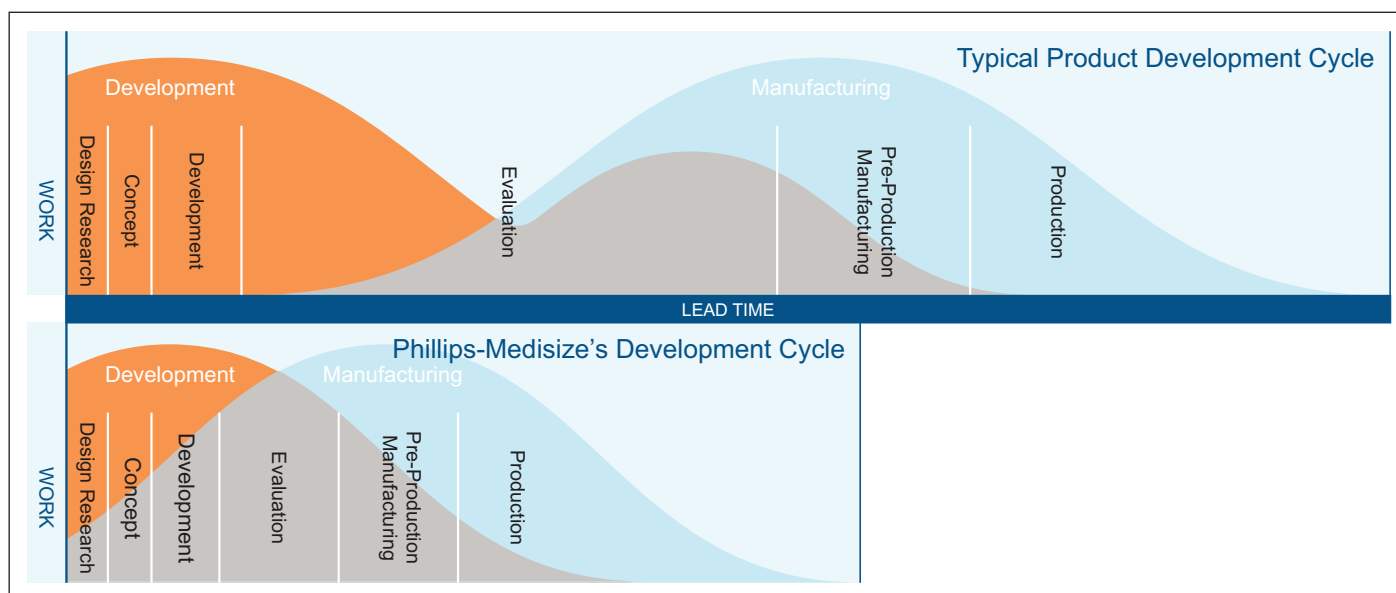
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**Figure 1: Comparison between a typical product development cycle and a Phillips-Medisize product development cycle.**

ed. Exchange of information and data becomes seamless, and the ability to meet key delivery and launch dates is enhanced.

Pharmaceutical companies save money and time partnering with a medical device manufacturer that provides full, one-stop service from concept through commercialisation. The right partner for successful product development efforts will have – in addition to the other necessary capabilities – comprehensive experience in quality systems management. This experience is vital because there is considerable overlap in the drug and device regulations. For the most part the overlap is apparent. For example, both establish requirements for management, organisation, and personnel, and both require documentation and record keeping. The US FDA considers both sets of regulations to be similar, and that they are meant to achieve the same goals. However, differences do exist of course because each set of regulations is tailored to the characteristics of the types of products for which they were designed. The ideal product manufacturer will need to be able to assess how best to comply with both sets of regulations, during and after joining the constituent parts together, by carefully considering the requirements of the cGMPs and quality systems regulations in relation to the constituent parts, and the product(s) they manufacture.

Partnerships between drug and device companies can streamline efficiencies, enhance financial gains, and bring innovative product solutions to patients. The key to bringing a successful and profitable new product into the market is to keep the development process as seamless as possible, from concept through commercialisation.

This target is best met by working with a single supplier able to handle and package drugs, demonstrate complete knowledge of the complexities of medical product development, and offer a full range of engineering and product development services.

By applying adequate due diligence in choosing your partner, pharmaceutical and biotechnology companies can improve the odds of launching a successful new drug product into the marketplace – on time, and on budget.

### TODAY, SPEED IS KING

Phillips-Medisize has a history of manufacturing complex drug delivery devices such as inhalers, injection pens and safety syringes. The company has produced dry-powder inhal-

ers much higher. Big Pharma companies require functioning inhalers before they make decisions concerning new inhaler platforms. Good ideas or drawings are not enough.

Phillips-Medisize's strategy has been to develop its services continuously in order to keep up with the new challenges from customers. "Speed is king" in new developments today. In order to be able to deliver speed in all the development phases, the company has focused the investments into very fast manufacturing of both one- and multi-cavity tools. As this service is combined with the best metrology service available on the market the customer gets components and devices in record time. Having all the critical services in-house, such as design & development, tool manufacturing, metrology, injection moulding and long

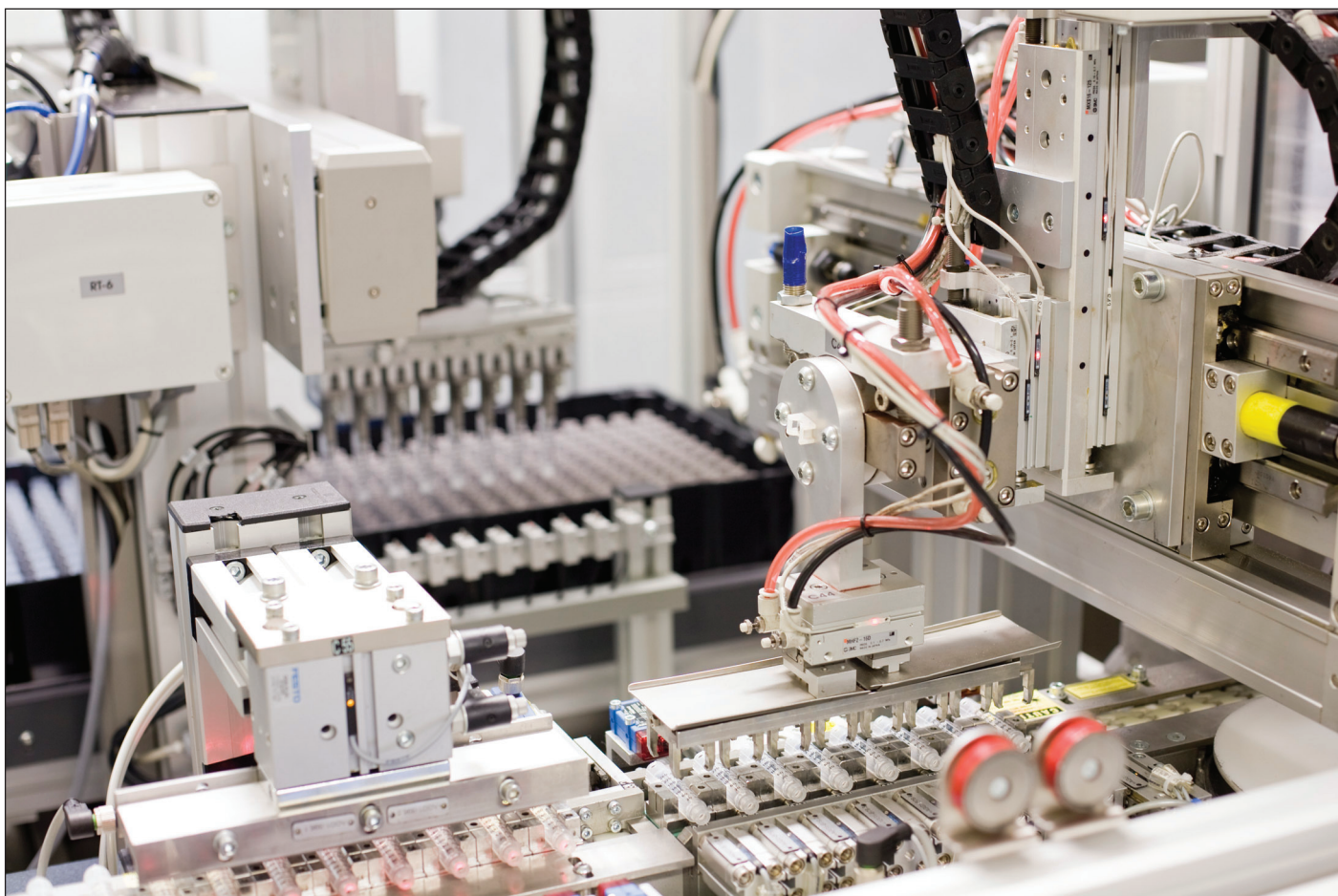
**"PHILLIPS-MEDISIZE HAS A HISTORY OF MANUFACTURING COMPLEX DRUG DELIVERY DEVICES SUCH AS INHALERS, INJECTION PENS AND SAFETY SYRINGES. THE COMPANY HAS PRODUCED DRY-POWDER INHALERS SINCE 1985, AND HAS BEEN INVOLVED IN THE DEVELOPMENT OF ABOUT 10 DIFFERENT INHALER PROGRAMMES"**

ers since 1985, and has been involved in the development of about 10 different inhaler programmes.

Looking back, Phillips-Medisize was the development partner of the first DPI, and comparing it with the market demand of today one can only be amazed. The speed of turning a new inhaler platform design into clinical trials

experience of assembly automation, has been a resoundingly successful strategy. Customers are satisfied with seeing their new devices turn into full production in a continuously shorter time period (see Figure 1).

Thanks to Phillips-Medisize's successful implementation of the strategy of delivering fast development programmes, customers have



**Figure 2: High-speed automation at the Kontiolahti, Finland site, which recently underwent a 6,000 m<sup>2</sup> expansion.**

**“SPEED IS KING IN NEW DEVELOPMENTS TODAY...  
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awarded it with new business. This is why in February 2013, the company added a 6,000 m<sup>2</sup> expansion to its facility in Kontiolahti, Finland (see Figure 2). The site focuses on the production of complex drug delivery devices such as inhalers, injection pens and safety syringes. This state-of-the-art facility manufactures various products from multi-component drug delivery devices in prototype form to finished drug deliv-

ery devices in a high-speed automated production environment.

This expansion was driven by new opportunities that Phillips-Medisize has been awarded over the past 12 months, as well as, to support increased global demand for devices with precise dosage drug delivery requirements that the company currently manufactures at the Kontiolahti site.

#### **ABOUT PHILLIPS-MEDISIZE**

Phillips-Medisize is a leading global out-source provider of design and manufacturing services to the medical device and diagnostics, drug delivery and commercial markets. The company has annual sales of just under US\$500 million (£325 million), with 75% of the total revenue coming from drug delivery, medical device and diagnostic products such as: disposable insulin pens, glucose meters, specialty inhalation drug delivery devices, single use surgical devices and consumable diagnostic components.

Phillips-Medisize Corporation is headquartered in Hudson, WI, US, and employs over 2,100 people in 12 locations throughout the US, Europe and China. The company also has design centers in Wisconsin, US and California, US, and The Netherlands.

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## Proven Production Systems

Based in Freiberg/Germany, teamtechnik has been making intelligent and reliable automation solutions for medical and pharmaceutical industries and for the automotive and solar technology for over 35 years. teamtechnik is considered an international leader in highly flexible automation technology. With a total of 750 employees throughout the world, the company achieves sales of over €145 million. The teamtechnik Group has production sites in Germany, Poland, China and the USA.

## Innovative Process Technology

teamtechnik develops innovative process-optimized production solutions for medical technology that meet customers' requirements right up to serial production. The systems are designed with a modular approach, a highly flexible concept which allows the manufacturers of medical devices to adapt their production quickly and economically to changes in the market.



## From Start-up to High-Speed

For cost effective production from Start-Up to High-Speed production the company has brought to market three different platforms: START-UP, the platform for prototype production to verify processes early in their final execution and for clinical trial production; TEAMED, a highly flexible and upgradeable platform for assembly and testing; and RTS, the high-speed platform for economical mass production.

### Reiner Zeidler

Sales Manager Medical Device Technology

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These platforms are realizing almost 80% of all customer solutions in the medical technology sector. Superior process technology, SPC test systems and 100% end-of-line testing can be integrated specifically for the production of medical devices and pharmaceutical products. The teamtechnik production systems allow production compliant with global guidelines and monitoring systems such as GAMP5, FDA and CE and meet class 6 clean room specifications.



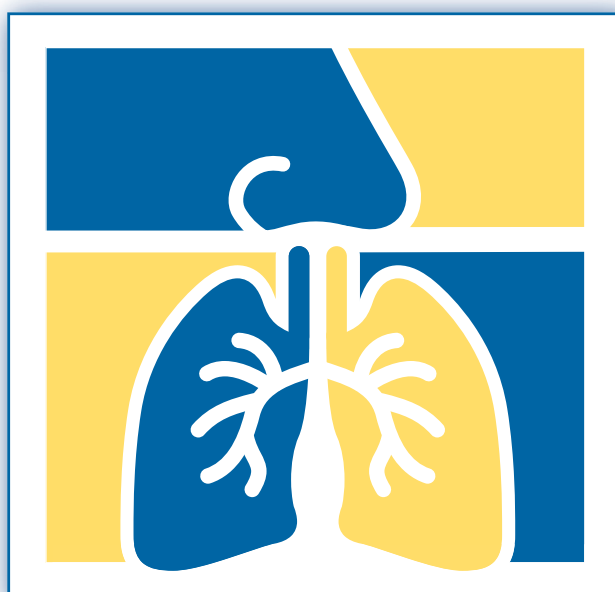
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