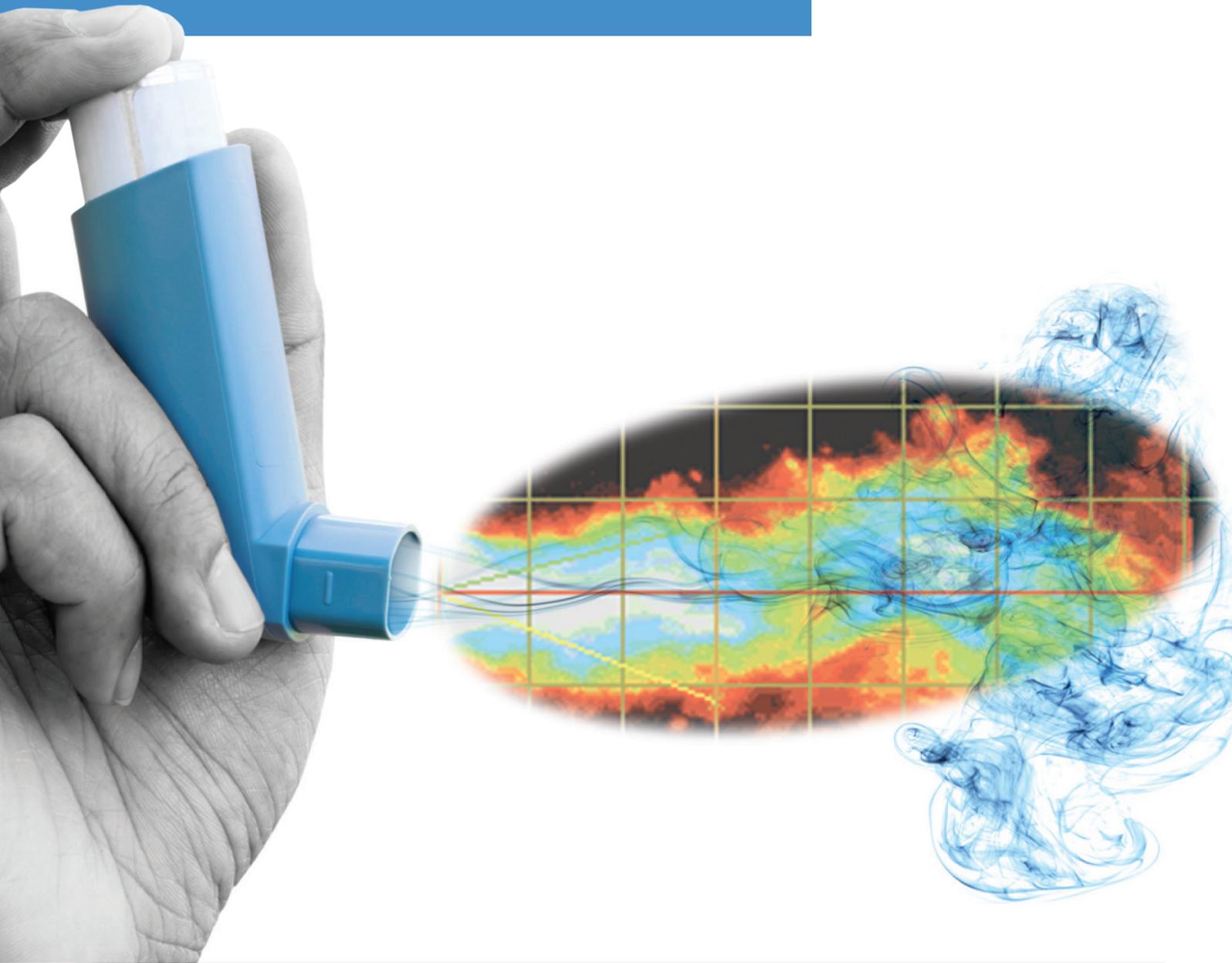


PULMONARY & NASAL DELIVERY



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PULMONARY & NASAL DRUG DELIVERY

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INFLUENCE OF THE HUMAN FACTOR ON NASAL DRUG DELIVERY DEVICE EVALUATION

In this article, Pascale Farjas, Global Category Manager, Alain Regard, Technology Product Manager, and Guillaume Grevin, Senior Design Engineer, all of Nemera, discuss what is required of a modern nasal spray pump and how introducing the human factor to a study of five nasal spray pumps, including Nemera's own Advancia device, showed a significant impact on the variability of delivered volume.

INTRODUCTION

Intranasal delivery is a common route of administration for treating various indications, from allergic rhinitis to breakthrough cancer pain. On the one hand, nasal delivery is an attractive option for locally acting medications (e.g. saline solutions, decongestants, corticosteroids or antihistamines) which treat allergic rhinitis and nasal congestion. On the other, the nose is also the entry point for systemic delivery of numerous drugs and therapies for a variety of diseases. In these cases, common drugs used include calcitonin (osteoporosis), fentanyl, triptans (pain management), estradiol (hormone replacement therapy), nicotine (smoking cessation), desmopressin (enuresis), and metoclopramide (motion sickness).¹

Ever more drugs targeting other therapeutic fields and diseases may join the increasing ranks of marketed products for systemic delivery using the nasal route, such as drugs that act upon the central nervous system to treat disorders like Alzheimer's disease and obesity.² The main reason for this trend in achieving systemic delivery via the nasal route is the advantage of delivering treatments directly from the olfactory region into the brain, allowing the drug to circumvent the blood-brain barrier.

Furthermore, nasal vaccination is an attractive alternative to injection that causes little discomfort to patients. Mucosal vaccines not only promote

"Ever more drugs targeting other therapeutic fields and diseases may join the increasing ranks of marketed products for systemic delivery using the nasal route, such as drugs that act upon the central nervous system to treat disorders like Alzheimer's disease and obesity."

good local immune protection, but also a systemic response similar to that of injection.³ FluMist® (MedImmune (AstraZeneca), Gaithersburg, MD, US), is a nasal influenza vaccine currently on the market and is a popular alternative to the traditional influenza vaccine injection, particularly for children.

Also, preservatives, such as benzalkonium chloride, are commonly used in nasal drug formulations. However, preservatives can irritate the mucosa, deteriorate ciliary clearance and cause unpleasant adverse effects, such as itching, which may negatively impact compliance. For instance, long-term use of intranasal corticosteroids with benzalkonium chloride can lead to high-grade dysplasia in the nasal mucosa.⁴ The development of preservative-free nasal medications is especially important for chronic treatments which, by their nature, require daily use over several months (e.g. for allergic rhinitis therapies) and require appropriate multi-dose delivery systems that prevent contamination.



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Nemera has developed a new preservative-free nasal pump, designed to increase compliance and deliver a precision dose independent of user actuation profile, ensuring the full dose is administered every time.

HOW IS THE PERFORMANCE OF A NASAL SPRAY PUMP DEFINED?

Nasal spray pump performance can be evaluated in accordance with different regulations, such as those set out by the EMA, US FDA or one of the pharmacopeias. Physical characteristics of the spray are then measured with precise methods.

- **Dose delivery**, or shot weight, consists of single actuation weighing and gives information about the consistency of dose delivered to the patient.
- **Droplet size distribution** is measured by laser diffraction.
- **Particle size** is measured by cascade impactor.
- **Spray geometry** consists of the plume geometry and spray pattern measurements.

These characteristics are also important for evaluating the performance of the pump in order to predict nasal deposition. In particular, taken together the droplet size distribution and particle size measurements inform about the overall particle size distribution of the spray, enabling prediction of how the spray deposits in the airways.

Although these physical parameters are relevant to describe the spray produced by nasal pump, *in vitro* spray characteristics evaluated in accordance with different standards/guidelines are mainly assessed using automatic spray actuation controlling the velocity, timespan and strength of actuation. This is restrictive as it does not mimic the variation in actuation profile demonstrated by humans. Previous studies have demonstrated the influence of the actuation parameters on spray characteristics,⁵ questioning the robustness of standard *in vitro* methods for predicting the spray performances when, in practice, the device is manually actuated by patients.

EVALUATION TAKING INTO ACCOUNT THE HUMAN FACTOR

Nemera proposed a study in which the evaluation of intranasal delivery devices took into account the human factor. First, Nemera evaluated the dose delivered

under real use conditions with volunteers. *In vivo* measurements were taken in terms of delivered volume via manual actuation for evaluating the influence of the human factor on the variability of the nasal spray pump's performances. The same devices were then evaluated using an automatic actuator system to measure the delivered volume as per standard methodology. *In vivo* and *in vitro* results were then compared to determine *in vitro/in vivo* correlation.

The delivery system is a critical element for nasal spray performance, in particular it needs to deliver a uniform dose upon each actuation. Hence, the device must be user-friendly and convenient for "on the go" use so that the patient can rely on the nasal spray at any time during the treatment, especially during a migraine or allergy related symptoms, which often occur outside the convenience of the patient's home.

Furthermore, adherence is a key parameter which can influence the efficacy of the treatment. Indeed, not only should the therapeutic efficacy and molecule safety be taken into account for a treatment, but ease of use and comfort of the dispensing system for the patients as well. The nasal spray should help the patient to accept the treatment and therefore improve patient compliance. To achieve patient acceptance and improved compliance, ergonomics should be applied to the nasal device design to ensure overall attractiveness and user-friendly features, such as intuitive handling, good grip, uniform delivery accuracy regardless of actuation profile, etc. These attributes should allow the patient to use the device properly and receive their daily dose of medication required, by improving overall patient compliance.

As with all self-administered drugs, the most critical parameter affecting device performance is the patient themselves. A patient, most of the time untrained, relies on their personal appreciation and the instructions for use to operate the device properly. This perspective constitutes the fundamentals of Human Factors Engineering (HFE),^{6,7} an inclusive design process that aims to identify and mitigate all user-induced risks. The HFE process is based on user studies to identify risks and user misunderstandings, then improve the device design accordingly. HFE also highlights user competence and satisfaction as equally important in ensuring patients' adherence to their treatment. Verifying both a safe and user-friendly device eventually relies on a combination of very different factors; ranging from functional to more perceptive

ones, such as overall ergonomics or daily-use adaptability.

In the second step of this study, Nemera evaluated the performance of the devices in terms of perception and feeling because even the best drug, in the best container, with the best delivery device, can end up being useless if patients don't, or can't, use it properly.

IN VIVO STUDY

Thirteen healthy adult volunteers (seven male, six female) were included in this single-centre study (Figure 1). The study was performed in 2017 at Nemera (Innovation Center, La Verpillière, France). Five different nasal spray pumps from different companies were filled with water and were tested in a randomised order,

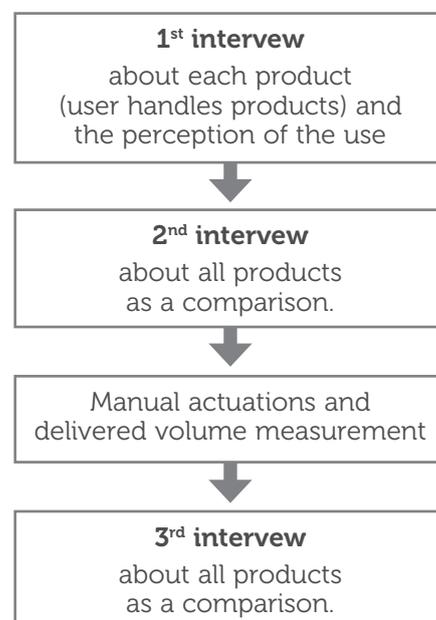


Figure 1: *In vivo* study protocol.



Figure 2: *In vivo* volume delivery test with Advancia nasal pump.



Figure 3: *In vitro* volume delivery test with Advancia nasal pump.

including Nemera's own next-generation pump, Advancia (Figure 2). A first interview was conducted with the volunteers before the test. Each product was observed and manually manipulated. A second interview was conducted for product comparison. The device was manually primed and then given to the healthy volunteer. The device was actuated in ambient air and the weight difference was measured to calculate the delivered volume by the volunteers. Three actuations were performed per device and per user, resulting in 39 results per nasal pump. After the five pumps were tested manually by the volunteers, a last interview was conducted about the five nasal pumps. Participants were asked to rank the different nasal pumps in three boxes: the green box (for those they would like to use for a long-term daily treatment), the red box (for those they wouldn't like to use for a long-term daily treatment), the yellow box (for those in between).

Participants were asked to rank all nasal pumps into one of three categories:

- **green** (for those they would like to use for long-term daily treatment)
- **red** (for those they wouldn't like to use for this treatment)
- **yellow** (for those in between)

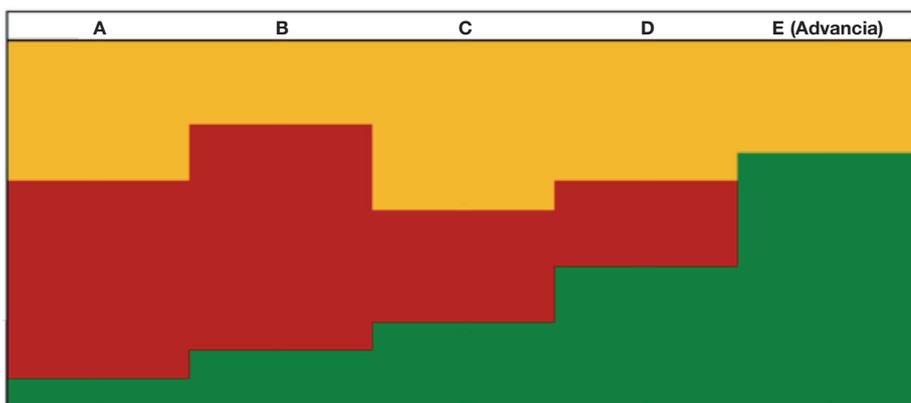


Figure 4: Results from interviewing the 13 volunteers.

they wouldn't like to use for this treatment) or the yellow box (for those in between). Results to these questions gave a ranking from the most appreciated pump to the least appreciated one.

IN VITRO STUDY

The same devices used in the *in vivo* study (provided from the same batches) were tested in a randomised order in an *in vitro* study (Figure 3). They were filled with water and manually primed. Devices were placed in an automatic actuator (Proveris NSx, actuation speed of 80 mm/s, acceleration of 7000 mm/s²). Devices were actuated in ambient air and the weight difference was measured to calculate the delivery volume. 39 actuations were performed per device to match the number performed in the *in vivo* study.

RESULTS

Figure 4 clearly shows how the volunteers ranked the different pumps. Advancia proved to be the pump that volunteers felt most positively about, with no appearances in the red box and almost 70% of the time being placed in the green box (nine in the green box). Contrarily, Devices A and B were the two pumps that the volunteers felt the least affinity for (one and two in the green box respectively).

Figure 5, and the associated data in Table 1, shows the mean average of the delivered volume across the devices for the *in vitro* and *in vivo* studies. All products have a relatively low *in vitro* variability, with a maximum of 5% for device B and a

minimum of 0.6% for device D. However, manual actuation by the 13 volunteers shows larger variability in terms of delivered volume, with the exception of Advancia (device E). There was a good correlation between the mean of *in vitro* delivered volume (x) and the mean of the *in vivo* delivered volume (y) ($y=0.93x$, $R^2=0.97$). Nevertheless, Figure 5 shows a trend towards lower volumes delivered by manual actuation, most keenly observed in device D, with a dose decrease of 12% between *in vitro* and *in vivo* actuation.

Regarding data dispersion, we can observe a high user dependency on volume delivery for devices A, C & D, around 25% in terms of variability, and a lower user dependency for devices B and E (Advancia), around 5% in terms of variability. These results confirm the influence of a manual actuation of the device on delivered volume variability.

CONCLUSION

A correlation in terms of mean delivered volume was found between *in vitro* and *in vivo* tests, showing a lower delivered volume by manual actuation in comparison to automated actuation (-7%). Different manual actuations by users were visually observed, explaining a partial delivered volume from the device when the actuation was incomplete. Furthermore, a high difference in terms of delivered volume variability was observed between *in vivo* and *in vitro* results, demonstrating the difficulty of predicting real device variability from automatic actuation only. Nemera's Advancia device was the only device to show a good correlation between *in vitro* and *in vivo* results in terms of delivered volume and variability.

Regarding the user satisfaction for the five nasal pumps, nine out of the thirteen volunteers said they would prefer using the Advancia device for a long-term treatment, more than for any of the other devices in this study. However, whilst Advancia had the best results both in terms of the user satisfaction test and delivered volume variability, interestingly there was no overall correlation found between patient satisfaction and spray volume variability.

The conclusions drawn from this study have limitations, in particular with regard to the low number of participants who tested devices, and therefore complementary tests should be performed in order to confirm these results. However, similar conclusions have been obtained by droplet size distribution

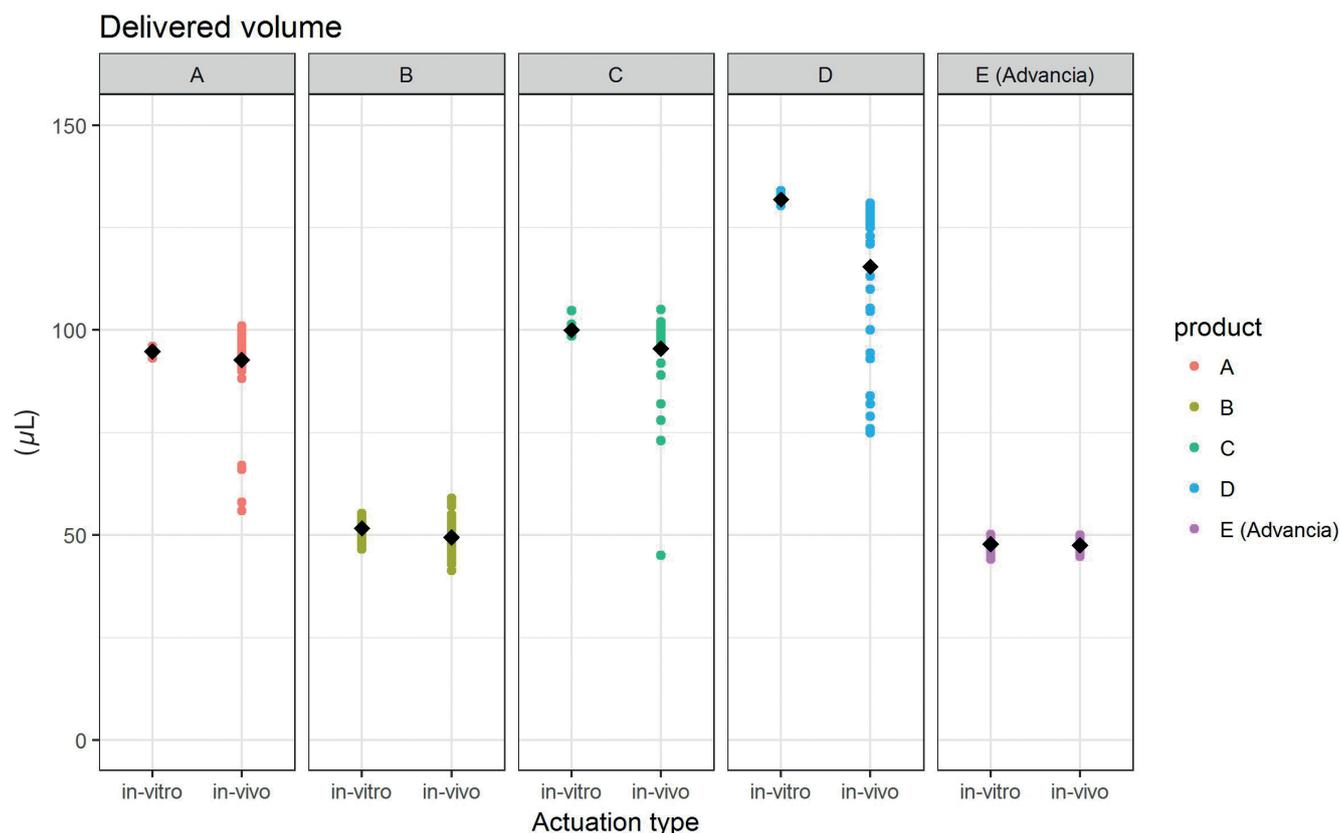


Figure 5: Volume delivery by automated actuation (*in vitro*) and by manual actuation (*in vivo*) for the five nasal pumps (n=39 actuations per device) with the mean value shown in black.

Device	<i>In vitro</i>			<i>In vivo</i>		
	Mean (µL)	SD (µL)	Min-Max (µL)	Mean (µL)	SD (µL)	Min-Max (µL)
A	95	1	93-96	92	12	56-101
B	52	3	47-55	50	5	41-59
C	100	1	99-105	96	10	45-105
D	132	1	130-134	116	19	75-131
E (Advancia)	48	1	44-50	48	1	45-50

Table 1: Volume delivery by automated actuation (*in vitro*) and by manual actuation (*in vivo*) for the five nasal pumps (n=39 actuations per device) in terms of mean, standard deviation (SD) and minimum-maximum (Min-Max).

measurement,⁸ showing a higher variability in terms of droplet size by manual actuation compared with automated action.

Nevertheless, an automatic actuator is recommended by multiple regulatory agencies for spray performance evaluation. This may be due to automatic actuation having the advantage of being able to evaluate variation associated with different batches of drug product. Furthermore, controlling the actuation force or the velocity can help to give a better understanding of the inherent device performance by eliminating them as variables. Therefore it can be stated that

an automatic actuator is a good option for evaluating device quality but seems poorly suited for predicting *in vivo* results.

ACKNOWLEDGEMENT

The authors would like to thank Laurent Vecellio for his contribution.

ABOUT THE COMPANY

Nemera is a world leader in the design, development and manufacturing of drug delivery devices for the pharmaceutical, biotechnology & generics industries.

Nemera's services and products cover several key delivery routes:

- Nasal, Buccal, Auricular (pumps, valves and actuators for sprays),
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- Dermal and transdermal (airless & atmospheric dispensers),
- Parenteral (auto-injectors, pens, safety devices & implanters).

Nemera always puts patients first, providing the most comprehensive range of devices in the industry, including innovative off-the-shelf systems, customised design development and contract manufacturing.

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Pascale Farjas is the Global Category Manager for the ear, nose, and throat (ENT) segment at Nemera. Her role encompasses understanding patient needs, and regulatory requirements, to develop and market packaging solutions that improve the patient experience. She is in charge of the market introduction of new pump platforms for nasal sprays. Ms Farjas joined Nemera in 2011 and holds a Chemical Engineering degree from the National Institute of Applied Sciences of Rouen, France, completed with a marketing-focused Masters degree from the Business Administration Institute (France). Prior to joining Nemera, Ms Farjas held various positions in strategic (market intelligence and market studies) and operational marketing in the pharmaceutical industry for international markets.

Alain Regard, Technology Product Manager, graduated with a degree in Polymer Engineering and Processing from ESP in Oyonnax, France. After a long experience in design and development in the automotive industry, he joined the company in 2010 as a product development leader. Mr Regard, today one of the key technical experts of Nemera's Innovation Center for Devices (ICD), leads the nasal and dermal developments. He drives some of Nemera's own IP projects as well as working on several customer product developments in the field of nasal and dermal applications.

Guillaume Grevin, Senior Design Engineer, graduated from ISPA, Alençon, Normandy in Industrial Plastics. In 2008, after gaining experience in the plastic films industry, and in medical primary packaging R&D, he took part in the transformation of Nemera's R&D department into the Innovation Center. After a major role in the development of an innovative ophthalmic platform, Guillaume has been strengthening its expertise in nasal segment since 2012. Today he contributes both to the development of Nemera's own IP projects and upscaling product knowledge.

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MEETING FUTURE NEEDS FOR RESPIRATORY DRUG DELIVERY DEVELOPMENT

There's a lot of work going into developing smart devices at the moment, but few examples of smart devices getting to the stage where they can be launched on the market. In this article, Mark Knowles, Head of Product Engineering, and Collette Johnson, Alliance Manager, both of Bespak, explore the different elements that need to be considered when developing a smart inhalation drug delivery device to ensure that maximum benefit is obtained.

Currently, there are around 300 million asthma and chronic obstructive pulmonary disease (COPD) sufferers that rely on inhalation devices for effective delivery of their medication.¹ However, using an inhaler is not easy – it takes skill and practice, whatever the design of the device, to ensure that inhalation and device actuation is synchronised, allowing the correct dose to be taken. To date, the focus has been on the medications, the device design and optimising how both work together in the hands of the patients, who themselves are a diverse and varied group.

As the drive towards connected health gains momentum and the benefits this can bring for patients, clinicians, payers and manufacturers start to be realised, one thing is becoming clear: putting electronics into a device is not a simple task.

GETTING COMPLEX DEVICES RIGHT

Any drug and drug delivery mechanism should always start with the patient's needs in mind – and getting the device right first

“As the drive towards connected health gains momentum and the benefits this can bring for patients, clinicians, payers and manufacturers start to be realised, one thing is becoming clear: putting electronics into a device is not a simple task.”

time is everyone's goal. To achieve this, establishing a multidisciplinary team from the outset is vital. However, inhalation devices in particular are extremely difficult to develop, and there is a storied history of failures for novel drugs and generics.

Device experts, like ourselves, have partnered with drug developers over the years to produce essential inhalation devices – we started work with Beecham (now GSK) in Worthing, UK, on Ventolin inhalers in the mid 1960s. Since then, innovation has driven the creation of many new technologies including metered dose inhalers (MDIs) and the introduction of dry powder inhalers (DPIs) (Figure 1). Nowadays, Bespak manufactures over 500 million inhalers per year (Figures 2 and 3).



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Figure 1:
Chiesi
NEXThaler®,
a multi-dose
metered
dry powder
inhaler.





Figure 2: Integrated dose-counting actuator devices in testing.

PROBLEMS WITH INHALER USE

Fundamentally, inhalers need to be intuitive devices that can be easily operated with simple or no instructions. As an industry, we are always trying to meet the challenge of right drug, right time, right amount. Although significant resources are going into educating patients and their families on how to use inhalers properly, such as ensuring breathing and actuation are correctly timed, there remains a significant amount of misuse. Shockingly, data shows that 76–94% of inhaler users are not using their devices correctly² and around 60% do not always take their medication.³

Typically, the correct breathing pattern for a standard inhaler is to breathe in slowly for around six seconds, with a force of around 30 N, and then hold your breath for about six seconds to maximise drug intake. Realistically, patients very rarely achieve this, but correct usage would potentially drive up yield significantly. Unfortunately, there are a number of asthma-related deaths that might have been prevented if patients were taking their medication regularly and properly.⁴

HOW CAN SMART INHALERS HELP?

Assessing Value

When it comes to smart technology and connected health, we need to assess what



Figure 3: High-volume manufacture of dry powder inhalers.

“Although significant resources are going into educating patients and their families on how to use inhalers properly, such as ensuring breathing and actuation are correctly timed, there remains a significant amount of misuse.”

benefits it brings, particularly for patients, and be realistic about what it cannot deliver. At the moment, smart inhalers can determine if a device has been actuated, thus

it is able to provide feedback on frequency of use. But the technology has not yet been developed such that it can say how much of the drug has entered the lung and, until

“Smart devices could perhaps be used to provide information about user habits and the local environment, and potentially help us better understand an individual’s condition.”

there is some flow detection in the device, it wouldn’t even be able to say if the drug had entered the lung in the first place.

So if smart inhalers at present can’t solve this clinical problem, it’s difficult to justify a significant increase in the device cost through the addition of electronics into a standard asthma inhaler. However, if you look at biologics, drug addiction therapy or pain relief, which are an order of magnitude more expensive than asthmatic drugs, then the economics shift. Additionally we can also start thinking about the value of secure devices where only a specific user will be able to administer a particular drug, for example in drug addiction therapy.

Smart devices could provide us with data and usage patterns, but will that information be valuable? Not just valuable to the pharmaceutical company, but ultimately for patients because, if they don’t see the value, they won’t understand the importance of using the device properly.

Making Devices Attractive

Smart devices need to fit into people’s lifestyles and habits so that they can carry on with their lives without their condition drastically impacting it. Although we have made significant advances to tailor devices for specific patient groups and their carers, we need to go beyond that. Can we make devices more attractive for the user so that they actually want to use their device?

When designing devices we also need to look at the target demographic. For example, with children there can certainly be a stigma surrounding taking inhalers and being labelled a “sick” child at school, which may discourage use at the expense of their health.

For primary school children, ordinarily the responsibility lies with the teacher to ensure that they take their medication properly. But for high school children, the responsibility is more with the child so we need to do more both to help them better understand the impact of not correctly taking their medicine, and consider how to make the device more attractive to them in general. Perhaps we should be doing more to make inhalers customisable, enabling

children to choose, for example, a suitable reward system for using their device correctly so that the device is perceived as having more “fun” elements by the user.

Harnessing Connectivity

With the rise of wearable devices and activity tracking, could smart devices be tethered to a mobile phone through a specifically designed app? If patients were not using the device correctly or had forgotten to take their medication, could this information be gathered and fed back to improve usage or set off a reminder for the user?

Smart devices could perhaps be used to provide information about user habits and the local environment, and potentially help us better understand an individual’s condition. If location, air pollution and usage data could all be recorded, there may be observable usage patterns that would have otherwise gone undetected and measures could be put in place to manage their condition. For example, synthetic fertilisers can cause COPD patients to have severe exacerbations. Could we put sensors in a smart device for COPD users that maps the environment, or has an alarm that is activated when synthetic fertilisers are detected?

Then comes the challenge of implementing connectivity – how do we want the device to be connected (GPS, WiFi, Bluetooth) and how important would it be to be connected all the time versus potentially being offline and updating the app occasionally?

What about patients where connectivity just simply won’t work for them? We have to remember that connectivity isn’t going to be for everyone so, as we advance with connected devices, there still need to be adequate solutions for those whose devices, for whatever reason, are not connected.

Using Biometrics to Improve Security

Safe delivery of the correct drug to the correct individual is a challenge where connected devices and biometrics could potentially help. If something like fingerprint technology was included, it would shift capability beyond a simple Bluetooth device that is basically set with a defined

inventory that says whether or not the inhaler has been taken, to then enabling safety lock-outs, child lock-outs and others. The right type of smart device could also be a powerful tool to help address drug misuse problems.

The challenge is that fingerprint technology is relatively expensive and so raises questions of cost-effectiveness. A whole layer of fingerprint verification decision making would have to be added in, which increases complexity both mechanically and on a software level.

SOCIO-ENVIRONMENTAL & ENVIRONMENTAL RESPONSIBILITIES

There are also socio-environmental and environmental factors to consider. Reducing plastics is a hot topic at the moment, and where we can, we are developing devices where certain elements can be replaced rather than needing to replace the whole device.

In terms of replacement, there are two types of multi-dose delivery devices: ones with an interchangeable add-on and ones where the whole device needs to be replaced once all the drug has been used. A large amount of plastic would be saved if we just shipped drug canisters alone, rather than the canisters and actuators.

However, shifting from a completely disposable device to an interchangeable one can be a challenge for patients, as it may take some time to use the new system correctly, i.e. remembering to only replace the add-on and not throw away the whole device. Proper education is therefore important but there could be a mechanism in the smart device that reminds the user not to throw the device away.

In addition, we need to consider correct disposal of the various parts. Smart devices that use battery technology fall within the scope of the EU Waste Electrical and Electronic Equipment (WEEE) recycling directive; how do we dispose of them and who has the responsibility to do this? Typically people throw batteries in the bin rather than taking them to a specific disposal area at say, the local supermarket. How do we change this behaviour?

Of course, pharmaceutical companies have a much bigger environmental responsibility for medical devices, particularly if batteries are included, so they need to consider how best to dispose of them. For example, could patients drop off used devices at the pharmacist,

when they pick up their new prescription? But what happens when patients or carers forget to do this because they are too busy with other things? Should there be some sort of secure envelope that the devices need to be sealed up in, and could this be securely posted or even collected by a pharmaceutical representative? We certainly don't want to increase the burden for the user or their carer.

CONCLUSION

Primarily, for a connected device to be successful, it needs to have features that keep the patient engaged in using it correctly and at the right frequency. It needs to be able to help address the challenge of patient compliance often seen with the current passive devices. In summary, it should be:

- Easy (ideally engaging) to use – promoting right time, right technique
- Low maintenance – minimal setup; easy to dispose or recharge
- Highly portable and easy to find.

If a device achieves the above, it should make a positive contribution to usage statistics. And subsequently, additional connectivity features can be considered, such as delivery history, security and tracking technology, to further contribute to the overall goal of right drug, right time, right amount.

ABOUT THE COMPANY

Bespak, a Consort Medical company, is a full-service drug delivery partner, specialising in innovative patient-centric medical devices. With over 50 years' experience in drug delivery Bespak seeks to apply its proven know-how and technologies to address the ever-changing needs of the pharmaceutical industry, across multiple applications. Bespak partners with customers to design and develop drug delivery devices, as well as providing contract device manufacturing from pilot to commercial scale. As part of the Consort Medical Group, Bespak works with its Aesica colleagues to offer customers an accelerated route to market

through a streamlined service, at any stage of the development cycle. As a group, Bespak currently has 10 facilities across Europe supported by a global sales presence including North and South America, China, India and Japan.

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ABOUT THE AUTHORS

Collette Johnson works for Bespak in strategic relationship and alliance management, driving successful customer partnerships across multi-functional disciplines to maximise commercial success. Previous to working at Bespak, Ms Johnson worked at Plextek, leading the company's medical business and corporate marketing. She also worked at NHS Innovations with a lead role in bringing together industry and clinical organisations for product adoption and was the programme lead for the national SBRI healthcare programme. While in this role she focussed on the connected healthcare sector and developed a network bringing together industry, clinical and academic stakeholders. Her experience also includes a strategic role in healthcare at Cambridge Consultants for world-leading corporate organisations and innovative start-ups.

Mark Knowles works for Bespak as the Head of Product Engineering, furthering technology and product offerings to support Bespak's respiratory, drug delivery and *in vitro* diagnostic device portfolio. Mr Knowles has over 30 years' experience in R&D, the last 20 years in medical device development. Previous to working at Bespak he worked at Cambridge Consultants (medtech diagnostics) and Elekta Ltd (invasive radiotherapy). Mr Knowles has a great deal of experience translating customer needs into technology solutions, designed for high-volume manufacturing in highly regulated environments. He has an MBA in technology management.

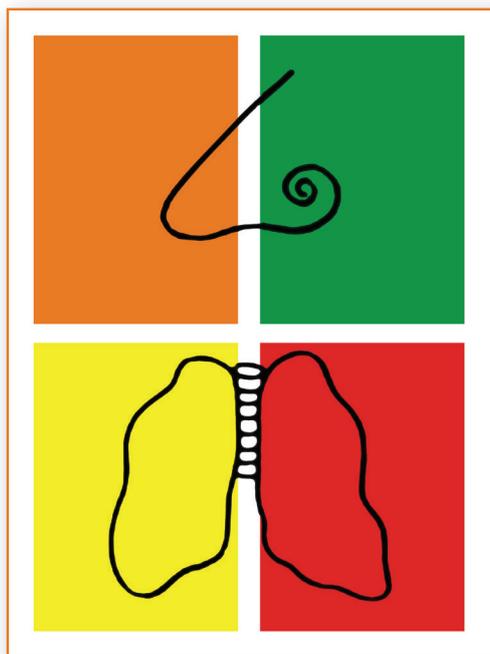


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CHOOSING THE RIGHT DOSATOR FOR DPI DOSING

In this article, Jamie Clayton, Operations Director, and Rajeev Dattani, PhD, Applications Specialist, both of Freeman Technology, and Dave Seaward, PhD, Projects Director, 3P Innovation, discuss the operation of dosators for reliable and accurate filling of DPI capsules and blisters, elaborating on a case study that demonstrates the value of analysing the dynamic properties of a powder in order to determine a profile of suitable characteristics for use in a dosator.

Most dry powder inhalers (DPIs) operate with pre-metered doses of drug formulation held in a capsule or blister pack. Dosator systems are routinely utilised for the production of these packaged doses because of their ability to deliver the requisite filling accuracy at a high throughput. However, DPI formulations often exhibit properties that make them difficult to dose precisely at the low volumes required, with poor flowability a recognised issue. Choosing dosing technology that is well-matched to the properties of the formulation therefore is essential for a reliable, efficient manufacturing pipeline.

In this article we examine the properties of DPI formulations and the conditions they are subjected to during dosator operation. The benefits of multi-faceted powder characterisation are discussed within the context of measuring powder properties for equipment selection and process optimisation. Experimental data highlight the ability of dynamic powder properties to provide a basis for dosator selection for a given DPI formulation.

DOSING DPI FORMULATIONS

To reach the lung, the particle size of the active pharmaceutical ingredient (API) in a DPI formulation must be in the region of five microns or less. Powders with particles in this size range usually are highly cohesive and have poor flow properties, making them difficult to process and disperse. Formulating

“A free-flowing powder is required to fully fill the dosator tube but the powder must also be cohesive to prevent loss of the dose during transfer, compressing to a stable plug that that locks into the tube.”

the API with a relatively coarse carrier, such as lactose, is a well-established strategy for addressing these issues. Attaching the API to a more free-flowing carrier makes it much easier to dose, and the carrier is then stripped away during product use by the force of the patient’s inhalation, ending up deposited in the mouth and throat.

The pre-metered dose required for DPIs varies considerably, from less than one, to tens of milligrams, depending on the developed formulation. Dosator technology is routinely used for applications in the 10-600 mg range,¹ with appropriate technology robustly delivering highly accurate DPI dosing at an acceptable throughput. Figure 1 shows a schematic of a dosator system.

In operation, powder flows into the open end of the dosator tube as it is pushed into the loosely packed powder bed. The captured dose is lightly compressed by the dosator pin or piston, forming a compacted powder plug which is subsequently ejected into the receiving capsule or blister. The outlet of the dosator is typically matched to the packaging being used, with commercially produced dosators having fixed diameters to match standard capsule sizes. Dosing performance for a given dosator/powder combination, defined in terms of dose weight uniformity, is influenced by the magnitude of the applied compressive force, the initial height of the piston and the powder bed’s depth and consistency (i.e. the ease with which the powder bed flows and recovers following the removal of a dose).

Because of the way in which they operate, dosators are more sensitive to the physical properties of the powder than alternative dispensing systems. A free-flowing powder is required to fill the



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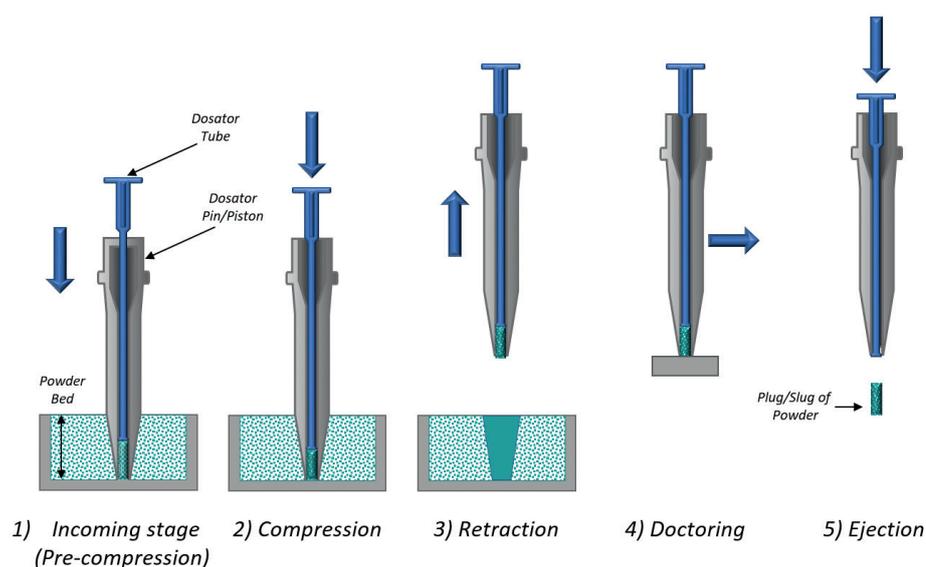


Figure 1: Dosator systems are routinely used to pre-meter DPI formulation doses.

dosator tube fully but the powder must also be cohesive to prevent loss of the dose during transfer, compressing to a stable plug that locks into the tube. Dosators are therefore suited to only a limited range of powders.

Furthermore, for any given powder density and dosator diameter, the target weight can only be achieved by altering the depth of the powder plug. Varying the ratio of dosator diameter to plug depth can have a direct impact on dose weight uniformity, so this can be challenging with respect to achieving robust process performance. With a small diameter to plug depth, inconsistent dose weight is most likely to be due to incomplete or inconsistent filling of the dosator tube. Conversely, with a large diameter to plug depth, it may be associated with the powder failing to lock into the tube such that it falls out during transfer. Ensuring a good match between the properties of the powder and the selected dosator is essential.

USING A POWDER RHEOMETER FOR FORMULATION CHARACTERISATION

Useful measurement of powder flow properties, in the context of assessing dosator performance and compatibility, requires a technique that sensitively differentiates powders in a relevant way. As such, dynamic powder testing with a powder rheometer can be a productive choice for the optimisation of dosing technology (Box 1). Though many techniques are available for powder flow measurement, including the relatively simple methods listed in the US Pharmacopeia (USP 1174), few both offer the sensitivity needed for robust process optimisation and measure properties that

reliably correlate with dosing performance.

With dynamic testing, powders are measured in motion. The resistance that a powder presents to flowing, quantified in terms of flow energy, is determined from precise measurements of the force and torque acting on a blade as it rotates along a prescribed path through a sample of known volume. This can be done under a range of conditions, with a sample that is consolidated, under moderate stress, aerated or even fluidised, to directly simulate a desired process.

“Though many techniques are available for powder flow measurement, including the relatively simple methods listed in USP 1174, few offer both the sensitivity needed for robust process optimisation and measure properties that reliably correlate with dosing performance.”

The measurement of flow energy during a downward traverse of the blade yields the parameter Basic Flowability Energy (BFE). This rotation profile subjects the powder to forced flow conditions, pushing it down against the confining base of the test vessel. In contrast, an upward traverse of the blade exerts a gentle lifting action, generating the parameter Specific Energy (SE), which is indicative of how the powder will behave when flowing in low stress conditions, e.g. under gravity. The parameter Aerated Energy (AE)

BOX 1: A PRAGMATIC APPROACH TO POWDER TESTING

Over the course of manufacture and use, a DPI formulation is likely to be subject to various significantly different conditions, which will alter the way the powder behaves. For example, when lightly compacted in a dosator the powder behaves as a stable plug whereas when aerated the powder behaves as an aerosolised cloud. Though it may not be clear from the outset which powder properties will correlate most closely with observed behaviour in either situation, it is reasonable to suggest that it will not necessarily be the same properties, highlighting the limitations of a single number approach.

In addition to generating dynamic powder properties, powder rheometers can assess shear and bulk powder properties – compressibility, permeability and bulk density. These instruments can therefore be used to generate a

database of properties for any given powder. Correlating these properties with performance data highlights those of most relevance for any given process. Such correlations make it possible to develop a specification characterising powders that will process well, therefore supporting the development of a robust design space and/or optimised formulation.

The case study here highlights the relevance of SE and AE in determining metering performance, and previous studies² have also identified a direct correlation between fine-particle dose, the dose delivered by a DPI that lies in the sub-five micron region, and AE. These findings underline the value of being able to measure multiple powder properties and the broad relevance of dynamic data to both manufacturing (dosing) and product performance (dispersion and drug delivery).

directly quantifies a powder's response to air and is generated by measuring BFE as air flows upwards through the sample at a known velocity. Measuring AE as a function of air velocity makes it possible to compare how aeration impacts flowability, up to the point of fluidisation.

CASE STUDY: CORRELATING DYNAMIC POWDER FLOW PROPERTIES WITH DOSATOR PERFORMANCE

Five lactose powders, with varying particle size distributions, were processed through a lab-scale dosator (Figure 2) using outlets of progressively decreasing size, from Dosator 1 to Dosator 4, whilst keeping all other process conditions constant. The goal was to produce doses of 50 mg consistently with a relative standard deviation (RSD) of <2%. The results of the trial in terms of RSD values for each lactose-dosator

combination are shown in Table 1. The results demonstrate that this type of analysis helps optimise dosator geometry for a given powder.

Powder Characterisation

Using a powder rheometer, a range of dynamic, shear and bulk powder properties were measured for each of the lactose samples in order to determine a rationalisation for the observed trends in dosator performance. Dynamic powder properties, particularly AE and SE, were found to correlate most strongly with dosator performance.



Figure 2: A lab-scale dosator is a useful tool for experimental investigations and confirmation of an optimal configuration for a given formulation.

	D ₅₀ Particle Size Range (µm)	Dosator 1	Dosator 2	Dosator 3	Dosator 4
Lactose 1	180-250	2.27	2.4	2.06	0.89
Lactose 2	110-155	3.77	1.54	1	1.08
Lactose 3	70-110	1.84	0.85	0.79	0.56
Lactose 4	40-70	1.34	2.02	2.13	4.41
Lactose 5	4-11	3.76	7.05	7.59	8.32

Table 1: Dosator performance figures (expressed as %RSD) show that the different lactose grades exhibit significantly different performance depending on the dosator outlet used.

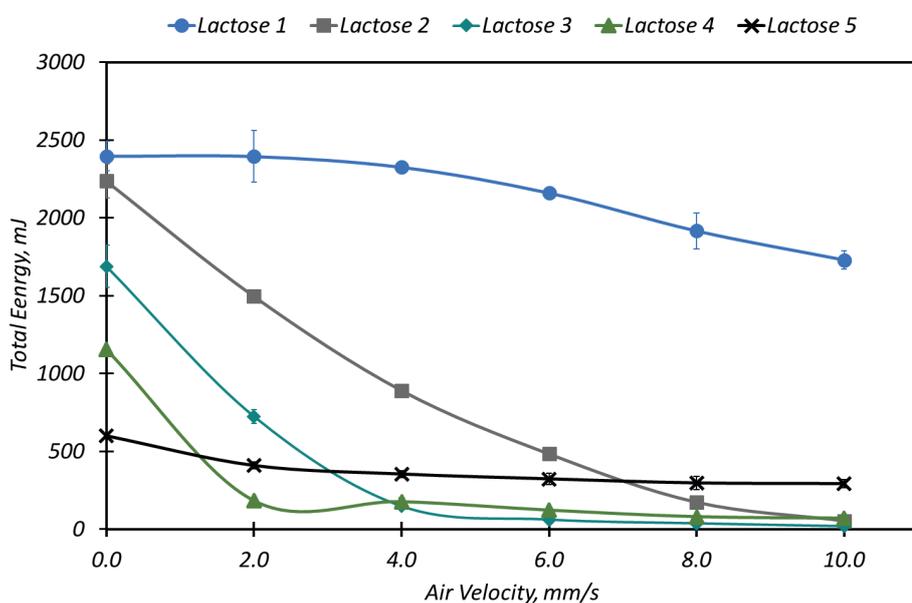


Figure 3: Plots of AE as a function of air velocity indicate that the lactose samples vary significantly in terms of their response to air.

Figure 3 shows how AE varies as a function of air velocity for each of the lactose samples. AE data measured at 2 mm/s (AE₂), shown in Table 2, summarises the observed differences for correlation with dosator performance. The flow energies of Lactose 1 and Lactose 5 are substantially less impacted by air than those of the other three. Lactose samples 2, 3 and 4 all exhibit a similar aeration profile but again there are differences in AE₂, which increases from Lactose 4 through to Lactose 2.

Very fine, cohesive powders with high interparticulate forces, tend to have a relatively low flow energy because of their ability to entrain and retain air. Entrained air dampens the transmission of shear through the powder bed, thereby reducing the energy needed to move the powder,

	AE ₂ (mJ)
Lactose 1	2395 (±7%)
Lactose 2	1500 (±1.7%)
Lactose 3	725 (±6.1%)
Lactose 4	180 (±3.5%)
Lactose 5	410 (±5.6%)

Table 2: AE at 2 mm/s.

“Correlating dynamic properties with dose consistency makes it possible to predict more optimal dosator configurations for given powders.”

as seen in Figure 4. The introduction of air tends to have little effect on such powders because the upward flowing air cannot easily break the strong interparticulate forces of attraction. Lactose 5 exemplifies this behaviour. It has a low flow energy that is minimally impacted by air velocities of up to 10 mm/s.

When interparticulate forces of attraction are lower, as is the case with larger particles, air flowing through the powder bed can separate and lubricate individual particles, easing their movement relative to one another. However, Figure 4 also demonstrates that lower interparticulate forces reduce the ability of the powder to entrain air. Such powders therefore have a relatively high flow energy that decreases significantly with aeration. Lactose 2, 3 and 4 all display this characteristic.

In powders with sufficiently coarse/regular particles a third pattern of behaviour emerges, associated with highly uniform packing within the powder bed. Stress is transmitted extremely efficiently in such powders giving rise to a high flow energy. However, as a result of low interparticulate forces and high permeability, any air introduced flows freely through the bed with little to no impact on the particle packing structure. High air velocities are therefore needed to separate the larger, denser particles. These effects are clearly evident in Lactose 1, but also help to rationalise the trend in AE_2 observed in Lactose 2 through to Lactose 4.

Figure 5 shows SE values for the five lactose samples. In an SE measurement the powder is unconfined and the movement of particles, relative to one another, therefore tends to be highly influenced by interparticulate friction and mechanical interlocking. Particles that are irregularly shaped and/or have a rough surface move less easily with respect to each other and may lock together, resulting in higher SE values. Lower SE values are usually associated with smooth, regularly shaped particles. Here the finest lactose,

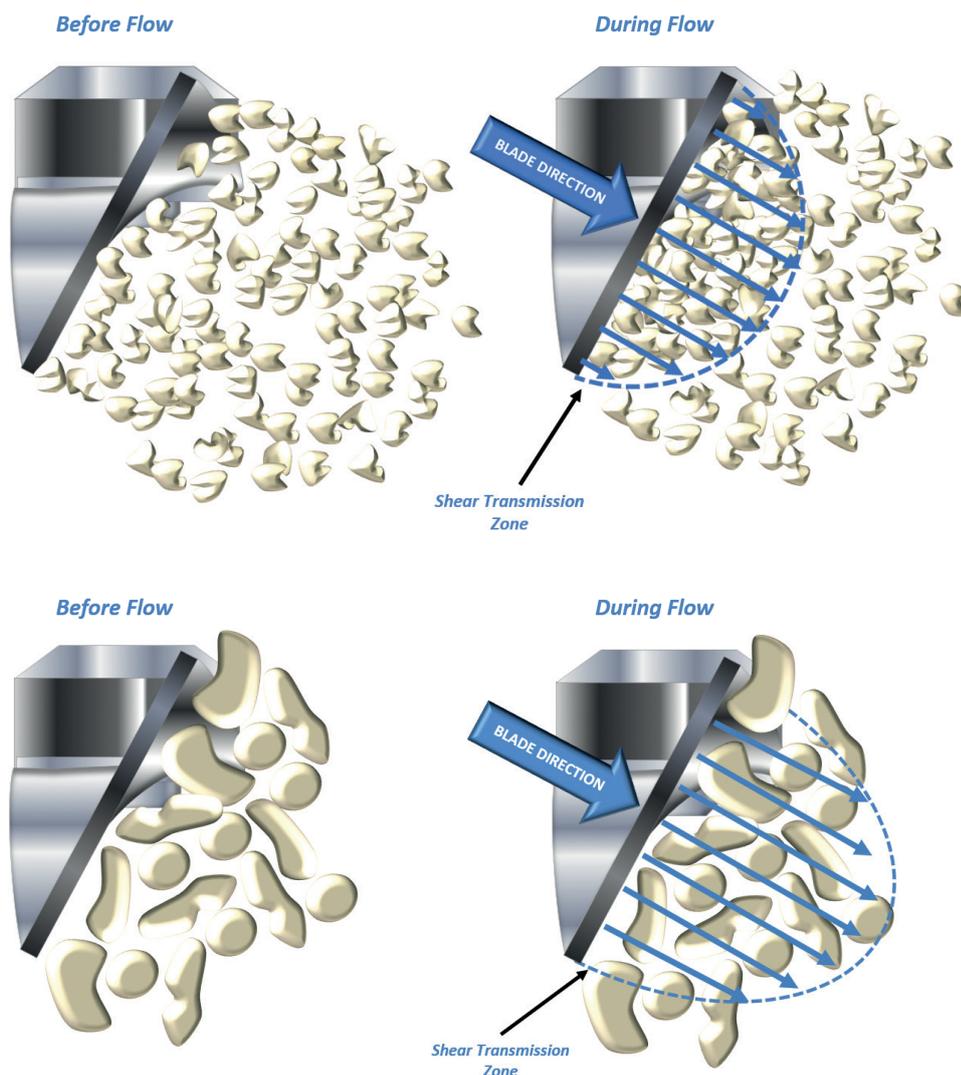


Figure 4: The air entrained in a cohesive powder (upper image) dampens the shear transmission zone giving rise to low BFE values relative to those for powders with larger particles and lower interparticulate forces of attraction (lower image) in which shear is transmitted far more effectively.

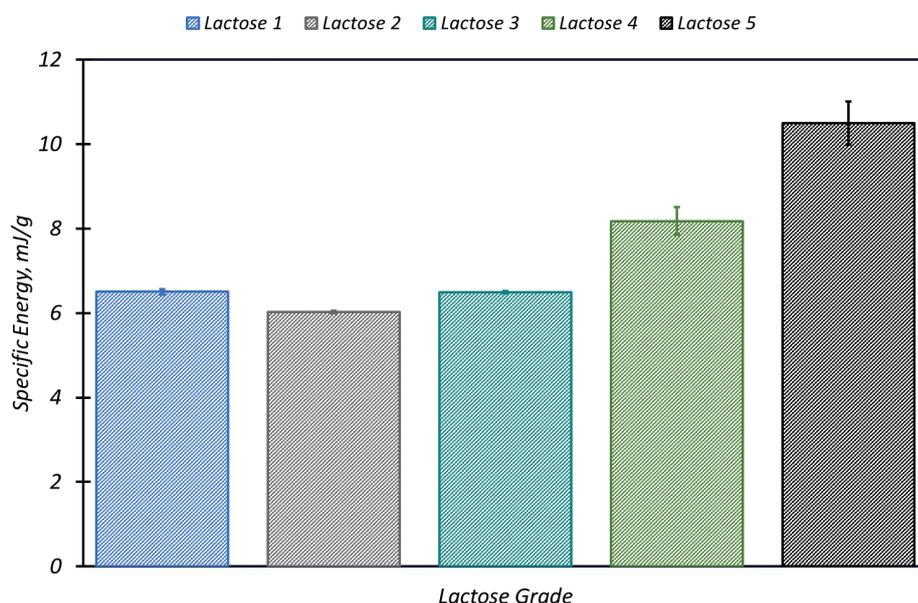


Figure 5: SE values for the five lactose samples indicate that they vary significantly in terms of interparticulate friction and mechanical interlocking.

Lactose 5 exhibits the highest SE, while the two coarsest lactose samples, Lactose 1 and 2 have similarly low values.

Rationalising Dosator Performance

Correlating dynamic properties with dose consistency makes it possible to predict more optimal dosator configurations for given powders. With the largest dosator outlet, Dosator 1, Lactose 3 and Lactose 4 are the only samples to deliver acceptable performance. These powders have a relatively low AE_2 coupled with a low to mid-range SE. Lactose 5, also has a low AE_2 , but its SE value is high, indicating greater mechanical interaction. Dosator 1 appears to be optimally suited to powders that combine a low AE_2 with a moderately low SE.

Dosators 2 and 3 deliver acceptable performance for Lactose 2 and 3, and near-acceptable performance for Lactose 1 and 4. Lactose 2 and 3 exhibit similar low SE values and a similar AE profile. Lactose 1 has a similar SE but a much higher AE_2 , whilst the poorer performance of Lactose 4 can be attributed to its relatively high SE value. These outlets appear to require a powder with a lower SE than Dosator 1 but can tolerate a higher AE_2 .

Lactose 1, 2 and 3 all exhibit acceptable performance in the smallest dosator outlet while Lactose 4 and 5 perform relatively poorly. In this case performance appears to be heavily influenced by SE, which is similar and low for Lactose 1, 2 and 3. There is minimal correlation with AE_2 . The inferior performance of Lactose 4 and 5 can be directly attributed to higher SE values.

These results indicate that powders that combine a low SE with a low AE_2 perform best in all configurations. However, as the outlet size of the dosator decreases, AE_2 becomes a less influential factor and sensitivity to SE increases. A larger dosator allows for a greater interaction with air at the outlet, thus reducing the impact of interparticular interactions. This is reflected in a stronger correlation with AE_2 . With smaller outlets, there is little opportunity for interaction with air and the physical interactions that define SE dominate performance.

CONCLUSION

Different DPI formulations are optimally processed with different dosing technology, with the flow properties of the formulation

influencing equipment choice and performance. When considering a dosator system, how easily the formulation flows directly impacts filling of the dosator tube and, by extension, dose weight uniformity. The case study described here illustrates how dynamic flow testing with a powder rheometer generates data that can be used to scope and rationalise dosator performance. In this way dynamic testing can support the development of more easily processed DPI formulations and the selection of equipment that will securely deliver a consistent pre-metered dose.

ABOUT THE COMPANIES

Freeman Technology specialises in systems for measuring the flow properties of powders and has over 15 years' experience in powder flow and powder characterisation. Freeman's systems are installed around the world across a diverse range of industries.

Freeman Technology is headquartered in Gloucestershire, UK, with operations in China, Germany, Japan and the US, and distribution partners in key global territories. In 2007 the company received

the Queen's Award for Enterprise in Innovation and in 2012 the Queen's Award for Enterprise in International Trade.

3P Innovation is an engineering company delivering solutions to major pharmaceutical, medical and fast-moving consumer goods companies. The company develops custom automation, usually associated with product launches. Its approach ensures robust products are manufactured on efficient machines. From low speed laboratory equipment to high speed assembly lines 3P can develop an appropriate custom solution. It also has a range of standard machines, products and technologies. All 3P's standard systems have been designed to reduce the time to market associated with new product developments.

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Jamie Clayton is Operations Director at Freeman Technology, based at the company's headquarters in Tewkesbury, UK. He graduated from the University of Sheffield with a degree in Control Engineering and is responsible for all daily activities of the company, including overall management of the administration, production, R&D, sales and customer support teams. Mr Clayton also works with the company's clients to provide application based support.

Rajeev Dattani is an Application Specialist at Freeman Technology, based at the company's headquarters in Tewkesbury, UK. He obtained a MSc in Microsystems and Nanotechnology from Cranfield University, followed by an MRes in Plastic Electronics and a PhD in Polymer/Fullerene Solution Processing at Imperial College London. Having joined Freeman Technology in 2017, Dr Dattani is involved with supporting users of the company's powder testing instrumentation from initial installation and training to ongoing education and application support.

Dave Seaward, a founding director of 3P, is a chartered engineer with a first degree in joint electrical and mechanical engineering and a control theory PhD. His PhD focused on the application of servo motors to packaging machinery. This early work has led to a career spanning 30 years associated with the development of custom automation for a variety of industries. These include the pharmaceutical and medical device sectors. Many of his projects have included advanced powder or liquid dispensing. Seaward is named inventor on multiple patents. He has worked on 14 dry powder inhaler programmes and nine different injectable drug delivery and autoinjector projects. At 3P, he developed high speed gravimetric powder dispensing technology capable of dosing pure API including biologics into devices and capsules for inhaled and injectable applications. More recently he has helped develop the processes to manufacture a number of drug eluting polymer/modified release products.



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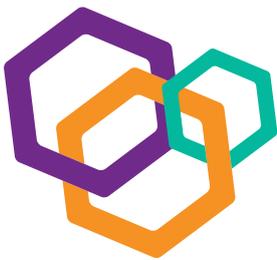
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COMPLETE SOLUTION FOR PMDI PRODUCTS: FROM DEVELOPMENT TO QUALITY CONTROL TESTING

In this article, Heli Chauhan, Senior Applications Chemist, Proveris Scientific, outlines the major challenges encountered in testing pressurised metered dose inhalers, and how Proveris' portfolio of instruments can be an invaluable addition to the testing workflow.

Pressurised metered dose inhalers (pMDIs) are currently the largest revenue-generating segment in the asthma and chronic obstructive pulmonary disease (COPD) drug delivery devices market and are expected to maintain this position until 2020.¹ This results in extensive testing needs for pharmaceutical companies developing and manufacturing these products. The large volume of complex tests presents many challenges. With industry-leading instruments, support and lab services, Proveris provides a complete solution for pMDI testing throughout the life of the product.

KEY CHALLENGES IN PMDI TESTING

Today, the industry faces a number of challenges in testing pMDI products. Robust testing methods ensure the integrity of data over time. Consistent actuation parameters are important for accurate and reproducible

actuation of devices. Actuating devices by hand is not consistent over time and can introduce variability from person to person. Figure 1 demonstrates the observed variation in results from manual actuation, showing the stroke length, actuation velocity and hold time as recorded from the manual actuation of a pMDI product by five testers. The variability in results exists from person to person as well as across different shots (x axis).

Automated actuation of devices eliminates the variability observed in manual actuation altogether. Vereo[®] actuators, controlled by Viota[®] software, ensure that the actuation parameters (velocity, stroke length, hold time) are controlled in a user-defined manner and are consistent across multiple actuations. Moreover, keeping the actuation parameters consistent throughout, across tests, results in high reproducibility of data. Proveris' software platform offers complete traceability of all actuation events

along with force-position-time profiles to aid in root-cause analysis during an out-of-specification (OOS) analysis.

Since most pMDI products are suspensions, the shaking profile is crucial for accurate dose delivery. Lack of appropriate shaking delivers a high amount of the drug in the early doses followed by very little to no drug towards the end of product life. As can be seen in Figure 2, in non-shaking

"Automated actuation of devices eliminates the variability observed in manual actuation altogether. Vereo[®] actuators, controlled by Viota[®] software, ensure that the actuation parameters are controlled in a user-defined manner and are consistent across multiple actuations."

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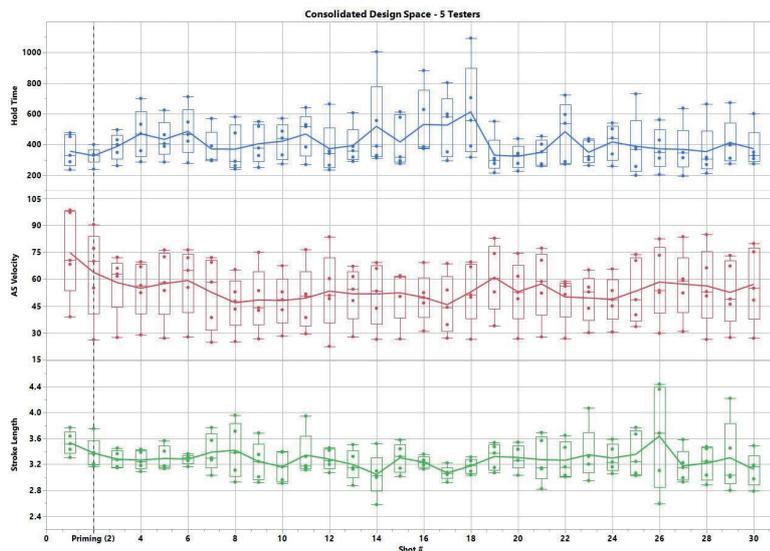


Figure 1: Range of actuation parameters recorded for a pMDI product from manual actuation by five testers.

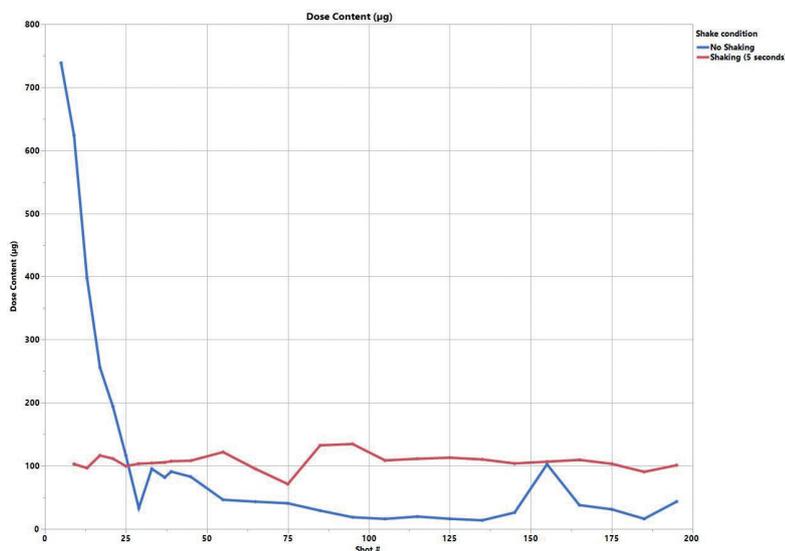


Figure 2: Effect of shaking on the dose content of drug over the life of the product.

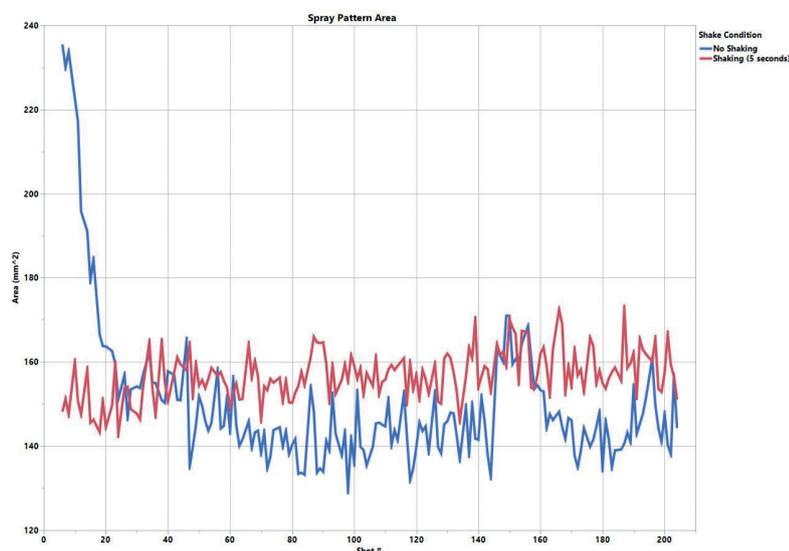


Figure 3: Effect of shaking on spray pattern area over the life of the product.

“This lack of shaking could be fatal for some patients, should they get huge amount of drug in the initial shots from the device and mostly just propellant afterwards.”

conditions (blue line), the amount of dose delivered is multiple times the intended target dose for the first few actuations and then drops over the life of the device. Since the drug formulation and the propellant are not mixed in this scenario, the emitted spray may have a very high concentration of drug formulation and less propellant. In comparison, the doses delivered after five second shaking profiles were more uniform throughout product life. This lack of shaking could be fatal for some patients, should they get huge amount of drug in the initial shots from the device and mostly just propellant afterwards.

The shake-to-fire delay time (i.e. time between shaking the device and its actuation) of a pMDI device is known to play a role in dose content variability.² Furthermore, specific shaking profiles are required for certain products depending on the type and number of excipients present.³ This underlines the importance of determining and performing the proper shaking profile to ensure the correct dose is delivered every time.

The same effect as described above was observed when spray pattern (SP) area was measured using Proveris' Sprayview[®] measurement system over the entire life of the device (Figure 3). Initial high SP area followed by a steep drop was observed for the “no shaking” condition. In comparison, a more uniform SP area was seen for the five-second shake duration.

These observations highlight the importance of shaking properly and reproducibly when testing pMDI devices both during development and as a quality control measure. Proveris instruments provide the user with the flexibility of programming the shaking angle, frequency, shaking duration and shake-to-fire delay so that all the devices have a uniform shaking profile for all the required tests. This will also eliminate shaking as a cause for inconsistencies in dose content and spray performance results.

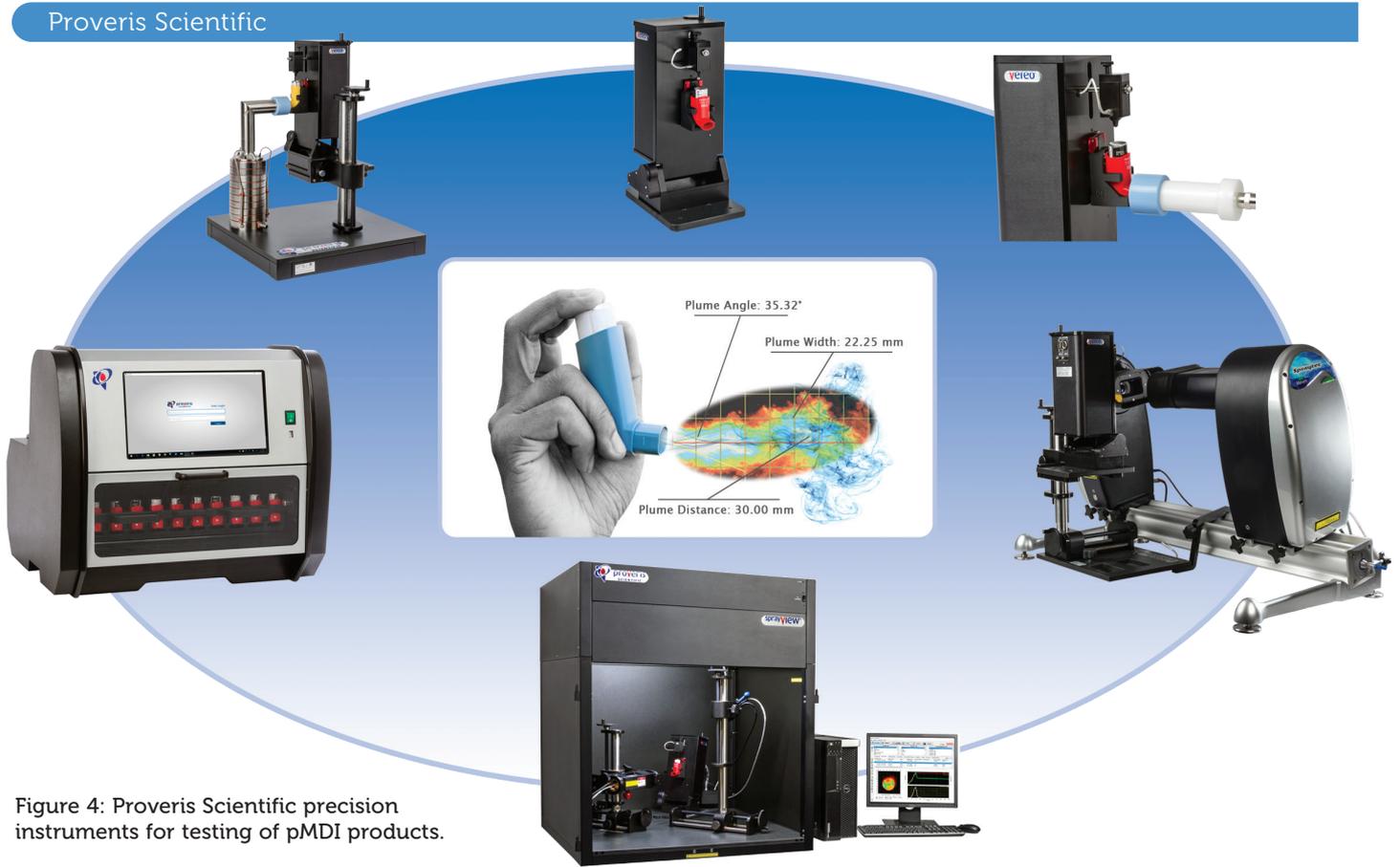


Figure 4: Proveris Scientific precision instruments for testing of pMDI products.

PROVERIS AS A PMDI TESTING SOLUTION PROVIDER

Proveris aims to provide a complete solution for testing pMDI products with its precision instruments (Figure 4). The Vereo® SFMDx Automated Actuators are flexible and fit seamlessly into multiple testing workflows, such as:

- Shot weight measurement
- Dose content uniformity
- Aerodynamic particle size distribution (cascade impaction)
- Particle size distribution (laser diffraction)
- Spray pattern and plume geometry
- Fire-down of sprays between testing.

Spray Pattern and Plume Geometry as a Prescreening Tool for Clinical Trials

Spray pattern measurements from the SprayVIEW® instrument are a valuable screening tool during early development. The spray pattern is sensitive to changes in individual parameters, such as orifice length, orifice diameter and chamber depth, which are crucial design characteristics of the pMDI actuator.⁴ Gaining the ability to see the effects of these parameters on spray performance can have a significant impact on successful product development and prevent costly late-stage development failures.

Spray pattern and plume geometry measurements give a substantial amount of

valuable information, irrespective of being a regulatory requirement by the US FDA. To illustrate this, take the measured spray pattern for two pMDI devices using the same canister and only a slight difference in the actuator. As displayed by Figure 5, the spray duration for the two are significantly different (60 ms versus 140 ms).

Further, the plume geometry data and the playback video of the plume from these devices gives a qualitative insight about the direction of the spray. Direction of spray is important to determine during development, as any skew can lead to higher deposition on the sides of the mouthpiece and low

availability to the patient during clinical study, ultimately leading to failure *in vivo*. This quantitative and qualitative set of data can be invaluable for decision making prior to running an expensive clinical study. Proveris also offers lab services that include patient usage studies, device characterisation, formulation/device screening as well as qualitative/quantitative analysis of product performance. These studies can be especially helpful for companies who do not plan on testing in-house but nevertheless want to evaluate the product performance on a small scale or require consulting during early development.

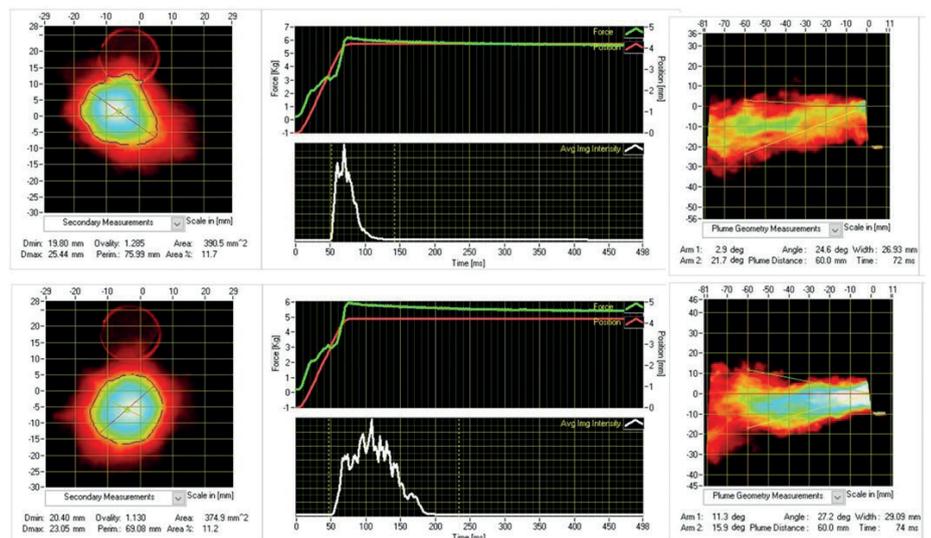


Figure 5: Changes in the spray duration between two identical pMDI devices with slight differences in the actuator.

Kinaero™ High-Throughput Fire-Down System

The newest addition to Proveris' family of instruments is the Kinaero™ High-Throughput Fire-Down system for pMDIs. Firing down pMDI devices can be tedious and time consuming. Proveris' Kinaero system addresses this issue, capable of firing down either canisters only or entire devices with actuators using specific easy to insert cassettes (Figure 6).

By replicating human use of inhalers, the Kinaero™ system provides reproducible actuation throughout product life. The software platform, with database storage and retrieval is compliant with 21CFR Part 11. Programmable shaking angle, frequency, duration and inter-actuation delay along with multiple modes of actuation (force, position or time based) provides greater flexibility during automated fire down. The compact benchtop model with a large touchscreen display offers the following key features and benefits:

- Automated fire down for up to 10 pMDI devices
- Multiple modes of actuation based on force, position and time
- Programmable shaking angle, frequency and duration
- Self-contained evacuation system that eliminates tedious waste disposal methods
- Updated operation and data management software with database storage and retrieval
- US 21 CFR Part 11 compliant.

Since the entire system is self-contained and requires only AC power, no vacuum or pressurised air connections are necessary. The multi-level filtration system containing high efficiency particulate air (HEPA) and activated carbon filters can withstand tens of thousands of shots before replacement is required. Moreover, no additional cleaning steps are required along with easy replacement of filters and system alerts to remind the user that a filter is due for replacement. The software platform also offers multiple operator levels with differences in privileges depending on whether the user is in an R&D or QC setting. Additional features such as the Break/Resume mode allows the user to pause a method, walk away from the instrument and resume it easily.

The Kinaero™ system fits into the pMDI testing workflow with ease, allowing



Figure 6: Kinaero™ high-throughput fire down system.

users more control over their testing parameters. It also reduces the ergonomic burden on the analyst of firing down multiple devices. The time saved increases the operational efficiency of the lab and reduces testing backlog.

CONCLUSION

This article described some of the key challenges in pMDI testing, including the importance of consistent actuation and shaking parameters along with the need for traceability for OOS results. Proveris Scientific provides a solution to these issues with its portfolio of instruments that fit into most of the testing workflows, from shot-weight testing and spray characterisation to firing down of devices between tests. Consistent actuation and shaking profiles ensure accurate and reproducible actuation during each run. Along with supporting these workflows, spray pattern and plume geometry results from the SprayVIEW® instrument give insight into product performance early during development, thereby improving the chances for success during *in vivo* studies.

ABOUT THE COMPANY

Proveris Scientific delivers innovative technologies, services and deep product

knowledge to a worldwide customer base of branded and generic pharmaceutical companies, device manufacturers, CDO/CRO/CMOs and regulatory agencies working with orally inhaled and nasal drug products (OINDPs). Its team of engineers, scientists and service professionals has developed a more complete understanding of the critical quality attributes affecting the performance of OINDPs, and in effectively controlling them from a testing and patient usability perspective.

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REALISTIC PULMONARY DELIVERY SYSTEM TRAINERS: BENEFITS FOR PATIENTS, PHYSICIANS AND DRUG MANUFACTURERS

The use of training devices has been shown to improve correct inhalation device technique in patients. In this article, Craig Baker, Executive Vice-President, Noble, discusses the prevalence of improper use and how addressing this issue via training devices is of benefit to manufacturers, healthcare providers and patients.

Many treatments for respiratory conditions, such as chronic obstructive pulmonary disease (COPD) and severe asthma, are self-administered through pulmonary delivery systems, including nebulisers, metered-dose inhalers (MDIs), dry-powder inhalers (DPIs) and soft-mist inhalers (SMIs). As this form of targeted drug delivery continues to grow, so too does our understanding of the complexities and challenges associated with this route of administration, particularly those that can result from improper use by patients.¹ The most common failings are related to inhalation timing and force, but this is compounded by the fact that patients are often unaware when they are using improper technique, thus not realising

they are not receiving the proper drug dose. This incorrect usage and subsequent under-dosing inevitably has detrimental consequences for patient health.²

Understanding the need for innovation in patient onboarding and training, Noble has developed a wide range of patented technological advancements to design training devices for pulmonary delivery systems, mimicking the look, feel and operation of the prescribed product and user experience (Figure 1). These training products afford patients a hyper-realistic experience during the onboarding period (defined as the initial 30, 60 or 90 days of delivery system usage), boosting patient confidence and encouraging proper device use, which may ultimately enhance patient health.

Numerous studies suggest the use of realistic trainers in familiarising patients with the operation of pulmonary delivery systems could help ensure that they are being utilised properly. Additionally, the impact of comprehensive onboarding and training can offer benefits to healthcare professionals (HCPs) and drug manufacturers.

ENHANCING PATIENT CONFIDENCE AND HEALTH

While there is no question that pulmonary delivery systems can help save lives, patient error is still a concern because it is crucial that actuation and inhalation are performed by the patient in proper sequence with



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“The use of realistic trainers can play a role here by allowing an improvement in the quality of individualised medication self-management programmes initiated by HCPs, which have been shown to increase a patient’s medication adherence.”



Figure 1: MDI training device designed to replicate an actual MDI's form factor and operation while providing the user with multisensory feedback.

correct timing. This issue is more prevalent than one might expect.

For example, according to a widely reported study published in the *Annals of Allergy, Asthma & Immunology*, only 7% of inhaler patients follow proper technique when using their device.³ Additionally, a pair of studies from Rice University (Houston, TX, US) concluded that the users of MDIs may be limiting their medication's effectiveness by getting only half the medication they need, again as the result of device misuse. The vast majority of the time, between 70–90%, patients commit errors resulting in only a fraction of the medication, usually less than 40%, actually reaching their lungs, as reported in *COPD News Today*.⁴

A solution to this problem lies in the latest generation of pulmonary delivery system trainers, incorporating an array of both mechanical and “smart” features, such as realistic actuation simulation. To ensure proper sequencing, calibrated whistles have been incorporated as well. As long as the patient is inhaling at the proper rate, a whistle will sound during the process but will stop sounding if the drug intake is occurring improperly.

Additionally, “smart” features on Noble's pulmonary delivery system trainers are designed to monitor the key steps involved in usage of these devices and can give the user feedback in real time. If the patient does not perform the proper

sequence of steps or is not inhaling at the proper rate, these errors can be detected immediately and reported to the patient through the use of light or sound effects. Depending on the specific configuration requested by a drug manufacturer, this feedback can be conveyed both via the trainers themselves and in tandem with an app that runs on a smart device, such as a smartphone or tablet. The latter configuration allows the use of interactive videos that can further educate patients on proper use of the trainers.

HELPING HCPs PROVIDE BETTER INSTRUCTION TO PULMONARY PATIENTS

Enhancing patient confidence may also help HCPs to ensure a prescribed treatment is working as intended for a patient, thereby mitigating complications and resulting in an overall better quality of care.

Part of the problem in the pulmonary space is that studies have indicated that only a minority of HCPs are familiar with the proper way to use aerosol devices.⁵ At the same time, studies have shown a strong correlation between poor adherence to prescribed inhaled medications and risk

“In one study, 94 patients with COPD were observed using a pulmonary delivery system; although 96% self-reported that they utilised the proper inhalation technique, a successful first inhalation attempt was performed by only 30% of patients.”

of hospital admission due to exacerbations, as well as increased healthcare costs. These studies also spotlight the importance of HCPs taking extra steps to promote patient adherence to these medications, including improving patient education on how to use these medications properly. Studies suggest it is important for HCPs to demonstrate proper use of pulmonary delivery systems to improve the effectiveness of therapy.⁵

The use of realistic trainers can play a role here by allowing an improvement in the quality of individualised medication self-management programmes initiated by HCPs, which have been shown to increase a patient's medication adherence.⁵ For example, in one randomised, controlled study of subjects with moderate-to-severe asthma, researchers reviewed the effect of an individualised self-management education programme on medication adherence and markers of asthma control over a 24-week

period. It was concluded that subjects who received such individualised sessions had higher medication adherence compared with a control group.⁵

It is evident that the patient onboarding process is just an initial concern for HCPs. Because whether or not a patient is using their pulmonary delivery systems properly is such a critical factor in the efficacy of a treatment, it becomes a challenge for the HCP to evaluate the drug's effectiveness once the patient is sent home, leading to reliance on patient self-reporting. If patients believe they are utilising their pulmonary delivery systems correctly when in fact they are not, this can throw off the analysis of the medication and disease management. Evidence suggests this is a substantial and current issue. In one study, 94 patients with COPD were observed using a pulmonary delivery system; although 96% self-reported that they utilised the proper inhalation technique, a successful first inhalation attempt was performed by only 30% of patients⁶ (Figure 2).

Given the evidence of disparities between patient self-reporting and actual pulmonary delivery system use, advanced training technology can serve a twofold benefit for HCPs. Firstly, a patient who practices with realistic trainers is more likely to adopt proper technique from the start of their treatment and continue to do so when self-administering at home, ensuring more effective drug delivery. Second, certain advanced trainers are capable of generating feedback that patients can share with their physicians and other HCPs in order to verify that the devices are actually being used in the proper manner.

WHY PHARMACEUTICAL & DEVICE MANUFACTURERS TURN TO TRAINING

Finally, manufacturers stand to benefit from the new generation of realistic pulmonary delivery system trainers, as proper administration resulting from training may positively impact the device's perceived effectiveness. This can be the case not only when starting a new therapy, but also when switching to a new brand or class of treatment. Additionally, manufacturers should realise that patients and their physicians, given a choice between competing therapeutics, might select a brand that can be simulated by a realistic trainer over a competing brand for which no realistic trainer is available.

Of additional interest to manufacturers,

Only **30%** of patients performed a successful first inhalation

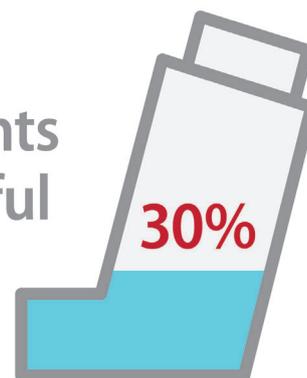


Figure 2: Study finding – 96% of patients self-reported correct inhalation technique, although observations revealed only 30% of participants actually performed a successful first inhalation attempt.

“Given the level of precision built into Noble’s production process, manufacturers can be assured that the finished product will precisely simulate their actual device.”



of patients don't read the IFU

Figure 3: Study finding – IFU alone may be insufficient for patients to learn correct administration technique.

whilst Instructions for Use (IFU) have traditionally been included with devices, research suggests that these are not always effective in conveying proper pulmonary delivery system technique to patients. Research demonstrates that many patients who self-administer medication do not fully understand, or even read in some instances, the IFU that accompanies their device (Figure 3). A study conducted by Noble and researchers from Auburn University (Auburn, AL, US) surveyed more than 700 patients and found more than half did not read their device's IFU prior to beginning treatment.⁷ Noble has the capability of working with manufacturers to produce training IFUs specifically for pulmonary delivery system trainers, incorporating user-friendly literacy level messaging, multiple language options and simple, step-by-step written and visual instructions. While still

an important part of the device package for manufacturers in this area, IFUs can be usefully supplemented with realistic trainers. Noble can work with manufacturers to simulate the attributes of real MDIs, DPIs and SMIs; these are available both as off-the-shelf and customised platforms.

Aside from pioneering the technology behind the trainers themselves, Noble has developed processes and systems to optimise the development and commercialisation of training devices. Given the level of precision built into Noble's production process, manufacturers can be assured that the finished product will precisely simulate their actual device. Noble can also work with a drug manufacturer during the global launch of a specific pulmonary delivery system to ensure that trainers are made available in the necessary quantities at locations worldwide in a timely manner.

It is clear there is a multitude of benefits that pulmonary delivery system trainers can provide to patients, HCPs and drug manufacturers. Especially compelling are the studies illustrating the need for these training devices, which might be able to raise the percentage of users who correctly utilise their devices up from the 7% noted in the *Annals of Allergy, Asthma & Immunology* study, and consequently raise the amount of medication that is actually inhaled above the average of less than 40% noted by *COPD News Today*. As a result, the innovative design and production of Noble's sophisticated, patient-centric trainers may have an impact on the overall quality of healthcare administration.

ABOUT THE COMPANY

Noble® works closely with the world's leading pharmaceutical and biotechnology companies to develop respiratory device, autoinjector and prefilled syringe training solutions designed to provide positive patient onboarding experiences, reduce errors and improve patient outcomes. Cross-disciplinary designers and engineers provide fully customised solutions from the first concept sketch through to production, in both regulated and non-regulated environments.

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ABOUT THE AUTHOR

Craig Baker is Executive Vice-President at Noble, a product development company with a focus in designing and manufacturing drug delivery training and patient onboarding solutions. Joining the company just a few years after its creation, Craig holds an undergraduate degree from the University of Iowa and a Masters degree from the University of South Carolina. In addition, he has 10 years of management experience in the marketing industry and the pharmaceutical & healthcare field. This insight into both industries is an important advantage for the future growth of Noble.

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THE NEW EU MEDICAL DEVICE REGULATIONS – IMPLICATIONS FOR INHALATION DEVICES

In this article, Mary Hutchens, Regulatory Affairs, Coalesce Product Development, gives an overview of some of the changes wrought by last year's introduction of the new EU Medical Device Regulation, with a specific view to its effect on inhalation devices and inhaled medical products.

INTRODUCTION

On May 5th 2017, the new Medical Device Regulations (MDR) were published in the *Official Journal of the European Union*. The MDR will replace the Medical Device Directive (MDD) and the Active Implantable Medical Devices Directive (AIMDD).

The MDR represents a major change in the regulation of medical devices in the EU and was prompted by well-publicised incidents involving breast implants and hip replacements. The development of the MDR has taken nearly a decade, with the EU Commission launching the consultation process in 2008. The new MDR is intended to provide greater scrutiny of medical devices at all stages of the product lifecycle and has implications for all parts of the medical device industry. The promotion from directive to regulation ensures harmonisation across member states by preventing alterations in local implementations.

The MDR will have a broader scope than the preceding directives, imposing greater supervision of Notified Bodies, while at the same time requiring Notified Bodies to undertake greater scrutiny of device manufacturers. Unlike its predecessors, it encompasses the whole lifecycle of a medical device and has a significant emphasis on safety, which is now mentioned 290 times. There are changes in classifications, better traceability via an improved European Medical Device Database (EUDAMED), unique device identifiers (UDIs), and more

extensive requirements and scrutiny for clinical evidence and postmarket vigilance. Furthermore, there is a new requirement for manufacturers and authorised representatives to appoint a suitably qualified person to be responsible for regulatory compliance.

Outlined hereafter are some of the key changes in medical device regulation resulting from the publication of the MDR and the implications for inhalation devices and inhaled medicinal products.

MEDICAL DEVICE OR MEDICINAL PRODUCT?

It is important to note that in the EU not all inhalers are regulated as medical devices. The Medical Device Regulation, as for its predecessor MDD, makes provision for those products that are intended to be “placed on the market in such a way that the device and the medicinal product form a single integral product which is intended exclusively for use in the given combination and which is not reusable” to be regulated as Medicinal Products under the Medicinal Product Directive (MPD), with the caveat that the relevant Annex 1 requirements (General Safety and Performance Requirements for MDR, Essential Requirements for MDD) are fulfilled. Such devices are not required to carry a CE Mark. Examples include certain pressurised metered dose inhalers (pMDIs) and multi-dose dry powder inhalers (DPIs).

The MDR refers to this approach in Article 10. In addition, a new requirement has been incorporated as Article 117, to amend the MPD. This article requires the involvement of a suitable Notified Body to grant an opinion on the fulfilment of the Annex I requirements, whereas historically under the MDD this could be stated by the Marketing Authorisation Application (MAA) applicant themselves, whilst holding supporting evidence.



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“It is important to note that in the EU not all inhalers are regulated as medical devices.”

Reusable devices, devices that can be used to deliver different medicaments or those devices that are not fully integrated with the drug product are regulated as medical devices, therefore they need to fulfil the full MDR and carry a CE mark. Typical examples are capsule DPIs and nebulisers. Accessories to medical devices, for example pMDI spacers, are also considered medical devices.

This article will concentrate on those inhalation devices that fall under the MDR and which require a CE Mark. The implications of the new regulations for manufacturers of such devices will be discussed.

NEW CLASSIFICATIONS

Under the MDD, devices that are non-active, that is to say devices that do not rely on a source of power other than that generated by the human body or gravity, were classified under Annex IX, rule 5, as low risk (Class I) devices. A manufacturer could formally self-certify a Class I device and apply the CE mark with no requirement for a Notified Body conformity assessment. An example would be a reusable capsule inhaler.

The MDR now incorporates 22 classification rules (including five new rules) in Annex VIII. The classification groupings are set out in Table 1.

Rule 20, will have significant implications for many CE marked inhalation devices, since it states:

“All invasive devices with respect to body orifices, other than surgically invasive devices, which are intended to administer medicinal products by inhalation are classified as Class IIa, unless their mode of action has an essential impact on the efficacy and safety of the administered medicinal product or they are intended to treat life-threatening conditions, in which case they are classified as Class IIb.”

Inhalers previously classified as low risk Class I devices have now been moved into a higher risk classification (Class IIa or IIb) and will require conformity assessment by a Notified Body, therefore a manufacturer will

Rules 1-4	Non-invasive devices
Rules 5-8	Invasive Devices
Rules 9-13	Active Devices
Rules 14-22	Special Rules

Table 1: MDR rules classifications.

“Inhalers previously classified as low risk Class I devices have now been moved into a higher risk classification (Class IIa or IIb) and will require conformity assessment by a Notified Body, therefore a manufacturer will no longer be permitted to self-certify and apply the CE Mark themselves.”

no longer be permitted to self-certify and apply the CE Mark themselves. This has many implications, some of which will be highlighted through the rest of this article.

The Competent Authorities for Medical Devices (CAMD) has established an implementation taskforce and a roadmap has been created to guide their activities during the transition period of the MDR. Provision of “information and guidance on classification for medical devices (changes on classification rules)” carries medium

priority, and guidance is expected to emerge in the coming months. Unfortunately, one key area of “guidance for combination products around appropriate level of interaction with relevant authorities” has been considered low priority.

The requirements are set out in Chapter V, Section 2, Article 52, of the MDR and the applicable procedures are outlined in Annexes IX–XI. Similar to the MDD, the MDR requires that a manufacturer has a quality management system (QMS) in

BOX 1: COMMON ABBREVIATIONS IN EU MEDICAL DEVICE REGULATION

Abbreviation

Definition

AIMDD	Active Implantable Medical Devices Directive
CAMD	Competent Authorities for Medical Devices
CEAR	Clinical Evaluation Assessment Report
CER	Clinical Evaluation Report
CS	Common Specification
ER	Essential Requirement
EUDAMED	European Medical Device Database
GSPR	General Safety & Performance Requirements
MDD	Medical Device Directive
MDR	Medical Device Regulation
MPD	Medicinal Products Directive
PMCF	Post Market Clinical Follow-up
PSUR	Periodic Safety Update Report
QMS	Quality Management System
SSCP	Summary of Safety & Clinical Performance
UDI	Unique Device Identifier

place. It is important to note that EN ISO 13485:2016 includes direct references to incorporating regulatory requirements into the QMS and is compatible with requirements of the MDR. The assessment involves auditing the QMS, the technical documentation supporting the device and an unannounced audit every five years for both Class IIa and Class IIb devices. These audits may also extend to critical subcontractors and crucial suppliers. This may affect the contractual relationships between medical device developers and suppliers. The classification and conformity criteria are based on risk, as shown in Figure 1.

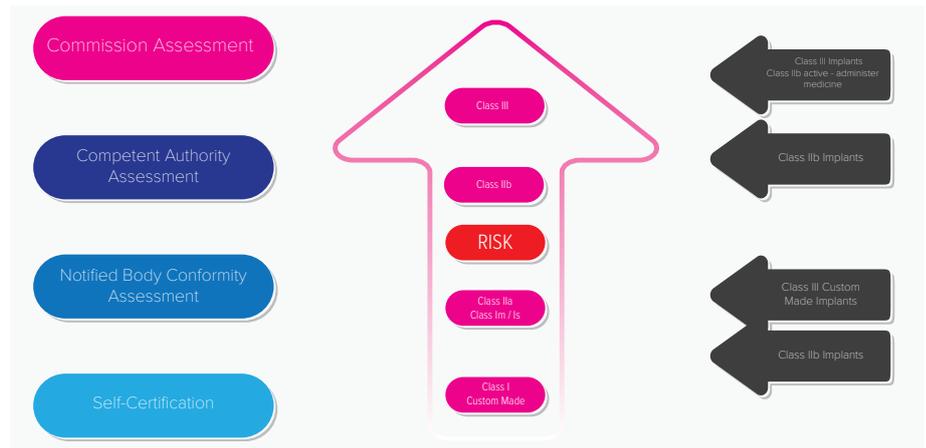


Figure 1: Classification and conformity criteria.

CLINICAL REQUIREMENTS AND POST MARKET CLINICAL FOLLOW-UP

Clinical Evaluations and Investigations are covered in Chapter VI (Article 61) of the MDR and Annexes XIV and XV (Clinical Evaluations and Clinical Investigations, respectively). The MDR enhances the requirements currently outlined in the MDD and now defines the term “Clinical Evaluation”.

Under the MDD there was a requirement for a manufacturer to produce a Clinical Evaluation Report (CER). Under the MDR, this CER must, in addition to a review of the clinical data available, include the results of clinical investigations, and must also refer to conclusions on the safety and performance of the device and a risk/benefit analysis.

The CER should also now be considered a “live” document, and thus should remain active throughout the lifetime of the device, with regular reviews and updates based on postmarket clinical follow-up (PMCF) and postmarket surveillance (PMS).

Not only have there been changes to the requirements, but also to the scrutiny of clinical evaluations and investigations. The MDR sets out a clear requirement for scrutiny of the CER by a Notified Body, and for Notified Bodies to produce a clinical evaluation assessment report (CEAR) for a device as part of a conformity assessment. The manufacturer will typically need to generate and provide more in-depth clinical data to prove their safety and performance claims and equivalency standards will be tighter.

The MDR introduces new mandatory requirements relating to post-market clinical follow-up (PMCF). A PMCF must be prepared as part of the overall clinical evaluation and must form part of the technical documentation of the device.

It will also be reviewed as part of the conformity assessment by a Notified Body.

The requirements for a PMCF are set out in Annex XIV, Part B of the MDR. The PMCF is a continuous process that updates the clinical evaluation. When conducting a PMCF study for a CE marked device, the purpose of the data generated is to:

- Confirm the safety and performance of the device during its lifetime.
- Identify previously unknown side effects and monitor identified side effects and contra-indications.
- Identify and analyse emergent risks.
- Identify possible systemic misuse or off-label misuse.

POST-MARKET SURVEILLANCE

In the MDR, Chapter VII is dedicated to post-market surveillance, vigilance and market surveillance, in addition to sections 1.1 and 1.2 of Annex III. A postmarket surveillance system must be prepared for each product as part of the QMS. Postmarket surveillance activities must include a PMS plan, a PMS

report and periodic safety update reports (PSUR). The requirements for a PSUR are set out in Article 86 of the MDR.

Class III, Class IIa and Class IIb devices will require PSURs, which must be updated annually for Class III and Class IIb devices. For Class IIb devices the PSURs should be updated when necessary and at least every two years. Accidents, injuries and deaths will need to be reported, and patients will have access to more safety-related information. Non-fatal incident reporting has been relaxed from 15 days to 30 days.

GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

The MDR replaces the Essential Requirements (ERs) of the MDD and AIMDD, with General Safety and Performance Requirements (GSPRs). The general principles of the ERs remain in the GSPRs, although there are more GSPRs, partly due to the combining of the two directives (Figure 2).

Annex I of the MDR sets out the GSPRs in three chapters:



Figure 2: MDR General Safety & Performance Requirements.

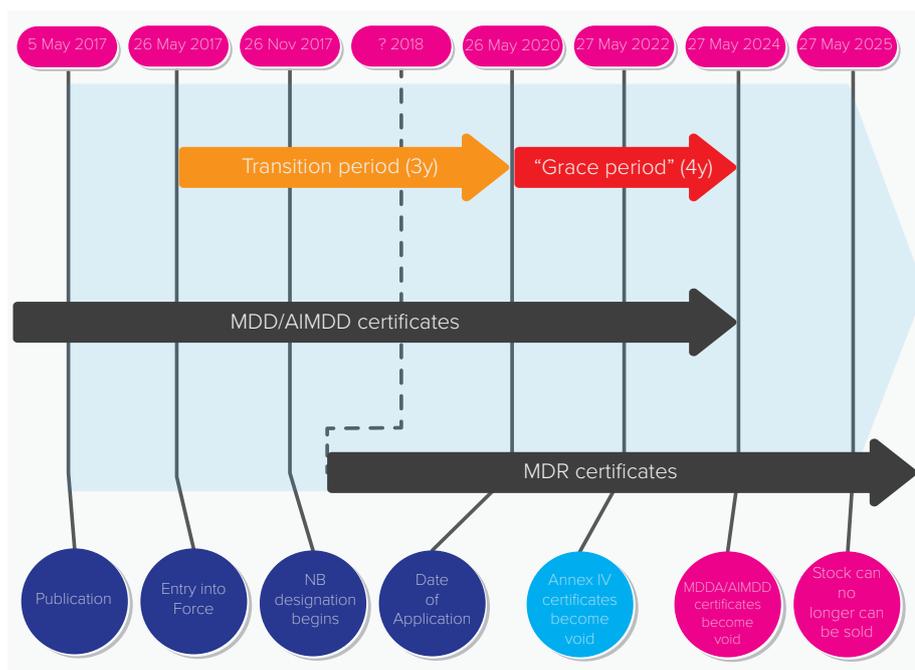


Figure 3: MDR timeline.

1. General Requirements (GSPRs 1-9)
2. Design and Manufacture (GSPRs 10-22)
3. Information Supplied with the Device (GSPR 23).

When compared with the ER lists, the new GSPRs have some numbering and organisational changes, expanded areas on risk and labelling, and some topics have been moved into annexes. Manufacturers with existing CE marked devices will need to conduct a gap analysis comparing the ER of the MDD with the GSPRs of the MDR to ascertain what additional data will be required.

PERSON RESPONSIBLE FOR REGULATORY COMPLIANCE

Article 15 of the MDR requires that a manufacturer must have a person responsible for regulatory compliance available within their organisation. However, given that many device manufacturers are small enterprises where having a suitably qualified individual within the organisation would be difficult, the MDR allows micro and small enterprises to have the person “permanently and continuously at their disposal”. A similar arrangement is allowed for EU representatives.

The individual must have a degree in a scientific or technical discipline and at least one year’s experience in medical device regulatory affairs (RA) or QMS, or at least four years’ professional experience in medical device RA or QMS (two years for custom-made devices).

UDI AND EUDAMED

A UDI is used to help track devices through the supply chain and will be required on labelling. In Article 27, a definition of the UDI is given. The UDI comprises:

- a UDI device identifier (UDI-DI) specific to a manufacturer
- a UDI production identifier (UDI-PI), the unit of device production.

The basic UDI-DI is the primary identifier of the device and will be stored in EUDAMED and will be referenced on labels and declarations of conformity. EUDAMED will allow access to the information stored about the device.

TRANSITION TIMELINES

The MDR came into force on May 26th 2017, following publication in the *Official Journal of the European Union* on May 5th 2017. There is a three-year transition period during which the MDD and AIMDD will still operate, meaning that devices will still be certified under the directives. Certificates granted during this period will still be valid under a “grace” period for four years. However, after this period, ending on May 26th 2024, the certificates will become void and the devices will have to conform to the MDR. Devices receiving certification after May 26th 2020 will need to conform to the MDR (Figure 3). There will be no

“grandfathering” of pre-MDR devices. This means that at the end of the transition process, all CE marked devices will have to be compliant with the MDR.

ACKNOWLEDGEMENT

The author would like to thank Dave Ahern, Chief Executive Officer, Coalesce, and Mark Chipperfield, Director, Corvus Device, for their contributions to this article.

ABOUT THE COMPANY

Coalesce Product Development develops medical and drug delivery devices for global markets. The company has ISO 13485 certification for the design and development of medical devices. Coalesce’s experienced team encompasses mechanical engineering, electronics, analytical science, industrial design, human factors, project management, regulatory affairs, and quality assurance. Its facility in Cambridge, UK, is equipped with a state-of-the-art design centre, an analytical science laboratory, an ISO Class 7 cleanroom, and an engineering development and testing suite.

ABOUT THE AUTHOR

Mary Hutchens is in charge of Regulatory Affairs at Coalesce Product Development. She graduated as a biologist and began her career working in the agrochemical industry. Having specialised in regulatory affairs, she moved into the medical device field in 2000. She has experience in the regulation of medical devices in a variety of global markets, particularly in the EU and US.

Ms Hutchens has worked for companies ranging from large multinationals to small start-ups. She has developed regulatory strategies for new products, encompassing the creation of Design History Files and compilation of Technical Files to satisfy essential requirements. She has also commissioned clinical trials for innovative products.



DRUG REPURPOSING – BROADENING PATIENT ACCESSIBILITY VIA A CHANGE IN DRUG DELIVERY SYSTEM

In this article, Badre Hammond, Associate Director, Market Development, Gerallt Williams, PhD, Director, Scientific Affairs, and Herve Pacaud, Business Development Director, all of Aptar Pharma, discuss the growing trend of repurposing, whereby an existing drug product is reformulated for a new route of administration and/or therapeutic area, with a particular eye on the advantages of repurposing for the nasal route.

New chemical entity (NCE) development and commercialisation requires 10 to 15 years of development and represents around US\$2.6 billion (£1.9 billion) in investment.¹ The huge scale of this requirement has led to a growing trend towards repurposing already existing molecules.² These developments are often undertaken by smaller technology companies and start-ups that are looking to explore new markets and new therapy areas.

For clarification, when we talk about repurposing, we mean the process by which pharmaceutical companies can leverage an existing drug and reformulate it by finding new routes of administration, new indications or new therapy areas. By doing so effectively, a whole spectrum of new lifecycle

management opportunities can be opened up. Larger pharmaceutical companies have also recognised the benefits of drug repurposing, in particular in the use of nasal products to treat central nervous system (CNS) conditions.

Why repurpose? The reasons for drug repurposing are many and varied, but the bottom line is that a reduced development time, and therefore significantly lower development costs, can only be good news for patients. This enables both large pharmaceutical companies and smaller organisations to be more agile and innovative in discovering new therapies with much less of the inherent cost/time risk associated with NCE development.

The combination of reduced development time/cost and lower regulatory risks makes repurposing a truly affordable, realistic and achievable opportunity. Ideally, this translates into more therapies getting to market faster and cheaper.

In this article we will explore the rise of drug repurposing with a particular focus on the repurposing of drugs for nasal drug delivery.

“The reasons for drug repurposing are many and varied, but the bottom line is that a reduced development time, and therefore significantly lower development costs, can only be good news for patients.”



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“Consider an emergency scenario where, for example, the patient has fainted or is unconscious. With a nasal spray, essentially anyone can be of assistance in administering the product.”

CLEAR BENEFITS FOR PATIENTS

The majority of drug repurposing projects Aptar Pharma has participated in have resulted in a nasal device being the administration route of choice. Why is this? Primarily because of greater patient convenience and improved user compliance, but also to circumvent particular objections to certain delivery routes. For example, patients may suffer from needlestick anxieties or tablet forms may make them feel nauseous.

There are other, very practical reasons to select nasal drug delivery as

the administration route. If we consider Aptar Pharma’s Unit Dose System (UDS) technology, it enables the systemic delivery of drugs without the need for injection. That means the patient does not need a healthcare professional to administer the drug, which is much more convenient for them and lowers overall cost to the healthcare system.

As another example, consider an emergency scenario where the patient has fainted or is unconscious. With a nasal spray, essentially anyone can be of assistance in administering the product. This is certainly the case for Adapt Pharma (Radnor, PA, US), whose nasal naloxone product, Narcan®, utilises UDS technology (Figure 1).

A SIGNIFICANT OPPORTUNITY

If we subscribe to Eroom’s law – despite improvements in technology, drug discovery is actually becoming slower and more expensive over time – NCE development cannot be the only focus for pharmaceutical and biotechnology companies in the future, particularly in the context of the investment and resources required, coupled to the very real risk that the product may never see commercial launch.

It is estimated that a grand total of approximately 3,250 drugs have been approved in at least one country.³ This represents a significant opportunity if some of these can be repurposed for other specific therapies, particularly when considering that the anticipated development time can be cut by two thirds and the level of investment is substantially

lower too, perhaps even as little as \$20 million⁴ compared to the \$2.6 billion price tag of an NCE.

NEW LIFE FOR EXISTING PRODUCTS

Repurposing an existing marketed drug product can also bring real added value to pharmaceutical companies by complementing existing ranges of products and increasing market share. In order to harness the total value of a drug product, nasal delivery devices, with their established technology and well-documented regulatory guidelines, can be useful lifecycle management (LCM) tools. The concept of an LCM strategy is not new. In fact, in 2014 50–60%⁵ of drugs or biologics approved or launched for the first time in the US were either existing drugs repositioned for new indications, reformulations or new combinations of existing drugs.

Let us examine the case of naloxone nasal spray as an example of how repurposing can be done both efficiently and effectively. Naloxone is a competitive antagonist to opioids in the CNS and has been approved for the treatment of opioid overdose as a prescription medication in the US since 1971.

Access to naloxone has been extended to home use through the prescribing of off-label injectable naloxone, which combines a prefilled syringe with a mucosal atomisation device for intranasal spray administration. The widening of this off-label practice suggested that there was an unmet medical need for a patient-friendly method of naloxone administration.

The parenteral dose was 0.4 mg, although several doses could be administered to address an opioid overdose crisis. A nasal formulation and device has since been developed by Adapt Pharma (Narcan®) using the Aptar Pharma UDS device at 2 mg and 4 mg per spray. This repurposed product was approved in Europe in 2017 and in the US in 2015.

THE 505(B)(2) PRODUCT REGISTRATION PATHWAY

The 505(b)(2) pathway is designed to allow the approval of a drug which isn’t new but differs in several meaningful aspects. The US FDA guidance explains that it was created with the intent “to encourage innovation without creating duplicate work and reflects the same principle as the 505(j) application: it is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug”.⁶

Importantly, the regulators offer a market exclusivity period of three years to products approved using this pathway,



Figure 1: The Unit Dose System (UDS) single shot nasal drug delivery technology from Aptar Pharma is utilised in Adapt Pharma’s Narcan® nasal spray.

compared with 180 days for a purely generic formulation. Equally important, IP challenges are minimised because a repurposed drug is a distinct offer, as opposed to a generic.

CHALLENGES YET REMAIN

Repurposed drugs still must make it through Phase II and III clinical trials for their new purpose. Naturally, such trials eliminate a significant number of compounds that make it that far.

Let us return to our nasal delivery example. Nasal drug delivery can be a challenge and several hurdles may have to be overcome. Reformulation, optimising pk performance, coupling the formulation with the right drug delivery device and selecting the right regulatory pathway are all challenges that may be faced when developing suitable formulations.

In specific respect to nasal applications, the repurposing of an approved drug requires consideration of certain elements, including molecular weight, charge and lipophilicity, which will strongly influence eventual local action or absorption. The technical and regulatory expectations for nasal and sublingual sprays have evolved over the past few years.⁷⁻⁸ Parameters such as droplet or particle size distribution, spray pattern, dose content uniformity and extractable and leachable profiles are now common expectations for the regulatory dossiers.

A PROVEN APPROACH

Table 1 shows several clear examples of drugs that have successfully been repurposed to nasal delivery. With the exception of nicotine, all of the drugs referenced were or are available as an injection.

There is also a considerable pipeline of repurposed projects, as shown in Table 2,

“In order to successfully repurpose a drug for nasal delivery, pharmaceutical companies must select a device partner that can clearly demonstrate capabilities and experience in the development of spray technology.”

“Importantly, the regulators offer a market exclusivity period of three years to products approved using the 505(b)(2) pathway, compared with 180 days for a purely generic formulation.”

which adds further credence to the argument that repurposing is a sustainable and attractive proposition for patients and pharmaceutical partners alike.

PARTNERING WITH APTAR PHARMA

In order to successfully repurpose a drug for nasal delivery, pharmaceutical companies must select a device partner that can clearly demonstrate capabilities and experience in the development of spray technology. They should also have demonstrable experience in helping partners navigate the 505(b)(2) pathway to compliance.

As a trusted partner to the pharma community, Aptar Pharma offers a comprehensive portfolio of specialised drug delivery devices, components and services, all designed to enable the success of our customers. Recognised and respected globally for our proven regulatory expertise, we simplify and accelerate our partners' path through approval and compliance processes.

This experience, expertise and global footprint of resources (including Aptar Pharma's specialist company, Next Breath, an intellectual leader in the field of inhalation and nasal spray development,

INN (Nasal Brand, Manufacturer)	Therapeutic Applications
Desmopressin (Minirin, Ferring)	Bedwetting
Testosterone (Natesto, Acerus)	Hormone replacement therapy
Nicotine (Nicorette, Pfizer)	Smoking cessation
Fentanyl (Instanyl, Takeda)	Pain management
Ketorolac (Sprix, Egalet) (non-narcotic analgesic)	Pain management
Naloxone (Narcan, Adapt)	Opioid overdosing
Nafarelin (Synarel, Pfizer)	Endometriosis
Sumatriptan (Imigran, GSK)	Migraine

Table 1: Drugs successfully repurposed for nasal delivery.

Examples of Drugs in Development/Clinic for CNS/Brain	Therapeutic Applications
Diazepam	Epilepsy
Glucagon	Diabetes, hypoglycaemia
Hypocretin-A	Narcolepsy
Insulin	Alzheimer's
Ketamine	Depression
L-dopa	Parkinson's
Octreotide	Acromegaly
Olanzapine	Bipolarism
Oxytocin	Autism

Table 2: Drugs presently being investigated for nasal delivery.

testing and regulatory strategy) has enabled us to develop a complete services package which includes support in R&D, solution development, device realisation and regulatory submission. This focus has delivered results. In the past five years, Aptar Pharma's regulatory and development teams have supported 35 INDs, 31 NDAs and 55 ANDAs in the nasal space alone.

CONCLUSION

There are many and varied reasons why a pharmaceutical company would consider drug repurposing as a viable option. The significantly reduced development time and, therefore, lower development costs mean that more therapies get to market faster, cheaper and with reduced risk than would otherwise be the case, ultimately benefitting patients and the healthcare system overall.

Very often in our experience, repurposing results in a nasal drug delivery system which

offers many patient benefits in terms of convenience, ease of administration and efficacy. Critically, it also negates the need for intervention from a healthcare professional.

Repurposing is not plain sailing and companies should be mindful to select a drug delivery systems partner that has a proven track record in repurposing. They should be able to demonstrate the necessary validation services and be able to guide through the regulatory process seamlessly. If they can do that, then repurposing could be a perfect opportunity.

ABOUT THE COMPANY

Aptar Pharma provides innovative drug delivery systems, components and services to pharmaceutical, consumer healthcare and biotech customers worldwide, spanning a wide range of routes of administration, including nasal, pulmonary, ophthalmic, dermal and injectable. Aptar Pharma's

mission is to provide complete solution services built around its drug delivery systems and to create stage-specific development packages designed to proactively address regulatory needs and accelerate approval. Overall, six billion components and systems are produced annually across 11 manufacturing sites and are accessed by 1.6 billion patients, and over US\$50 billion worth of pharmaceutical products depend on Aptar Pharma's systems. Aptar Pharma is part of AptarGroup, Inc (NYSE:ATR).

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Badre Hammond is Associate Director, Market Development, at Aptar Pharma, with a background in biochemistry and 14 years' experience in pharmaceutical product development focusing on nasal and pulmonary drug delivery systems. Mr Hammond has broad experience in managing development of novel drug product programmes for the pharmaceutical market from formulation development, preclinical, CMC, to clinical phase.

Dr Gerallt Williams is Director, Scientific Affairs, Prescription Division, at Aptar Pharma. After obtaining his PhD from the University of Wales (UK) in 1985, Gerallt has held various industrial positions at Monsanto Inc (UK), Fisons Ltd (UK), Valois (France) and Inhale/Nektar Therapeutics (US). Dr Williams is now in charge of scientific affairs for the Aptar Pharma prescription division in Le Vaudreuil, France, and is engaged in the development of new devices for nasal, inhalable and injectable drug products.

Herve Pacaud is Business Development Director at Aptar Pharma and has more than 25 years' experience in devices for drug delivery via the nasal and buccal routes. After graduating in Sales and Marketing at the University of Amiens (France), Herve held different positions in the automotive industry and then at Valois, now Aptar Pharma. At Aptar Pharma, Mr Pacaud has worked in various sales and business development positions in Europe and Asia. Based in France, he now has the global responsibility for business development for allergic rhinitis, vaccines and CNS applications.



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POWDER MICRODOSING WITH 100% IN-LINE FILL WEIGHT CONTROL BY X-RAY

Here, Karlheinz Seyfang, PhD, Principal Consultant, Harro Höfliger, discusses the need for filling verification in pre-metered DPI blister filling lines, going on to detail the role X-ray analysis could play in an automated verification process.

INTRODUCTION

The Global Asthma Network estimates that approximately 340 million people worldwide suffer from asthma.¹ Every day, almost 1000 asthma sufferers die from this disease.² In 2015, chronic obstructive pulmonary disease (COPD) caused about 3 million deaths worldwide and is forecast to become the third most common cause of death in the next few years.³ Pulmonary administration is the preferred treatment method for these respiratory diseases, in particular pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs). These devices enable the targeted application of locally active drugs, such as anti-inflammatory corticosteroids or bronchodilators.

Due to the large inner surface of the lung and the thin epithelium layer between alveoli and blood vessels, pulmonary administration also enables the use of systemically acting drug substances. In this capacity, characterised by a rapid onset of effect (such as with opiates) and by the potential to administer relatively large molecules (such as insulin), inhalation offers an attractive alternative to oral or invasive parenteral routes of drug delivery.

DPIs have superior user-handling characteristics and drug substance stability compared with other delivery systems. Within the sphere of DPI design, preference is given to devices that utilise individually sealed powder portions that have been pre-metered during production, due to their positive effect on dosing accuracy during application. The active pharmaceutical ingredient (API) particles must have an aerodynamic diameter no greater than approximately 5 µm to penetrate into the deep lung. Powders containing a high proportion of such particles are generally very cohesive, have poor flow properties and exhibit a tendency to adhere to surfaces. Together with the low fill weight, these

“Whenever possible, a system for the 100% in-line verification of fill weights should be integrated when processing inhalation powders.”

properties lead to an increased risk of under-dosing occurring in some individual units during production.

Transient process deviations like this could be caused by, for example, bridging of the powder in the feeding system. Issues of this kind cannot be detected with sufficient reliability by statistical in-process controls. Therefore, whenever possible, a system for the 100% in-line verification of fill weights should be integrated when processing inhalation powders. Such a system must be capable of capturing and evaluating the data in real time. However, it does not need to be as accurate as a weighing cell since the focus is on the detection of outliers and their reliable rejection.

BLISTERS FOR DPIS

Ideally, DPIs with pre-metered powder doses should contain a month's supply, usually 60 doses, in a minimum amount of space. This has an impact on DPI design and therefore on fill technology. In the case of blister-based DPIs, the blister cavities are designed to be as small as possible and, in order to make optimum use of the volume, are usually filled to the brim. Special fill methods are required for production since conventional dosing methods, such as dosator or vacuum dosing drum, cannot typically achieve a 100% filling level.

The so-called membrane filler is a proprietary technology, with which even small target receptacles can be filled



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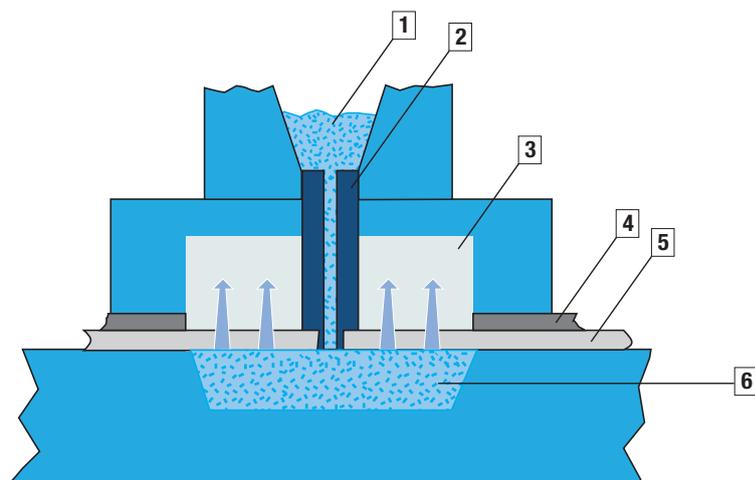


Figure 1: Operating principle of membrane filler for filling of blister cavities up to the brim.

completely.⁴ The system is operated on special thermoforming lines and enables the simultaneous filling of up to 80 blister cavities per machine cycle. A welcome side-effect during dosing is the masking of the sealing surface with the blister web, avoiding contamination by powder particles and thus the occurrence of poorly sealed blister strips. Figure 1 shows the operating principle of the membrane filler.

The blister cavity (6) to be filled is covered with an air-permeable filter membrane (5) connected to a pressure/vacuum system (3). An elastic base (4) provides the air-tight seal. A capillary (2), establishing the connection between blister cavity and powder reservoir (1), ends in the membrane. The dimensions of the capillary are so small that the inhalation powder cannot flow freely purely by gravity. However, if a vacuum pulse is generated through the membrane inside the blister cavity, the powder will flow into the cavity until it is filled to capacity.

Since the fill head of the membrane filler must rest on the blister to be filled, the integration of a capacitive method already in use for the in-line control of fill quantities⁵ was not possible. An alternative method for the control of the filled-to-capacity blister cavities had to be found.

SELECTION OF A SUITABLE CONTROL TECHNOLOGY

The optical control of filling material in blister packages has long been state of the art. Today's camera systems are not only capable of detecting missing objects, but also damage, colour and shape deviations, and double filling. This also works with non-translucent aluminium laminates, which are used for most DPI blisters because they provide the necessary moisture barrier. However, it has been found that only those underfilled cavities which are well below

75% of the target fill quantity are detected. In another approach, the topography of the powder surfaces was determined by means of a 3D laser scanner in order to calculate the dosed volume in the cavities based on the theoretical blister geometry. Unfortunately, inhomogeneities and small voids inside the powder-fill such as are prone to occur with such cohesive materials, are not detectable with this method.

Alternatively, a fill-quantity control method using X-ray technology can be utilised, as it is able to “screen” the closed blister. The absorption of the X-rays by the respective material essentially depends on its mass and is independent of the actual volume of the individual blister

chambers. Furthermore, the blister webs can also be inspected after sealing, making it easy to integrate such a system into the filling machine and greatly simplifying the handling of rejected blisters filled with highly potent drug substances.

Finally, it is safe to assume that the powder will not change during X-ray analysis as the product is exposed to a maximum irradiation dose of 120 μSv , roughly equivalent to the radiation exposure of a passenger during a flight from Frankfurt to New York and back. Uehara *et al* recently demonstrated that active ingredients in tablets do not change in their quality after being exposed to an X-ray dose of 300 Gy, which is 2.5 million times higher.⁶

X-RAY CONTROL – FEASIBILITY

X-ray systems are widely used for process monitoring in food packaging in order to detect damage to containers, underfilling and impurities, or foreign bodies. Until now, X-ray systems in pharmaceutical production and packaging have been something of a rarity. Here, too, they are primarily used for the detection of foreign particles, primary packaging defects and assembly faults. The quantitative determination of fill quantities using X-ray technology remains unusual. Furthermore, when it comes to powder-filled blisters, the relatively small powder dose is usually packaged into aluminium laminates. The absorption of X-rays, however, not only depends on wavelength, density and thickness of the irradiated material, but also strongly depends on its atomic number. The 3–4 mg of aluminium contained in the barrier layer per blister cavity, with an atomic number of 13, is thus a high background against the powder (primarily carbon, atomic number 6).

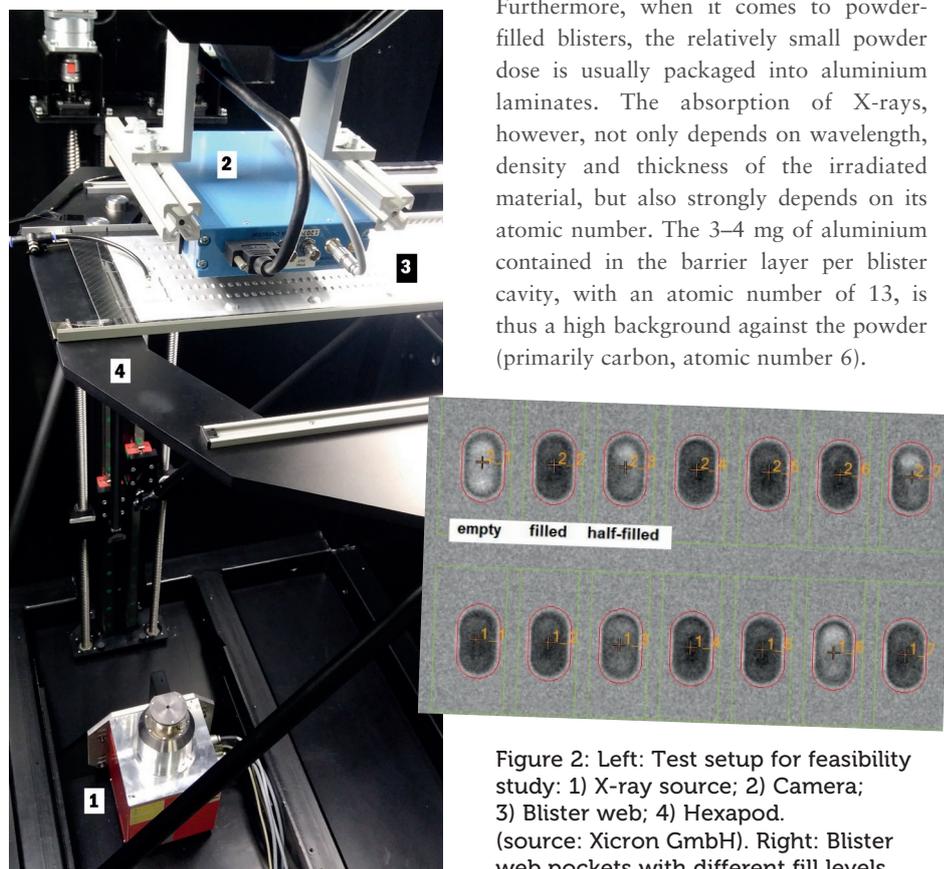


Figure 2: Left: Test setup for feasibility study: 1) X-ray source; 2) Camera; 3) Blister web; 4) Hexapod. (source: Xicron GmbH). Right: Blister web pockets with different fill levels.

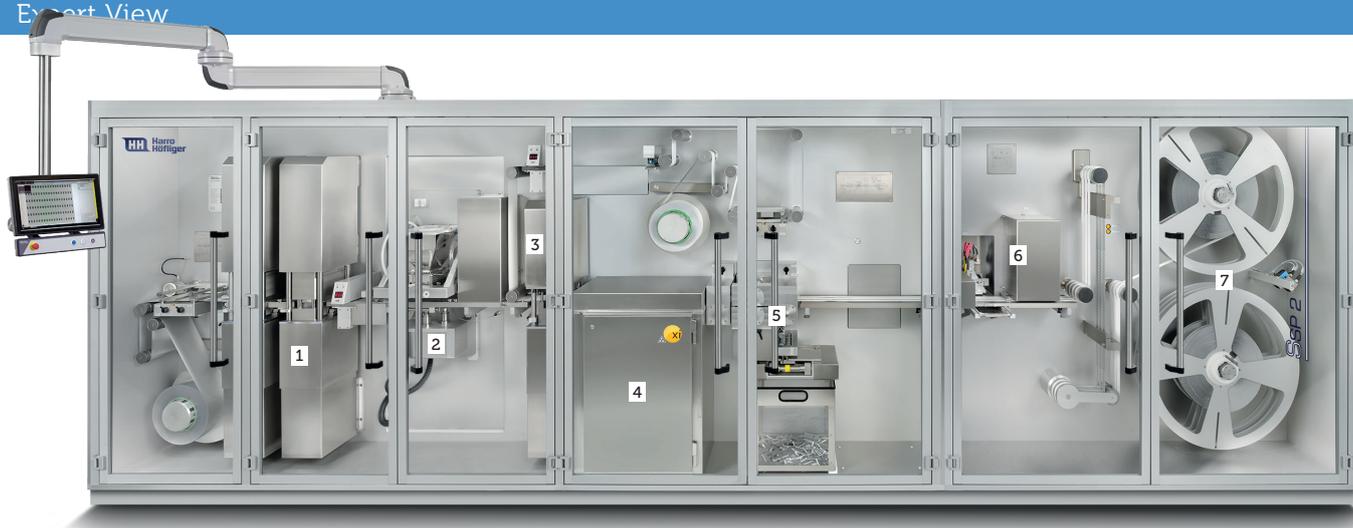


Figure 3: Machine for the manufacture of powder-filled blister strips: 1) Forming station; 2) Membrane filler; 3) Sealing station; 4) IPC X-ray module; 5) Longitudinal cutting; 6) Printing with camera control; 7) Winding.

For a first study, six-lane blister strips were manufactured with 60 cavities per lane. Some were filled correctly (13 mg), others had several cavities that were manually half emptied or vacuumed out completely (Figure 2). The measurements were carried out with different settings for tube voltage and/or cathode current in order to estimate the achievable measurement accuracy. In order to largely compensate for the influence of material tolerances, i.e. thickness of the carrier strip, as well as the intensity fluctuations of the X-ray tube and the detector on the measurement result, the area encircling the blister cavities was included in the calculation of the effective fill quantity as a kind of “tare weight”.

The evaluation of the detector images resulted in a greyscale value for each blister cavity, which could subsequently be compared with the actual fill quantity. The fill quantity was weighed after determining the gross/tare weights of the cut out individual blister cavities (Mettler MX5, resolution 1 µg). The measured greyscale values correlated quite well with the fill weights ($R^2=0.968$, $n=360$). One mg of powder corresponded to about 20 greyscale values. Consequently, a sufficiently high resolution was expected in order to detect significantly underfilled blister cavities.

X-RAY CONTROL – INTEGRATION

Following the encouraging results of the preliminary study, a production system was designed which can be operated automatically and integrated into existing intermittent blister lines. The size of the flat panel detector was chosen so that up to eight lanes per cycle (this means 8 x 10 blister cavities) could be simultaneously controlled. The module was integrated into the machine after the sealing station (Figure 3). The sealed blisters are X-rayed, then pass through the

“The evaluation of the detector images resulted in a greyscale value for each blister cavity, which could subsequently be compared with the actual fill quantity.”

longitudinal cutting station where they are cut into three or four double strips. This is followed by printing the variable data before the strips are wound up for intermediate storage. Based on the printed data, the winding and assembly machine later detects any non-conforming single blister strips and discharges them from the assembly process.

The process checks blister cavities when the blister web is stationary for up to one second. During this period, several camera images are generated which are then used to calculate an average greyscale value for the evaluation of the fill quantity. The detector used has a pixel size of 50 µm and the X-ray tube generates a maximum output of 105 kV/450 µA (approximately

50 W). An internal compensation is carried out automatically in order to calibrate the system. Then some empty blisters are measured that serve to detect the impact of deformed and non-deformed blister foil on the greyscale values, as well as the impact caused by their position in the image window. Subsequently, filled blisters were measured, recovered after the longitudinal cutting station and weighed with an automatic checkweigher.

In order to test the system, blisters were filled with lactose monohydrate (Lactohale LH200, DFE Pharma, Goch, Germany). Figure 4 shows the evaluation of a test batch in which 48 blister samples with 60 cavities each (a total of 2880 blister cavities)

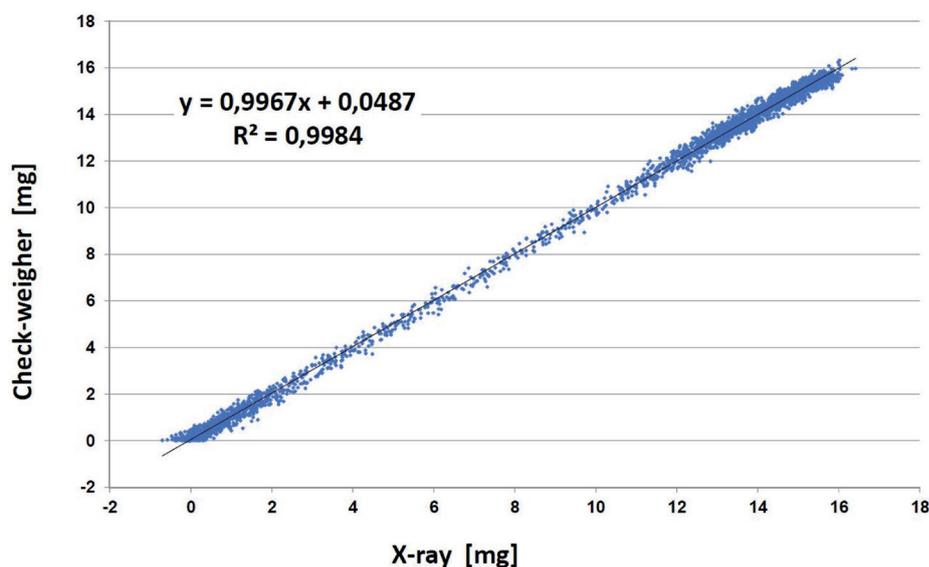


Figure 4: Correlation between fill quantities and the calculated values (48 X 60 blister cavities).

were weighed. In order to simulate possible under-filled cavities, individual fill nozzles or partial surfaces of the filter membrane were blocked so that some markedly under-filled blister cavities occurred. The deviation of the fill quantity prediction, based on the greyscale values of the checkweigher data, was in the range of -0.85 mg and +0.73 mg, respectively, corresponding to a standard deviation of 0.24 mg. With a target fill weight of 13 mg, this corresponds to a relative standard deviation of 1.8%. The method is sufficiently accurate throughout the entire measurement range to detect individual blisters outside specified limits

with a maximum deviation of +5–6%.

We also examined active ingredient containing powder mixtures with a typical combination of beta agonist and corticosteroid. As to be expected from their atomic composition, they showed the same absorption behaviour.

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Karlheinz Seyfang previously served as head of the business unit Pharma Service for Harro Höfliger, and is now Principal Consultant, Pharmaceutical Technology. Before joining HH he spent 20 years in different positions in the pharmaceutical industry. His experience covers pharmaceutical development, clinical trial supplies, manufacturing and packaging of solid dosage forms. Dr Seyfang graduated in Pharmacy from the University of Würzburg, Germany, and received his PhD in pharmaceutical chemistry. At HH his focus is on powder dosing systems and sensors for dose verification.



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A POSITIVE SPIN ON DPI FORMULATION

Here, Bert Dekens, Application Manager, Pharma, Hosokawa Micron BV, outlines some of the considerations that go into developing and processing dry powder inhaler formulations, and discusses the merits of conical high-shear mixers.

Oral inhalation is well recognised as an efficient method of drug delivery by many pharmaceutical companies, driving the continuing development of branded as well as generic dry powder inhalers (DPIs). However, the complexities of developing a DPI-suitable formulation are not straightforward; there are several often contradictory requirements these formulations must conform to.

One example of this is that, in order for the active pharmaceutical ingredient (API) to reach and be absorbed within the lung, the particle size of the API needs to be within the range of 1–5 µm. Individual material characteristics aside, any powder consisting of particles this fine is very cohesive by nature, therefore needing to be blended with a carrier, most frequently lactose, in order to facilitate effective handling and accurate dosing. Then, during inhalation, the carrier and API particles must separate so that only the API is delivered to the lungs.

It demands a profound understanding of powder particle size distribution, flowability, cohesion, adhesion and the mechanical bonding of specific powders in order to create a DPI-appropriate blend. Therefore, the choice of micronisation and mixing technology is crucial in achieving the

“It demands a profound understanding of powder particle size distribution, flowability, cohesion, adhesion and the mechanical bonding of specific powders in order to create a DPI-appropriate blend.”

required powder properties and needs to be tuned to the individual process step.

Typically, a DPI formulation consists of a blend of one or more APIs blended with a mixture of, in most cases, two grades of lactose. The lactose carriers are typically a mixture of coarse lactose, in the range of >100 µm and 5–10% fines. The effects of the fines are well documented but are predominantly influenced by the reduction of press-on forces and the coverage of active sites. In practice, the API(s) represent only a small fraction of the overall powder mixture.

For micronisation of the API, a spiral jet mill (Figure 1) or fluidised bed opposed jet mill are suitable choices. In a spiral jet mill the particles are accelerated by a high gas flow and crushed by collision. It is a simple mechanical construction without moving parts. Thus, inspection and cleaning are simple affairs. The fluidised bed opposed jet mill, on the other hand, has the advantage of an integrated classifier, resulting in a steeper particle size distribution.

For milling or micronising lactose carriers, a jet mill or an impact mill can be selected. Jet milling is better suited for the finer grades, an impact mill for the coarser material. Both technologies can be equipped with integrated classifiers to have a better control of the particle size distribution.

In order to select the powder mixer, typically low-shear, convective mixing is recommended for the blending of free-flowing powders. However, for cohesive powders, a high-shear mixing technology is

“The key to success is applying the correct balance of mixing energy to the formulation in order to break the cohesive forces of the fine API to produce an even distribution across the formulation.”



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Figure 1: The spiral jet mill micronises particles by accelerating them in high gas flow causing them to collide and fragment.

advised. Keeping this in mind, the blending sequence of coarse and fine lactose with API, as well as the cohesive/adhesive balance, needs to be observed for the selection and tuning of the mixing process.

The key to success is applying the correct balance of mixing energy to the formulation in order to break the cohesive forces of the fine API to produce an even distribution across the formulation. Too little mechanical energy and the cohesive forces will not be broken, whereas too much energy and you run the risk of strengthening the adhesion between the API particles and potentially damaging the carrier particles – resulting in poor formulation composition and limited separation during inhalation.

CONICAL HIGH-SHEAR MIXERS

Conical high-shear mixers are capable of blending the powder fractions of the formulation and fine-tuning the appropriate energy input. Offering distinct production advantages, plus multiple handling and contamination avoidance benefits, conical high-shear mixers can be used for various blending stages, including pre-mixing both lactose blends and API/carrier blends (Figure 2). Besides these blending processes, coating processes can be run as well, for instance, the coating of lactose with magnesium stearate.



Figure 2: A high-shear batch mixer with exchangeable product bowls, designed for blending DPI formulations.

The performance of conical high-shear mixers can be explained by the flow pattern of the powder in the vessel (Figure 3). In this case the powder is contained in a conical vessel with top-driven agitation. The product is rotated by an agitator with paddles and a knife blade. The rotational movement exerts centrifugal forces on the powder particles. This force moves the particles upwards along the wall of the conical vessel. At the top of the cone, the specially formed dome guides the

particles downwards again through the centre of the vessel. This flow pattern is combined with the rotational pattern from the agitator.

The shear energy is applied between the paddles and the wall of the vessel, resulting in a very large surface area where the shear forces are applied in relation to the product volume. Thus, conical high-shear mixers are very efficient compared with other high-shear blenders.

The top-driven rotor allows for seals to be outside of the product area, preventing contamination. Full product discharge through the bottom discharge valve combined with unit design facilitates easy cleaning in place (CIP) or sterilising in place (SIP) cleaning methods.

ABOUT THE COMPANY

Hosokawa Micron BV is a member of the worldwide Hosokawa Micron Group, which was founded in Osaka in 1916 and is the world's largest provider of processing systems for the field of powder and particle processing. Hosokawa Micron Group maintains facilities for research, engineering, manufacturing and service throughout Asia/Oceania, the Americas and Europe.

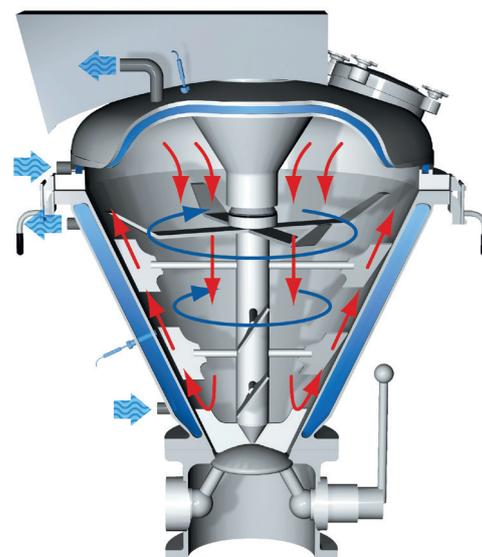


Figure 3: The performance of conical high-shear mixers can be explained by their flow pattern. The powder is agitated at the top of the mixer and forced out and up by centrifugal forces and the conical chamber shape respectively.

ABOUT THE AUTHOR

Bert Dekens is Application Manager, Pharma, for the Hosokawa Group, focusing on DPI blending markets. Mr Dekens holds a key position in the DPI network within the International Hosokawa Group and is well established in the DPI market.



H&T PRESSPART

GAS PLASMA PROCESSING: A LONG-TERM SOLUTION FOR RESPIRATORY DEVICES

Ameet Sule, Head of H&T Presspart's Inhalation Product Technology Centre (IPTC), discusses the new challenges arising in metered dose inhaler design since the change from CFC to HFA propellants, in particular focusing on the tendency for drug product to adhere or degrade when in contact with the aluminium interior of the canister. As a solution, Mr Sule proposes new developments in gas plasma processing.

SUMMARY

Hydrofluoroalkane (HFA) propellants are widely used in modern metered dose inhalers (MDIs) due to their lack of hazardous and environmentally damaging effects on the ozone layer, compared with chlorofluorocarbons (CFCs). However, an HFA formulated with an API can interact with the canister substrate, causing deposition of the drug on the canister walls or interaction with the pharmaceutical drug solution, causing drug degradation and resulting in reduced shelf life.

H&T Presspart's plasma process, manufactured under license from Portal

"With HFA drug suspension formulations, 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."

Medical Ltd (Swaversey, UK), treats the internal surfaces of MDI canisters so that the active drug content does not adhere to the canister wall, and enhances drug stability in formulations where interactions with the aluminium substrate can lead to product degradation.

Plasma technology can also be applied to plastic parts in a dry powder inhaler (DPI), where there are challenges of cohesive powders and the surrounding conditions causing drug to be retained in the device.

USE OF HFAS IN MDIS

MDIs are commonly used to treat respiratory diseases and nasal disorders. Ensuring that the device delivers a consistent dose and that the formulation is safe (non-toxic) is of paramount importance. The drugs are administered by aerosol and formulated as either a suspension or solution in a liquefied propellant gas. For over 50 years CFCs were the propellants of choice for MDIs, but these were phased out by the end of 2010 in line with the Montreal protocol, due to their contribution to ozone layer depletion.

Replacement propellants have been developed over the past two decades based on HFAs, most notably HFA134a and HFA227ea. These propellants are non-ozone depleting and chemically inert, making them the ideal candidates for medicinal products. However, some properties of



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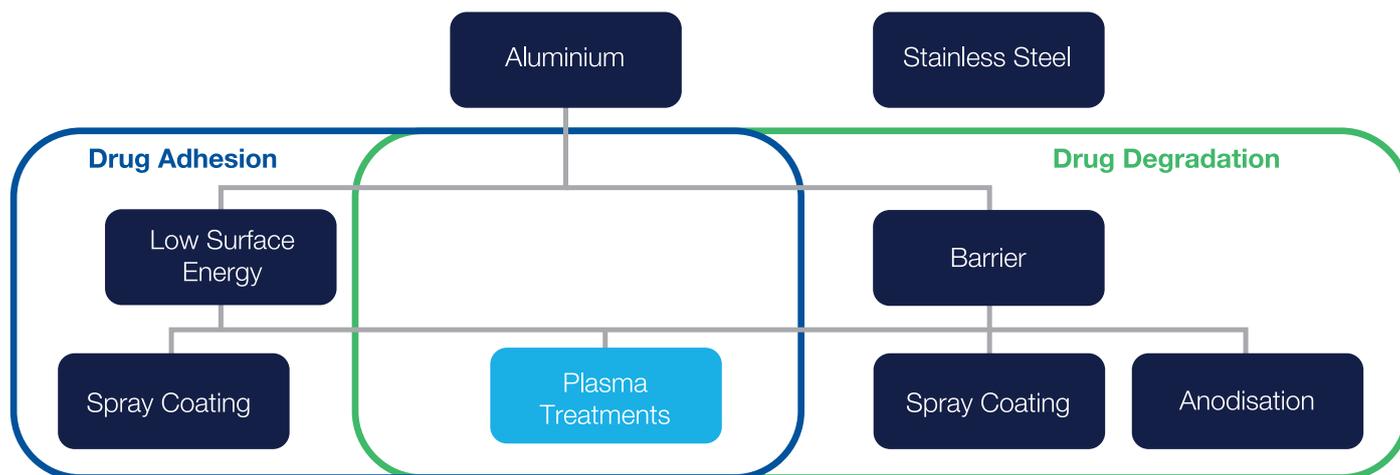


Figure 1: Types of surface treatment.

these compounds are substantially different from those of the CFCs traditionally used in MDIs, resulting in new challenges.

With HFA drug suspension formulations, 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.

The surface chemistry of the MDI canister therefore has a vital role in the overall performance of the MDI and the drug. To protect the contents from deposition and degradation, a number of surface coatings have been developed that can be applied to MDI canisters and valve components (Figure 1).

COATING MATERIALS & TECHNIQUES

Over some years a number of surface coatings have been developed to protect the drugs from deposition or degradation.

Fluorocarbon polymers (FCPs) are commonly used to coat the interior canister surfaces in order to eliminate adhesion or deposition of, for example, salbutamol on canister walls. These polymers can be made from multiples of one or more of a variety of monomers – particularly preferred coatings tend to be pure perfluoroalkoxyalkylene (PFA) or 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

“Gas plasma processing can create an ultra-thin layer that protects against deposition and corrosion or modify the surface to prevent degradation.”

as polyamides, are used for certain formulations to improve adhesion of the coating to the canister walls. Other coating types include epoxy-phenol resins.

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 via 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 and electrostatic dry-powder coating, all of which can be followed by curing.

Many of these processes require high temperatures, up to 400 °C when curing, which can create additional costs and complications, and increase the environmental impact. 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.

PLASMA PROCESSING TECHNOLOGIES

More recently, plasma processes have been developed to modify the surface of an MDI canister and this approach has proved to have a number of advantages over traditional coating methods. Gas plasma processing (GPP) is an industrial

technique that is carried out under vacuum to treat a wide range of substrate materials. The process involves constant or pulsed excitation of gas, either by radio frequency (RF) or microwave field, to produce an energetic plasma. The process can create an ultra-thin layer that protects against deposition and corrosion or modify the surface to prevent degradation.

It is a low-temperature process 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 GPP 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 improve the stability of formulations where interactions with the aluminium substrate would lead to product degradation and reduced shelf life. However, the process needs to be highly controlled to 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 have made plasma a viable choice.

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 extractables 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, be they RF or microwave, are particularly difficult to control when internal surfaces are to be treated. Poor penetration of plasma ions with low energy results in a non-uniform, thin or porous coating, which will inevitably perform poorly. 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. For nanometre thin 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.

Delivered dose through life, grouped by canister type

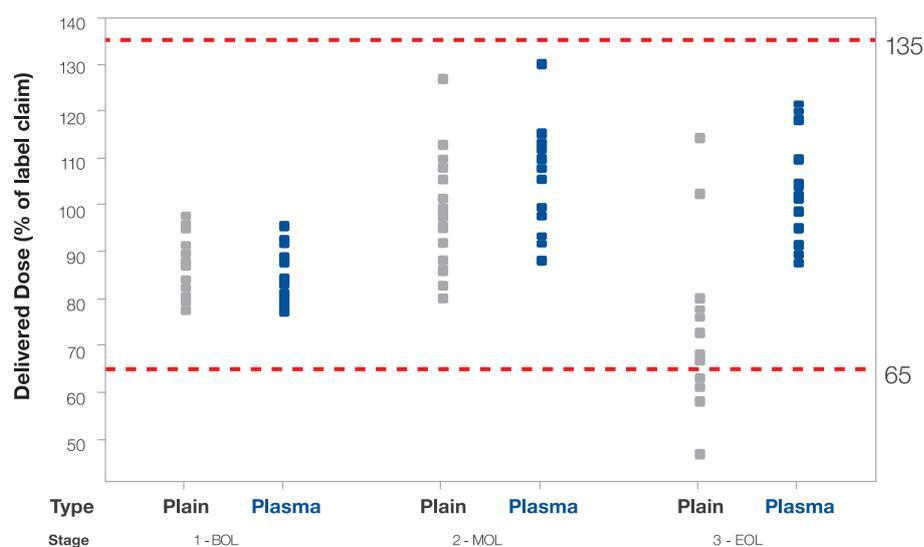


Figure 2: Comparison of delivered dose performance of a budesonide HFA suspension formulation at beginning (BOL), middle (MOL) and end of life (EOL), using plain aluminium and plasma-treated MDI canisters.

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 global MDI market.

Example: Budesonide HFA Suspension

GPP has been used to develop several different plasma coating options that have successfully prevented drug deposition on the can walls and drug degradation in solution or suspension. For example, a surface treatment has been especially developed for deep-drawn 5052 aluminium canisters, which is suitable for budesonide suspension in HFA.

As can be seen in Figures 2 and 3, plasma-treated canisters exhibited more reliable performance at the end of life. The difference in profiles observed with delivered dose and shot weight tests confirms that the primary tail-off effect relates to the concentration of drug in the formulation, as opposed to the weight of formulation emitted.

Figure 4 illustrates the conclusion that the improved end-of-life performance was achieved by reducing the amount of drug deposited on the canister walls throughout use. The canister contents were determined after depletion of formulation, with an additional 2.7 mg of residual budesonide

being detected in the mean of plain canisters compared with the mean of plasma canisters.

DRY POWDER INHALERS AND PLASMA TECHNOLOGY

Another possible application of plasma technology is in the plastic component surfaces of a DPI. The various flow paths the powder needs to take through a DPI can make it difficult to achieve a consistent delivery performance. Plasma treatments are suitable for a wide range of materials, including plastics such as PTFE, polypropylene, polyethylene and polystyrene. It might therefore be beneficial to treat these parts to achieve a smoother flow and more complete evacuation of the formulation from the capsule, blister, reservoir or cartridge.

Modifying the active sites to render them more hydrophobic or more hydrophilic, dependent on the particular drug substance of interest, could enable a formulator to achieve more consistent delivery of the drug from the DPI.

CONCLUSIONS

Respiratory devices are complex in nature. Even though the MDI has been in a generic form for the last 50-plus years, it has been a challenge for R&D chemists to deliver a robust product to the market. MDIs combine a mixture of mechanical components, physical dimensions, the

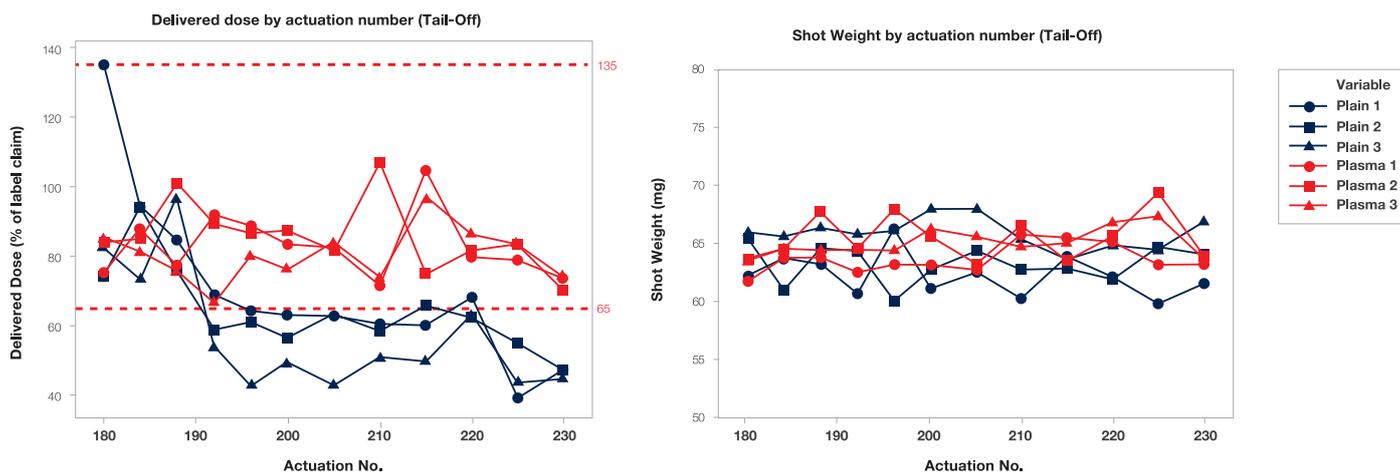


Figure 3: Tail-off characteristics for plasma-treated and plain canisters, using delivered dose testing (left) and shot weight (right), for a budesonide HFA suspension formulation.

chemical composition of the formulation and physical properties (e.g. temperature, pressure, moisture ingress), all of which affect the product characteristics.

GPP offers considerable advantages in the coating and treating of MDI canisters, 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 demand for high volumes from the MDI market.

Laboratory tests have already demonstrated that FCP plasma-treated canisters can provide improvements in end-of-life delivered dose performance compared with plain aluminium alloy canisters, when used in combination with a budesonide HFA suspension formulation. Other respiratory medicine applications which have been, or are being, developed include the prevention of drug degradation in solution MDIs, and the treatment of DPI components to aid the evacuation of formulation.

ABOUT THE COMPANY

H&T Presspart offers pharmaceutical customers high-precision, injection moulded plastic components and deep drawn metal cans for respiratory drug delivery systems. The company has more than 45 years' experience and a worldwide reputation for competence, quality and innovation in the pharmaceutical and other industrial

Deposition in mg, grouped by canister type

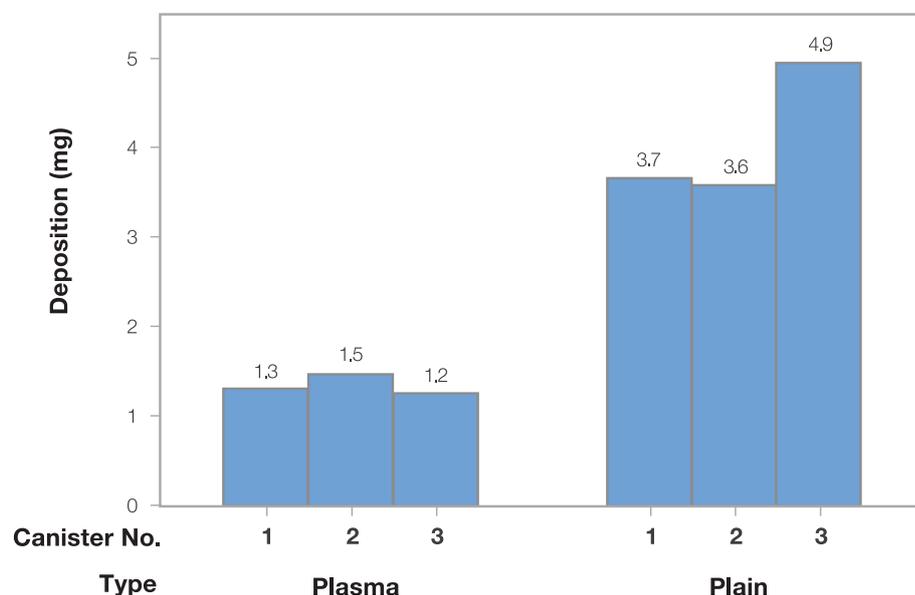


Figure 4: Drug deposition on canister walls after depletion of formulation.

sectors. The H&T Presspart Inhalation Product Technology Centre (IPTC) supports new product developments and strategic initiatives with its customers. Founded in 1970 and acquired by the Heitkamp and Thumann group in 2002, H&T Presspart has three European manufacturing sites in Germany, Spain and the UK, with sales offices in China, India, South America and the US.

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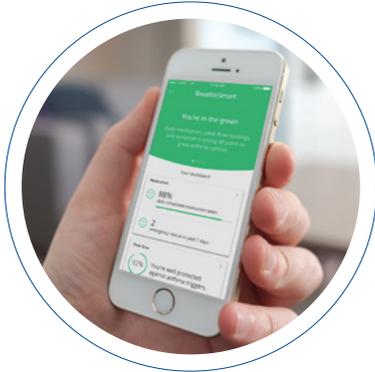
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ABOUT THE AUTHOR

Ameet Sule, Director of H&T Presspart's Inhalation Product Technology Centre, is a pharmaceutical professional having worked in the industry for more than 20 years, specialising in the development of inhalation products and devices.



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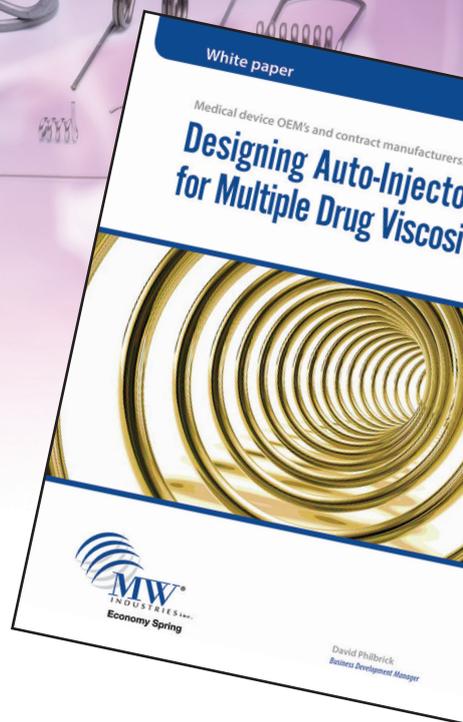
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5 THINGS TO CONSIDER WHEN MANUFACTURING CONNECTED DRUG DELIVERY DEVICES

The estimated number of connected drug delivery devices continues to increase and the impact of this trend could be significant, explains Phillips-Medisize



While digital connectivity or connected health can improve the coordination and delivery of patient care, original equipment managers need to keep these five things in mind when creating connected drug delivery devices:

- 1 Development strategy and design consideration**
- 2 Situation analysis and patient compliance**
- 3 Connectivity ecosystem**
- 4 Wireless subsystem**
- 5 Security of device and information**

As the Internet of Things continues to become an integral part of people's lives, the opportunity to use it within drug delivery device applications remains promising. The manufacturers and device designers must identify, investigate and overcome these challenges so that the implementation of wireless and other related smart technologies can be achieved. When done successfully, connected systems enable the patient and caregivers to have a 360° view of both the patient and the disease – not only to manage adherence, but to improve results by understanding the effect of the regimen.