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Pulmonary Drug Delivery

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EDITORIAL AND ADVERTISING:

Contact: Guy Furness, Proprietor & Publisher
 T: +44 (0) 1273 47 28 28
 E: guy.furness@ondrugdelivery.com

MAILING ADDRESS:

Frederick Furness Publishing Ltd
 The Candlemakers, West Street, Lewes,
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CONTENTS

04 - 09	Expert Opinion: Current Thinking on the <i>in vivo</i> Behaviour of Particles in the Extra-Fine Region David Lewis, Head of Laboratory, Chippenham Research Centre, Chiesi UK Chiesi
10 - 12	Why Success in Drug Delivery is Not Just About the Device Mark Tunkel, Partner & Business Development Director Insight Product Development
14 - 17	A New, Advanced High-Throughput System for Automated Inhaler Testing Adam Smith, Director Novi Systems
18 - 20	Inhalia®: a New pMDI Metering Valve Platform that Patients Can Count On Inga Meyer, Category Manager Nemera
23	Product Profile: DF30 Metering Valve Aptar Pharma
24 - 26	Human-Centred Design & Inhalation Device Development Bill Welch, Chief Technology Officer Phillips-Medisize
28 - 30	Patient Preference in Respiratory Device Training & Educational Tools Paul Sullivan, Associate Director, Business Development; and Craig Baker, Executive Vice-President Noble
33 - 35	Improving Drug Stability & Drug Delivery by Modification of MDI Canister Surfaces Richard Turner, Business Development Director, Pharmaceutical Presspart Manufacturing



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EXPERT OPINION: REVIEWING CURRENT THINKING ON THE IN VIVO BEHAVIOUR OF PARTICLES IN THE EXTRA-FINE REGION

The inhalation route is a fast and effective way of delivering medication, both locally to the lungs and systemically to the body. Conventional wisdom for the development of inhaled products is that the preferred particle size for drug delivery is one to five microns and it is typically suggested that particles less than one micron are exhaled, but is this true? In this review, David Lewis, PhD, Head of Laboratory, Chippenham Research Centre, Chiesi UK Ltd, reports the latest research on the changing view of the behaviour of particles in the extra-fine region and their potential for enhancing inhaled drug therapies.

Pulmonary drug delivery has generated a significant amount of interest in pharmaceutical research because of the lung's capacity to absorb pharmaceuticals for both local treatment and systemic delivery.¹ The large surface area and highly permeable air-to-blood barrier provided by the respiratory system make it a highly receptive site for drug delivery, most especially for the local, rapid and effective treatment of, for example, asthma and chronic obstructive pulmonary disease.

However, the development of inhaled drugs is complex, as to achieve targeted deposition three conditions must be met:

- 1) The inhaled aerosol formulation must be sized for drug deposition along the respiratory tract including in the deep lung
- 2) The drug delivery device and formulation must generate an aerosol cloud containing a high proportion of suitably sized particles
- 3) The deposition of the drug should translate into functional and clinical benefits.

Better understanding of these parameters and their interrelationship helps to maximise the benefits and efficiency of pulmonary drug delivery systems but the majority of such research has focused on the behaviour of particles within the 1-5 μm range, which

are known to deposit successfully in the pulmonary region. Particles larger than 5 μm will typically impact on the oropharynx and be swallowed. Assuming a continuum of behaviour, with finer and finer particles taking longer to deposit, the majority of particles less than 1 μm in size are expected to flow back out from the body on the exiting breath. Currently particles less than 1 μm in diameter are therefore not considered to be of consequence for drug delivery.

TIME TO RE-EVALUATE?

Recent technological developments have seen a wide range of industries look in more detail at particles in the 1-2 μm and nano range, and new evidence is emerging to suggest that assumptions about inhaled behaviour may not be correct. Indeed, studies investigating the deposition sites of extra-fine and sub-micron particles have found that it is possible that these particles could in fact be effectively delivered to the small airways in the deep lung.²

Clinically this might not only aid the efficiency of drug delivery, but could also result in a more uniform localised therapeutic response, if the drug was deposited in both the central and peripheral airways.^{3,4} A recognised trait in certain asthma sufferers is persistent small airway dysfunction and

Dr David Lewis
Head of Laboratory
Chippenham Research Centre
Chiesi UK

Address for Correspondence:

Chiesi Ltd
333 Styal Road
Manchester
M22 5LG
United Kingdom

T: +44 161 488 5555
F: +44 161 488 5566

www.chiesi.uk.com

this seems to be associated with poor disease control. By targeting deep lung deposition extra-fine formulations of inhaled asthma therapies may therefore also have the potential to ‘unlock the small airways compartment’ and improve treatment efficacy.^{4,5}

Furthermore there is evidence that when an aerosol is mainly composed of very fine particles the difference between *in vitro* aerosolisation and *in vivo* behaviour is less pronounced.⁶ This suggests that aerosols with a finer particle-size distribution could exhibit behaviour that is relatively independent of flow rate, a feature that would enable the delivery of more controlled deposition across patient groups with different inspiratory profiles.

Closer scrutiny of the behaviour of extra-fine aerosols in terms of pulmonary delivery calls for data generated both *in vitro* and *in vivo*. Interpretation of such data can be used to answer the following questions and to provide greater insight:

- How do aerosols of extra-fine particles behave?
- How do extra-fine particles behave in the respiratory system?
- Are current *in vitro* and computer based particle behavioural models sufficient for describing this behaviour?

Answering such questions will help resolve the potential pharmacological impacts and consequences of delivery of extra-fine aerosols for treatments for a wide range of applications. If particles around one micron and smaller are not simply exhaled then there are possible implications in terms of the sites of deposition with the lung, the dose received by the patient and the therapeutic activity of the drug. Further, improved insights may also provide a firm basis for future advancement in inhaled nano-medicine strategies.

DEFINING EXTRA-FINE & SUB-MICRON AEROSOLS

The development and quality control of orally inhaled and nasal drug products (OINDPs) relies on making *in vitro* measurements that reflect the likely success of drug delivery and targeted deposition. These include assessing the total quantity of drug emitted from the device and therefore available to the patient, and the aerodynamic size of the particles that make up the emitted aerosol. This impacts the percentage of the total dose that reaches the lungs during inhalation, as well as its regional intrapul-

monary deposition, and is therefore therapeutically active.

Inertial impaction, sedimentation and Brownian diffusion are all factors that are affected by particle characteristics and that influence the site of deposition in the airways. Influential particle characteristics include shape, density and, most especially, size. For inhaled product delivery, aerodynamic particle size measured by the technique of inertial cascade impaction, is the

“Recent technological developments have seen a wide range of industries look in more detail at particles in the 1-2 µm and nano range, and new evidence is emerging to suggest that assumptions about inhaled behaviour may not be correct”

metric used as a primary indicator of deposition behaviour because of its relevance, which stems from a shared dependence on shape and density. The mass median aerodynamic diameter (MMAD), one of the most commonly used inhaled product metrics, defines the size of aerosol particles, taking into account their geometric diameter, shape and density.

In terms of aerodynamic particle size, which is equal to the geometric particle diameter for spherical particles or unit density, a sub-micron particle can be identified simply as a particle with a diameter of less than one micron.¹

There is an increasing amount of research into extra-fine and sub-micron aerosols. However, as yet a definition has not been agreed. Aerosols can be either polydisperse, consisting of multiple particle sizes, or monodisperse, containing particles of uniform size. For a monodisperse aerosol to be sub-micron, the particles need to have an aerodynamic particle size of less than one micron. However, there are, in reality, no truly monodisperse aerosols – most contain a distribution of particle sizes. For polydisperse aerosols, it has not been formalised as to what percentage of the particles need to be extra-fine or sub-micron to merit the respective classifications.

Typically, when designing an inhaled delivery device, limits are set that define an optimal range for the MMAD of the particles and the fraction (based on mass or volume) of particles that can acceptably fall outside of this range. An evaluation

of dry-powder inhalers (DPIs), conducted by Krishnaprasad, found that the majority of devices investigated, contained approximately 50% of particles within the fine particle fraction.⁷ This suggests that many DPIs could already be delivering a proportion of the dose in the extra-fine range, even if the aerosol as a whole cannot be classified as extra-fine. This proportion can be quantified through analysis of the residual dose captured in the final filter of a cascade impactor.

The term “extra-fine” is now used routinely to describe inhaled particles and has been featured in several studies,⁸ but there remain discrepancies in the term’s definition that cause some confusion and make studies harder to compare. General consensus sees particles less than 1-2 µm referred to as extra-fine but some papers use this same term to refer to particles less than 0.1 µm in diameter.²

For the purposes of this article, extra-fine particles are defined as those that have an aerodynamic particle size of less than 2 µm, to differentiate them clearly from particles that are traditionally defined as lying in the fine particle fraction. This figure has been selected on the basis of clinical relevance, it being the upper size limit of particles that are able to penetrate to the small airways of the lung.⁹

PARTICLE BEHAVIOUR IN THE LUNG

In pulmonary delivery, there are three factors that influence particle deposition behaviour:

- 1) The characteristics of the aerosol
- 2) The anatomy of the respiratory tract
- 3) The airflow patterns in the lung airways.¹⁰

Deposition is quantified in terms of the ratio of the mass of particles deposited in the respiratory tract to the mass of particles inhaled¹¹ and governed, as mentioned earlier, by the mechanisms of impaction, sedimentation and diffusion.

The mass of a particle affects its travelling velocity, which is also determined by the velocity of the respiratory airflow. Larger particles will tend to travel more slowly but also have greater inertia making them more prone to impaction. Gravitational deposition is dependent on residence time and particle settling velocity and is therefore promoted by larger particle size and the longer residence times

performance. The reduced net effect of oropharyngeal deposition (by impaction) and high pulmonary deposition in the upper respiratory region (as a result of slow settling times) could potentially counterbalance the impact of losing a certain fraction of particles in the extra-fine range on exhalation. Therefore such particles may be not only pharmacologically relevant but could even enhance dose effectiveness as a result

rounding conditions. Larger agglomerates may break down into smaller particles, or smaller moieties may agglomerate further to form even larger particles.¹⁴

In the design of a DPI, particle deagglomeration is actively promoted by inducing an inspiratory airflow that creates turbulence and aerosolisation within the device. Low-resistance devices result in high inspiratory flow rates while higher resistances induce lower air velocities. Due to the settling velocity and agglomeration tendencies of sub-micron particles, the development of inhalers with highly effective deagglomeration mechanisms, typically those with high internal resistance, are therefore more likely to provide greater lung deposition than those with a lower internal resistance.^{15,16,17} At the same time as promoting successful de-agglomeration these devices deliver the low velocity needed to offset the slow settling rates and ensure the successful administration of extra-fine particles.¹⁸

“Aerosols with a finer particle-size distribution could exhibit behaviour that is relatively independent of flow rate, a feature that would enable the delivery of more controlled deposition across patient groups with different inspiratory profiles”

that more easily occur in the small conducting airways and the alveolated lung region.¹² Diffusional displacement, on the other hand, becomes more pronounced as particle size decreases and is the factor with the highest probability of promoting the deposition of extra-fine particles in the lung and small airways.

Settling velocity increases with the square of the particle diameter. This is why particles greater than 5 µm in size can quickly deposit after inhalation onto the oropharynx. Impaction is also an important mechanism for deposition in this area. The relationship between particle size and settling velocity means that extra-fine and sub-micron particles will take significantly longer to deposit, a primary reason why it is often thought that such particles are simply exhaled.

A typical recommended breath-hold period after dose by an inhaler is ten seconds, though this may be an overly optimistic figure when compared with the reality of clinical practice. Clearly the extent of breath hold is likely to have a marked effect on particle deposition behaviour, most especially for extra-fine particles.¹⁰ Indeed a suggestion for increasing the deposition of extra-fine and sub-micron particles, where desirable, is to introduce longer breath hold periods, but this would require the effective training of patients and may prove problematic for some groups including the elderly and young children.

If we explore the premise that extra-fine and sub-micron particles are not simply exhaled then these particles have the potential to significantly contribute to product

of precise delivery to a targeted and therapeutically-relevant site.² Although extra-fine particles only make up a very small contribution to particle mass, they may lead to significant dosing in terms of the number of particles deposited on a receptive surface.

Research from Bodzenta-Lukaszyk and Kokot provides some support for the suggestion that the mechanisms at play during inhalation do not result in the complete exhalation of sub-micron particles.¹³ This study concluded that, although almost half the mass of the inhaled aerosol from an MDI was composed of particles less than 1 µm, only approximately 10% of the emitted dose was exhaled, as measured by scintigraphy.

Particles that are not exhaled and avoid deposition in the extrathoracic and tracheobronchial airways reach the alveolar region. Generally, it is thought that the principals of deposition within this region are sedimentation and via diffusion, which is of particular importance for those in the sub-micron range.¹¹ This reliance on diffusion and Brownian movement make the deposition of the extra-fine particles more pronounced in the alveolar region.

Assessing the Impact of Agglomeration

The preceding discussion assumes that inhaled extra-fine and sub-micron particles will remain discrete. However, at this size particles have a sharply increased tendency to agglomerate due to inter-particle forces which increase exponentially with decreasing particle size. That said, agglomerates are not fixed units, a primary factor in inhaled drug delivery, and can change their size and shape depending on the sur-

Accounting for the Effect of Humidity

One further factor to consider when investigating the behaviour of particles in the respiratory system is the geometric expansion of particles that may occur as a result of the high humidity levels (of 99.5%). This effect means that hygroscopic particles will have different deposition patterns from analogously sized non-hygroscopic alternatives. The size increase experienced by hygroscopic particles will directly affect settling velocity and therefore the location of deposition.

In vitro it is very difficult to mimic the extreme humidity of the respiratory system due to the impact these conditions have on instrumentation. Interpretations and extrapolations therefore have to be made as to how 99.5% humidity will affect particle behaviour, with only *in vivo* investigations being able to demonstrate the impacts accurately.

INVESTIGATING & MODELLING EXTRA-FINE PARTICLE BEHAVIOUR

Experimental studies have demonstrated that factors including airway wall motion, inhalation waveform and geometric complexity all influence the deposition of aerosols in the respiratory system by affecting particle impaction and sedimentation.¹⁹ As such, much work has been undertaken to investigate the best physical models to develop correlations of aerosol depositions that can be used to predict the doses deposited at target locations within the lung, including the alveolar dose.

In routine OINDP testing, multistage cascade impactors are the instrument of choice for measuring data related to deposition behaviour as they enable generation of an aerodynamic particle size distribution specifically for the active pharmaceutical ingredient, across an appropriate size range. These instruments are precision engineered and separate a sample via particle inertia. However, they are designed primarily to determine the consistency and quality of inhaled products and do not accurately represent the anatomical complexity of the human airways.

The metric MMAD, generated from cascade impaction testing, excludes the particles depositing in the “throat” area of the apparatus. A number of studies have shown that extra-fine drug formulations with a low MMAD give greater lung deposition compared with larger particle formulations.²⁰

Physical models of the pulmonary acinus regions have been developed to investigate the deposition of pharmaceutical products further in order to predict therapeutic effect. Depending on the drug being delivered and its desired clinical effect, it can be necessary to target certain regions of the

pulmonary system. For instance, for some pharmaceuticals, the alveolar region may be the target for deposition due to the need to address impaired performance in this region which is often an issue for asthma sufferers.^{5,9} Conversely, for other drugs the tracheobronchial region may be the target

networks using a honeycomb structure of attached alveoli.¹⁹

It has been found that the behaviour of particles varies greatly depending on the characteristics of the model used, which makes it difficult to compare the particle behaviours observed in different studies.

“There is an increasing amount of research into extra-fine and sub-micron aerosols. However, as yet a definition has not been agreed”

and deposition in the alveolar region could potentially cause unwanted systemic exposure and increased side effects.¹⁹

Individual alveolus models consisting of a single hemispherical shell or single alveolus attached to a tube have been used to characterise general transport within the alveolar region. The complexity of such models has since been increased to include channels with multiple hemispheres attached. Other models include rectangular alveoli compartments and bifurcating

Models with multiple alveoli have been found to affect the flow field that pertains and particle trajectories, while bifurcations and complex airway geometry strongly influence aerosol deposition.^{21,22}

Further, Navvab Khajeh-Hosseini-Dalasm and P Worth Longest found that alveolar deposition is dependent on deposition in the upper airways because of the impact this has on the remaining fraction of particles that enters the deep lung region.¹⁹ Models mimicking wall motion,



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which drives alveolar airflow, have shown that such movement is also an important component with unsteady state flow having a large effect on particle transport and deposition.²³ It has also been suggested that truncated acinar models can be implemented to capture total deposition and, when combined with factors such as the impact of gravity, angles and sedimentation, these enable the development of new correla-

This type of work is exemplified by work conducted by Khajeh-Hosseini-Dalasang and Longest assessing models used for the study of particle behaviour in the pulmonary system.¹⁹ These researchers found that airway wall motion was important to match *in vivo* alveolar deposition data with one-dimensional (1D) models accurately. These models are used to implement analytical approximations of the

region. Physically relevant factors such as inhalation profiles consistent with pharmaceutical delivery still need to be taken into account.¹⁹ However CFD models can relatively accurately model the two inhalation manoeuvres most commonly applied when actuating inhalers – “slow-and-deep” and “quick-and-deep”, both of which are usually followed by a period of breath-hold. This period is often also included in CFD models to simulate particle deposition accurately.

In terms of the specific results obtained with CFD studies, one study found a significant difference in the prediction of particle deposition with both inhalation manoeuvres using a CFD alveolated model with moving walls, compared with a 1D solution.¹⁹ The conclusion from this work was that 1D models are not ideal for accurately predicting deposition in the alveolated airway. The CFD model however demonstrated the formation of accumulations of particles – deposition ‘hotspots’ – and so could be used to predict regional drug delivery within the airways.

The analysis of data from CFD models suggests that excellent approximations of *in vitro* extra-fine particle behaviour can be made in terms of velocity and deposition. Further comparisons of data with *in vivo* study findings see patients undergo CT scans after the administration of radiolabelled medication to establish deposition masks of the left and right lung regions, the oropharyngeal region and the gut.²⁸ Studies of this nature are crucial since it is widely recognised that *in vivo* investigations are the most pharmacologically relevant. The current limitations of computer simulations and *in vitro* methods means that well designed *in vivo* studies remain key to understanding the full potential and opportunity for extra-fine drug delivery to the lungs.

LOOKING AHEAD

Extra-fine aerosols potentially offer pharmacological benefit for pulmonary delivery. Not only is there evidence to suggest that extra-fine particles may reach the deep lung, rather than be exhaled, but also that this can result in a more uniform dosing^{3,4}. This can be a benefit for improved local therapeutic effect, and potentially for systemic drug delivery too.

To progress this field of study further, large scale *in vivo* studies are needed to clinically determine the path of extra-fine and sub-micron drug particles through

“The preceding discussion assumes that inhaled extra-fine and sub-micron particles will remain discrete. However, at this size particles have a sharply increased tendency to agglomerate”

tions to predict aerosol deposition from an inhaler device, from the tracheobronchial airways to the alveoli.²⁴

The measurement of extra-fine particle behaviour is technically challenging, regardless of the physical model. However for studies investigating the deposition of inhaled drugs at the extra-fine level, techniques that combine scintigraphy with computed tomography imaging do allow 3D assessment of the particles’ regional deposition with reasonable accuracy.¹³ Since research suggests that targeting the peripheral airways with smaller drug particle aerosols certainly achieves comparable and in some cases superior drug efficacy,^{4,5} such studies are important for the ongoing development of inhaled products.

THE COMPLEMENTARY ROLE OF MODELLING

When *in vitro* models are used to simulate discrete aspects of pulmonary particle behaviour, the data generated from such studies is often extrapolated using some form of computer model to provide a prediction as to how the results can be applied to the whole lung. Such models are used as a means to correlate *in vitro* and *in vivo* studies better by bridging the gap between *in vivo* behaviour and the data generated by cascade impactors and other physical set-ups that fail to capture particle behaviour precisely. As alveoli are extremely small, many studies use computational fluid dynamics (CFD) alongside scaled-up *in vitro* models for the analysis of aerosol transport and deposition.⁸

various particle transport mechanisms to predict deposition at the level of individual bifurcations throughout the airways.²⁵ 1D models, however, only consider distance travelled in a tubular network so omit the importance of considering oscillating flow and wall motion, which are important for matching particle behaviour and alveolar deposition *in vivo*.

CFD uses mathematical algorithms to simulate the motion of particles, fluids and gases and their interactions with surfaces and is increasingly being used in medical studies. CFD approaches have recently been developed to simulate the delivery of pharmaceutical aerosols throughout the conducting airways.¹¹ The spray and jet effects of the inhaler are captured in addition to the patient’s inhalation profile. By evaluating a sufficient number of stochastic individual path (SIP) models, the regional deposition fractions within the lung emerge. CFD models can successfully account for bifurcation asymmetry – alveolar branches have a random orientation in the airways – and physical effects on pharmaceutical aerosols, and enable the accurate prediction of highly localised deposition factors, which is crucial when studying the behaviour of extra-fine and sub-micron particles for pharmaceutical purposes.^{26,27}

These models can potentially also be used to help determine the aerosol penetration fraction that exits the bronchioles and enters the alveolar region over time. However, CFDs have not extensively been used for investigating alveolar deposition and are still in the developmental stages with respect to predicting deposition in this

the pulmonary region and to validate the *in vitro* and computational investigations being conducted. This is important to progress our understanding of the extra-fine fraction already produced by existing inhaled products. The exploitation of extra-fine particle behaviour through the development of a new generation of inhalers designed to deliver nanosized particles is a separate challenge that lies well beyond current capabilities.

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WHY SUCCESS IN DRUG DELIVERY IS NOT JUST ABOUT THE DEVICE

From game changing advances in new diabetes therapies such as Sanofi's inhaled insulin Afrezza to the expiration of blockbuster drug patents such as GSK's Advair – the pulmonary space in pharmaceuticals has never been more dynamic. These current developments present both opportunities and challenges to pharmaceutical innovators and generics manufacturers alike. Here, Mark Tunkel, Partner & Business Development Director, Insight Product Development, explains how companies developing and marketing inhalable pharmaceuticals can explore other strategies to improve patient outcomes over and above what the drug and device can achieve, and thus differentiate their products.

THE NUANCES OF PULMONARY DELIVERY

There has been a lot of activity in the injectable biologics space recently, ranging from new delivery formats such as wearable injectors to developers' ability to drive device differentiation for biosimilars therapies with relative freedom. In contrast, some respiratory combination products such as dry-powder inhalers cannot readily decouple the drug from the device. Generics entering the market are therefore largely confined to replicating current models.

With no difference in drug formulation or device, the challenge that generics manufacturers face is competing for market share against innovator respiratory therapies without a clear way to differentiate themselves. On the other side of the same coin, manufacturers focused on innovating novel

therapies face the challenge of introducing delivery systems that are commensurate with the new therapy. Despite these challenges, clear opportunities exist in both cases to innovate beyond the delivery device alone to drive adherence and effectively compete in this increasingly competitive space.

RESEARCH-FUELLED DIFFERENTIATION

Needs characterisation is critical to making better combination device product development decisions, and uncovering the most meaningful opportunities to drive adherence, adoption, and true differentiation in the market. By leveraging applied ethnography upfront in their innovation pursuits, developers can gain valuable insight to both the universe of key stakeholders for their respiratory device (Figure 1), and their key unmet needs.



Figure 1: Developers can gain valuable insights about the universe of key stakeholders for their respiratory device.

Mr Mark Tunkel
Partner & Business
Development Director
T: +1 773 907 9500
E: mtunkel@insightpd.com

Insight Product Development
4660 N Ravenswood Ave
Chicago
IL 60640
United States

Ultimately, this user-based characterisation affords developers the opportunity to synthesise these insights with other inputs from the technology landscape to launch tomorrow's market-dominating therapies.

APPLIED ETHNOGRAPHY

Applied ethnography offers the means to uncover leading opportunities to add value to key device stakeholders while differentiating solutions from the competition. Through a combination of interviews, in-context observation of practices, processes and experiences within their natural settings, and the environment and social contexts that influence them, it helps developers understand the behaviours and motivations of people at the most fundamental level (Figure 2).

By taking this deep dive into user behaviour, pharmaceutical companies afford themselves the opportunity to examine larger marketplace trend assumptions effectively, gain a clear understanding of their key target user needs, characterise those needs in a way that's meaningful, and ultimately define the leading features and benefits of solutions that will be required to make them successful. Even with delivery devices that remain fixed throughout an innovation initiative, leveraging this approach can help developers understand the patient journey in a broader context and use that as a baseline to understand where people having trouble, where are they falling out of adherence, what their drivers and motivations are underlying that, and identify ways to augment users' experience with the device.

DEFINING THE UNIVERSE OF STAKEHOLDERS

In many cases, there is more to designing a positive delivery device experience than focusing on the patient alone. To understand all the implications of the patient experience fully, it's necessary to examine the role of prescribing physician, caregivers that assist with drug delivery, respiratory therapists, nurse trainers and others that influence device selection decisions based on specific disease states, drug formulation and their own ability to administer it. Factoring the roles and leading values of multiple stakeholders in a drug's administration is critical to designing devices that drive adherence.

By examining the entire universe of stakeholders, developers can begin to determine their leading opportunities for innovation.

For example, research might uncover that a nurse practitioner is primarily concerned with the efficacy of new patient on-boarding materials for a respiratory therapy, while a patient may find the most value in the quality of written instructions for use that come with their drug therapy.

UNCOVERING STAKEHOLDER NEEDS

The first step in identifying opportunities to innovate is recognising that you are not developing solutions for a homogeneous population. For drug delivery, you can begin to analyse the vast array of stakeholder needs in two ways across the spectrum of the patient journey: first, by examining the patient journey as discreet steps through the healthcare system; and second, recognising the context of the different life stages of users participating within that journey.

The patient journey helps developers understand the emotional and physical disease management strategies and temporal stages of users, based on the common trajectory of feelings they have toward their disease and therapy. A deep understanding of the emotional drivers, attitudes, and behaviours within each stage of the journey – shifting from denial and resistance to acknowledgement and acceptance – reveals key adoption drivers, adherence and barriers to use, while helping developers determine tangible design guidelines for each patient archetype. As developers, a consciousness of these distinctions is necessary, as – for example – the way you would design for an 80-year-old patient that has



Figure 2: In-field research helps developers understand the behaviours and motivations of people at the most fundamental level.

dictate who the market leader in pulmonary delivery will be tomorrow. A few of the leading opportunities for developers to capitalise on include experience solutions for patients, prescribing physicians, and nurse trainers.

The quantification of adherence will continue to be a primary factor in determining what therapies make it into the prescription plans of healthcare systems all around the world, and what is preferred by prescribers into the future. For this reason, adherence solutions from user training programs, and digitally connected support communities to smart technology that provides motivation and

“Clear opportunities exist in both cases to innovate beyond the delivery device alone to drive adherence and effectively compete in this increasingly competitive space”

been successfully managing their disease for 20 years isn't likely the way you would design for a newly diagnosed 20-year-old.

LEADING INNOVATION OPPORTUNITIES

When the device is a fixed constraint, the leading opportunity for developers to differentiate their offering hinges squarely on the user experience with their device. The ability to drive therapy adherence will ultimately

feedback while highlighting the direct correlation between patient adherence and quality of life are leading opportunities for developers to capitalise on in the immediate term.

NEEDS CHARACTERISATION SUCCESSES

While the proprietary nature of our ongoing projects at Insight prevents us from disclosing our own work, a compelling solution that has recently made its way to market and

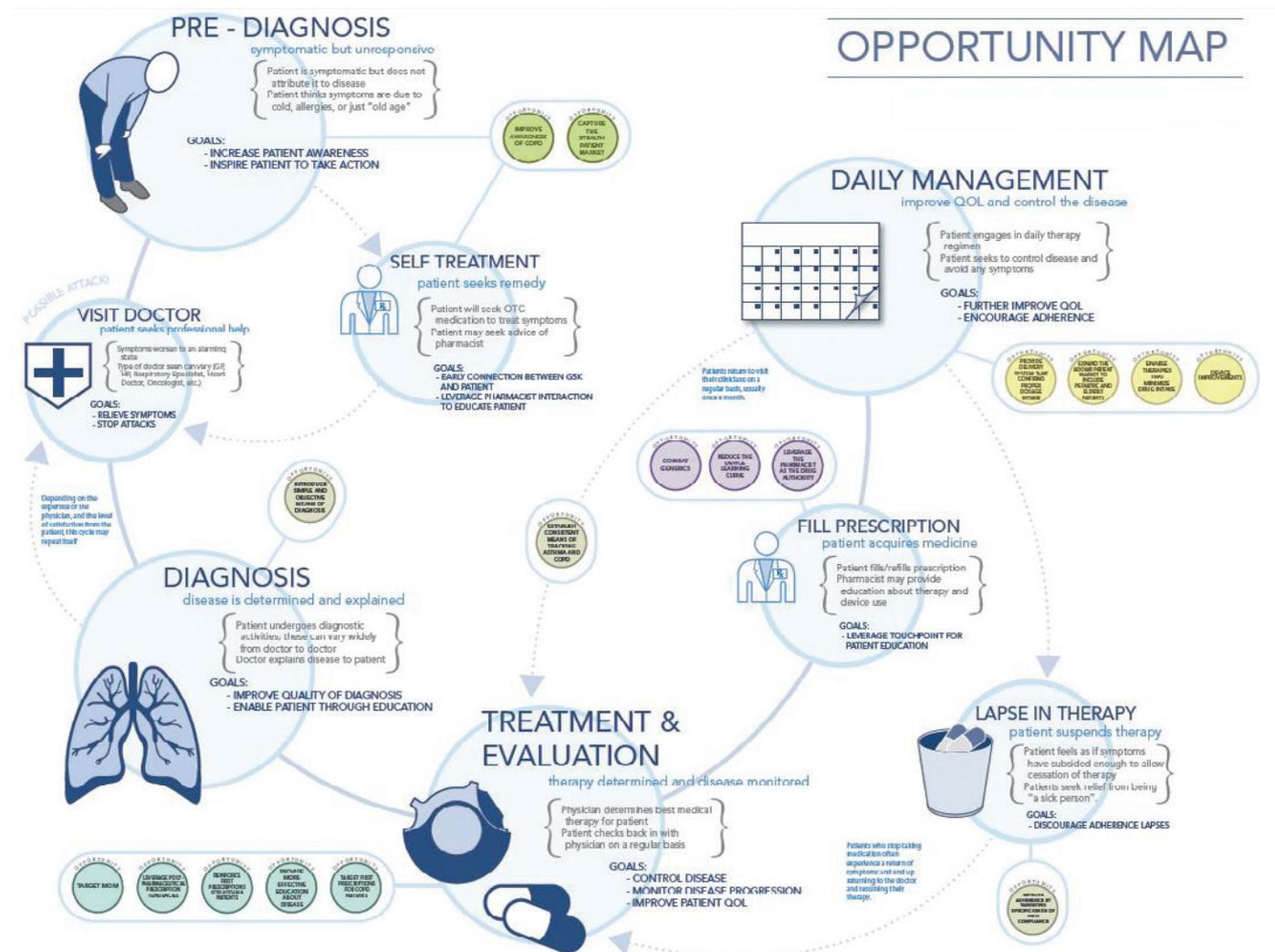


Figure 3: Opportunity map tracking opportunities to achieve greater product differentiation and better patient outcomes, following the patient’s journey through the healthcare system and their disease management.

effectively differentiates respiratory delivery devices on user experience alone is the line of respiratory device trainers from consultancy Noble (Orlando, FL, US). Addressing a published study revealing that 93% of inhaler patients are improperly receiving their self-administration medication based on a failure to follow all provided Instructions for Use (IFU), these trainers teach patients proper therapy administration technique to ensure they receive their full dose of medication with every use.

Noble’s Executive Vice-President, Craig Baker, explains that because “easy-to-use” is different from “easy-to-learn”, patient therapy on-boarding programs are a leading opportunity today in the pulmonary delivery space. Just consider the first time you got behind the wheel of a car, and contrast that against what the experience is like for you today. Unlike healthcare professionals who receive professional training on the safe and effective use of delivery devices, patients often have limited or no experience with such products, which can lead to a number of real challenges from improper technique and user errors to avoid-

ance behaviours. For this reason, Baker says the company developed its specialised training devices for nurse practitioners and patients, ultimately to inspire more confidence among prescribing physicians.

Designed to mimic the actual device and on-board patients through their first 30, 60 and 90 days of therapy, these solutions lead to good habits by teaching patients proper administration through multisensory learning technologies. They include error correction, LED notification, talking audio, and sensors that detect whether the patient has properly primed and inhaled with the correct force, and inhaled at the correct time.

CONCLUSION

Uncovering meaningful user needs, and the immediate challenges that users face in drug therapy administration through applied ethnography is the first step in achieving differentiation in an increasingly competitive marketplace. Figure 3 is an opportunity map developed by Insight Product Development which summarises the

opportunities that arise along the patient’s journey through the healthcare system and their specific states of disease management.

By gaining a solid understanding of the complexity of the physical and emotional dynamics of patients, and the preferences and values of all delivery device stakeholders, developers are well positioned to develop user-centric solutions capable of improving patient outcomes and growing market share.

ABOUT THE AUTHOR

Mark Tunkel is a Partner and Director of Business Development at Insight Product Development. With more than 20 years of global business development experience and a deep understanding of the marketplace challenges and trends impacting the pharmaceutical industry, Mark has advised many of the world’s leading companies on their product development and innovation strategies with an emphasis on driving realisation and the most favourable business outcomes. Mark holds a BA in Political Science from Indiana University.

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A NEW, ADVANCED HIGH-THROUGHPUT SYSTEM FOR AUTOMATED INHALER TESTING

Two years ago, Novi Systems Ltd set out to shake up the inhaler automation market. On December 8th, 2015, at the Drug Delivery to the Lungs 26 Conference (Edinburgh, UK), after numerous iterations and months of testing, Novi is officially launching the DecaVertus ten-way shake-and-fire testing system for pMDIs. Here, Adam Smith, Director at Novi, introduces DecaVertus, describing its single-inhaler predecessor the Vertus, and how the DecaVertus design evolved using the Vertus technology.

If you manufacture (or are planning to manufacture) inhalers, then you know that regulatory bodies around the world require

some degree of patient use. For pMDIs, this means that they must be shaken prior to each actuation (including waste shots), and that the airflow through the collection device is controlled.

“The technologies used on the bench-top systems are the same as used on large systems, meaning that the methods used are identical on both.

This gives a pathway from small-scale R&D to large-scale production that minimises the requirement for revalidation of methods every time a new system is introduced”

them to be thoroughly characterised – both at submission for approval and continuously through production. You also know that test results can vary greatly.

Regulators including the FDA and EMA require inhalers to be tested using an impactor (Andersen Cascade Impactor (ACI) or Next-Generation Impactor (NGI)) and a dose unit sampling apparatus (DUSA) as part of the regulatory filing and, ongoing during production, as part of the batch quality control process. Inhalers must be tested at beginning and end of life, meaning that waste shots must be fired in between. The regulatory bodies expect that the actuation of inhalers is representative to

COMMON ISSUES WITH MANUAL TESTING

pMDIs are susceptible to variations in the method used to deliver a dose. Some pMDIs are more susceptible than others, and one or more of the following parameters can be critical for any pMDI type:

- Shaking speed, angle and duration
- Firing force, speed of force application and release, duration of fire down-time
- Time between end of shaking and actuation of the inhaler into the collection device. (The impact of this depends on how quickly the suspension settles. It has been known to be just a few seconds.)
- Speed of air-flow through the collection device
- Leaks in the ACI or NGI.

This inherent variation means that it is difficult to characterise and interpret results from manual testing. When these variations are possible, the question arises: “How do I know



Adam Smith
Director
T: +44 7974 305591
E: amps@novi.co.uk

Novi Systems Ltd
6 Barle Enterprise Centre
Dulverton
TA22 9BF
United Kingdom

www.novi.co.uk

whether variations in my results are due to characteristics of the formulation and inhaler, or due to the test method?” This can be a very lengthy and costly question to answer.

Another time and cost consideration of manual testing is that it takes a lot of training effort to ensure that different analysts are delivering doses in the same way, and that they are doing so consistently over long periods. An additional risk is that the constant shaking and firing of inhalers can lead to repetitive strain injury (RSI).

BENEFITS OF AUTOMATION

A principle benefit of automating the testing process is that it eliminates the variation in how the dose is delivered, including variation within the shaking and firing steps, and the duration between the end of shaking and actuating the device into the collection device. Automation also greatly reduces the analyst training requirement and the set-up time as all the parameters you need to control are handled by the system.

With automation systems such as Novi's Vertus, there is no need for a pump as the system uses your pressurised air supply to generate the air flow required. Likewise,

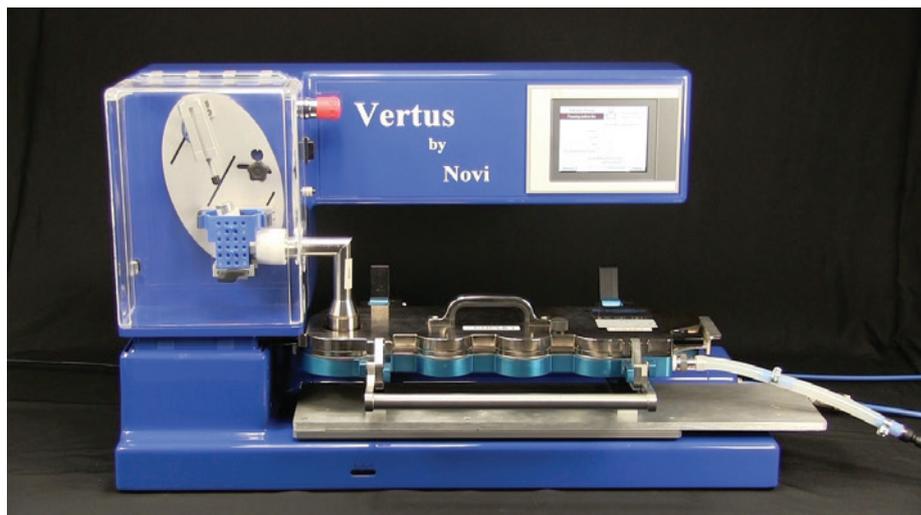


Figure 1: The Vertus can be used with a wide range of collection devices including NGI (shown here), ACI, DUSAs and waste filters.

leak testing is fully automated, so there is no need to set up a pressure meter, create a vacuum and measure the leakage.

Improvement in productivity is another important advantage. As everything is automated, the analyst can start the system and leave it until finished. Methods to perform through-life testing are available. Health and safety is also improved since the risk of an employee suffering

RSI from undertaking manual testing is completely removed.

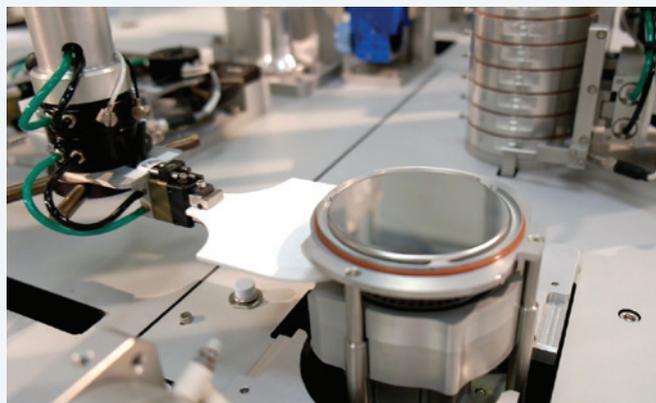
THE VERTUS

The predecessor to Novi's new ten-inhaler tester DecaVertus is the single-inhaler tester, the Vertus, shown in Figure 1. The Vertus has proven popular since its launch in 2010 and has been delivered

HISTORY OF NOVI SYSTEMS

Novi's first contact with the world of inhalers was more than 20 years ago when British multinational Fisons PLC asked it to create a system for automatically shaking an inhaler. This was the beginning of Novi's long association with the inhaler industry, which is now the entire focus of the company.

Novi's main technology platform is a fully automated ACI system called the Ictus (image below). The user loads up to thirty inhalers onto the system, presses "Go", and returns later to find rows of vials with drug recovered from ACI stages ready for HPLC analysis. Each Ictus is built according to the specification of



Ictus fully automates ACI testing including shaking, firing, dose collection and drug recovery

the customer and over the years has incorporated all elements of inhaler preparation and drug recovery for ACI test methods.

Variants of Ictus have included, amongst others, MDI and DPI versions, force-actuation and breath-actuation, critical flow control, leak testing, waste shots, DUSA automation, weighing, actuator changing (to remove dirty actuators after waste shots), anti-static measures, plate coating and dose detection/verification.

INTRODUCTION OF BENCH-TOP SYSTEMS

Using the tried and trusted Ictus technology base, Novi has created a family of bench-top devices that can be used in more flexible arrangements in smaller scale R&D and production environments. These include the Flutus Air airflow generator and controller and the WaSC waste-shot collector, in addition to the Vertus shake-fire-flow control automated pMDI tester discussed in more detail in the main article.

Why does this matter?

The technologies used on the bench-top systems are the same as those used on the large systems, meaning that methods used are identical on both. This gives a pathway from small scale R&D to large-scale production that minimises the requirement for revalidation of methods every time a new system is introduced.



Figure 2: DecaVertus can shake and fire up to ten inhalers at a time.

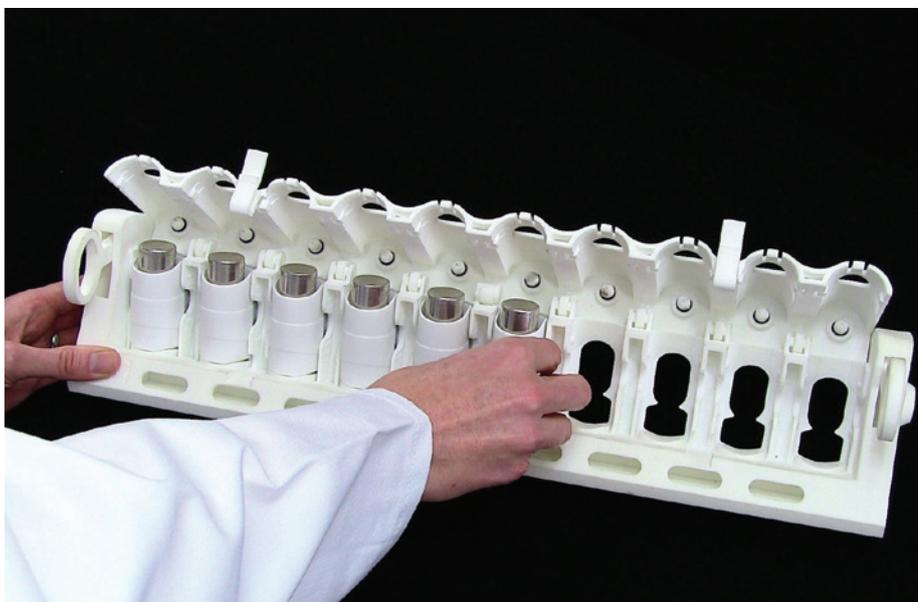


Figure 3: Loading inhalers into the DecaVertus is quick and easy.

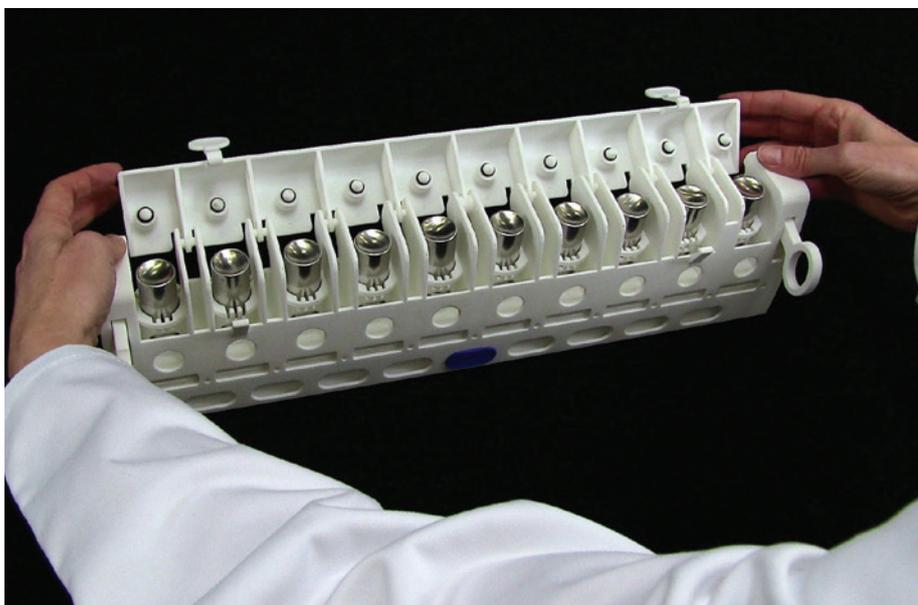


Figure 4: DecaVertus can test both cans on their own (shown here) and cans in actuators.

across the world. It automates all aspects of dose delivery of pMDIs to ACIs, NGIs, DUSAs and waste. The analyst simply fits a collection device to the system, fits an inhaler, selects the method to use and presses “Start”.

Advantages

The collection device (ACI, NGI, DUSA or waste) is integrated with the system, which means that no manual intervention is required during the process. This reduces potential variation in the method (especially the critical time between end of shake and actuation) and improves productivity as the analyst does not have to be present

Airflow control is part of the system, which means that no separate pump, air-flow meter or pressure meter is required and no measurements need to be recorded – these are all logged by the Vertus.

Other key features and advantages include:

- Automatic leak testing
- Log files may be copied to a USB stick or to your LAN
- Option for ER/ES compliance (e.g. 21 CFR Part 11)
- Option for printer
- Option to record temperature and RH
- Integrated touch-screen display with intuitive control. No separate PC required.
- Issues can be diagnosed and firmware updated remotely.

DECAVERTUS INTRODUCTION

Following the success of Vertus, Novi engineers set out to create a high-throughput version. Customers love the flexibility the Vertus gives in terms of the different collection devices that can be fitted to the system, but only one inhaler can be fitted at a time.

This is not so critical for impaction or dose uniformity tests because only a few shake and fire cycles are required and so the tests take a few minutes. Performing waste shots (to get from beginning-of-life (BOL) to end-of-life (EOL) for example) can take one to three hours or even more depending on the method. If you have a number of inhalers to test, this ties up the Vertus for long periods.

Given this clear need from customers to be able to waste-fire multiple inhalers at a time, the challenge to Novi engineers was to replicate the shake and fire technology of

Vertus on a system that can fit ten inhalers at a time for wasting.

Two years, three major system iterations, many mechanical and software iterations and months of testing later, the DecaVertus (see Figures 2-4) is being officially launched in December 2015.

DESIGN APPROACH

Novi engineers set out with a clear idea of what they wanted to achieve. Firstly, the DecaVertus must have identical shake and fire technology to Vertus to allow methods to be seamlessly transferred between the two. This also ensures that the range of movements, speeds, forces and timing settings that are available on Vertus are also available on DecaVertus.

Secondly, it must work with inhalers situated in their actuators just as the Vertus does; but it must also work with cans on their own just as effectively, as this is traditionally how wasting has been done.

Thirdly, the DecaVertus must give maximum assurance to the analyst that every inhaler experiences the same shake, fire and airflow on each and every shot.

Fourthly, the DecaVertus must require little cleaning, even given the quantity of drug that will go through it, and be easy to use and maintain.

ACHIEVING DECAVERTUS DESIGN OBJECTIVES

There are two cornerstones to the development approach at Novi. The first is risk management in which the risks of all aspects of the system and its functionality are listed and given scores of likelihood of occurrence, likelihood of detection and impact. This helps both to ensure that design effort is focussed on the most important areas and that every function provides a benefit that outweighs its cost to the customer.

The second is the purposeful use of iterations in all aspects of the design, both mechanical and software, in which each iteration is built and tested thoroughly and the resulting lessons are incorporated into the next iteration. In this way, early iterations can concentrate on the most important aspects of the design (as identified in the risk analysis) without unnecessary cost and delay in trying to finalise less important

aspects at the beginning. This approach also ensures a body of testing throughout the development cycle and so issues are identified early on.

TESTING AND CUSTOMER TRIALS

After a year of checking functionality priorities with customers and going through the first design and test iterations of the system internally, the first fully-functional pre-production model became available in January 2015.

Three customers in two countries took delivery of this model in the first half of 2015 and significant testing has been conducted at these sites and internally at Novi. One of these customers is using the DecaVertus to test a new product in-actuator, one customer is using it to test a number of well-established products can-only, and the third is a CRO testing a wider range of inhalers in-actuator.

This means that the DecaVertus has already been subjected to a wide range of uses and experienced both light formulations (which have a low impact on the waste channels) and very heavy, hydrophilic

- Gives a large range of programmable control over shaking, firing and airflow parameters
- Assurance that each inhaler is experiencing the correct shaking, firing and airflow parameters set
- Greatly reduced cleaning requirement and improved health and safety
- Flexible – any standard pMDI can be tested, in-actuator or can-only
- Independent airflow control at every channel
- Modern, slick and intuitive touch screen interface
- Fitting inhalers to the system is quick and intuitive
- Issues can be diagnosed and firmware updated remotely.

FULL COMPATIBILITY WITH THE VERTUS

The Vertus, which shakes and fires one inhaler at a time to ACI, NGI, DUSA or waste, uses identical technology to the DecaVertus to shake and fire the inhalers, and to control airflow through waste filters – which are again the same on both systems.

“Given this clear need from their customers to be able to waste-fire multiple inhalers at a time, the challenge to Novi engineers was to replicate the shake and fire technology of Vertus on a system that can fit ten inhalers at a time for wasting”

formulations (which tend to clog waste channels extremely quickly).

This testing regime has been invaluable to the development of the DecaVertus. In collaboration with these customers, functionality has been added and performance issues have been identified and resolved.

ADVANTAGES OF DECAVERTUS

The DecaVertus has been designed from the ground up to set a new standard in pMDI dosing to waste. The primary advantages of the DecaVertus are:

- The entire inhaler is tested as it would be used by a patient (although cans can also be tested on their own)

This means that methods can be readily transferred from one system to the other.

The Vertus and DecaVertus can work alongside each other and waste shots may be conducted on either with the assurance that the results will be the same.

CONCLUSION

After years of development, building on years of experience, many iterations, and thorough road testing by pioneer customers, the DecaVertus is officially being launched in December 2015 at DDL in Edinburgh, Scotland. If you are at DDL, be sure to visit the Novi Systems stand and take a look at the new standard in pMDI shake and fire to waste.

Nemera

INHALIA®: A NEW pMDI METERING VALVE PLATFORM THAT PATIENTS CAN COUNT ON

In this piece, Inga Meyer, Category Manager, Nemera, introduces the company's new pressurised metered-dose inhaler (pMDI) valve platform, Inhalia, and uses device testing study data to demonstrate some of the significant advances, advantages and benefits the platform brings.

Treatments for pulmonary diseases such as asthma and COPD can be delivered via a number of different routes. Due to the direct and immediate action onto the bronchi, the reduction of side-effects as well as patient convenience and relatively low cost per dose, inhaled treatments remain the preferred treatment route.

Nemera has designed a new platform of proprietary metering valves for pMDIs targeting local and systemic treatments delivered to and through the lungs. The valve platform, named Inhalia® (see Figure 1), is part of a portfolio of innovation platforms developed at Nemera's Innovation Centre for Devices near Lyon, France.

In 2015, Nemera performed a series of comparative studies between the Inhalia pMDI valve platform and other commercially available pMDI devices. In the study

the devices were tested on performance criteria such as prime retention, leakage and actuation force to deliver a dose.

IMPROVING PATIENT ADHERENCE

Good patient adherence plays a significant role in pulmonary treatments. Rates of non-adherence for asthma patients range between 30% and 70%¹ and adherence rates for regular preventive treatments are as low as 28% in developed countries.^{2,3}

When tested *in vitro*, pMDIs are usually primed by firing several times to waste, but this is rarely done by patients in practice.⁴ Therefore, removing the need for a priming actuation after extended periods of non-usage can help drive patient compliance.

In the study performed, five marketed devices with different active ingredients and meter-



Figure 1: Inhalia® valves, shown (left) on canisters and (right) alone.



Inga Meyer
Category Manager
T: +33 (0)4 74 94 06 54
E: information@nemera.net

Nemera
20, Avenue de la Gare
38290 LA VERPILLIERE
FRANCE

www.nemera.net

ing valves were tested at end-of-use for their retention of formulation in the dosing chamber. The test was performed after five and 14 days to mimic infrequent use by patients with up to two weeks between actuations.

As can be seen in Figure 2, prime retention varies significantly between devices tested with the average being below 90%, which is decreasing with time.

With a prime retention at 14 days of more than 90%, Inhalia decreases the requirement for a priming shot as it delivers complete shots between uses even for infrequent treatments.

OPTIMISING REPRODUCIBILITY OF DOSES

Throughout the life of the product, the pMDI device must remain a closed system to avoid leakage of the formulation and to minimise any potential moisture ingress, both of which could negatively affect the performance of the product and therefore prevent the effective delivery of the dose to the patient. Especially with smaller doses, the prevention of leakage is crucial as any leakage of hydrofluoroalkane (HFA) gas could impact the concentration and stability of the delivered dose.

Equally, moisture ingress into the device may negatively impact drug stability and performance and is therefore a critical measure for pMDIs. In particular, ethanol, which is often used as a co-solvent, can increase moisture uptake and HFA propellants used in the majority of marketed pMDIs today have a high sensitivity to moisture.^{5,6}

In the second part of the study, all devices were tested on leakage levels after accelerated ageing at 40°C and 75% relative humidity. As can be seen from the test results summarised in Figure 3, the benchmark shows that leak levels from a number of tested devices can be as high as 500 mg/year. Due to its unique engineered design and choice of materials, Inhalia achieves leakage rates that are close to zero and significantly below the average found on the market today.

FACILITATING THE USE OF pMDIS IN PATIENT HANDS

Two critical forces should be measured and controlled in pMDIs: the actuation force required to dispense a dose; and the return force required to ensure safe and proper functioning of integrated dose-counter mechanisms.

The actuation force, or force that needs to be applied to dispense a dose from a

pMDI, plays a significant role for patients, especially children and elderly patients who might not have as much strength to apply this force. It should thus be as low as possible to ensure that all patient groups are able to take their medication without difficulty.

In addition, with the increasing number of pMDIs with dose-counters fitted, valves have to be robust and need to have a return

force high enough to avoid any malfunctioning or blockage of the integrated dose-counter mechanism.

Therefore, in the final part of the study, valve force profiles were tested (Figure 4). Since the forces applied can vary significantly depending on the formulation, all tests were done with salbutamol formulations to maximise comparability. On average, actua-

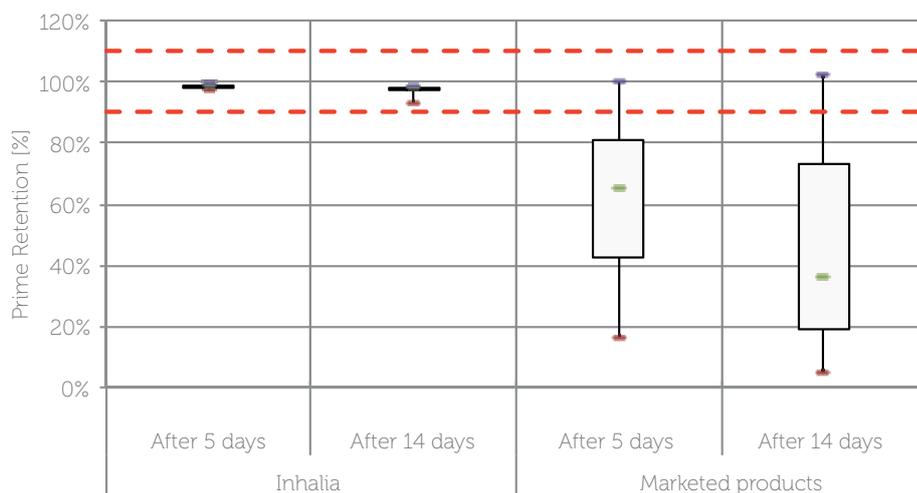


Figure 2: Prime retention after five and 14 days tested at end-of-use.

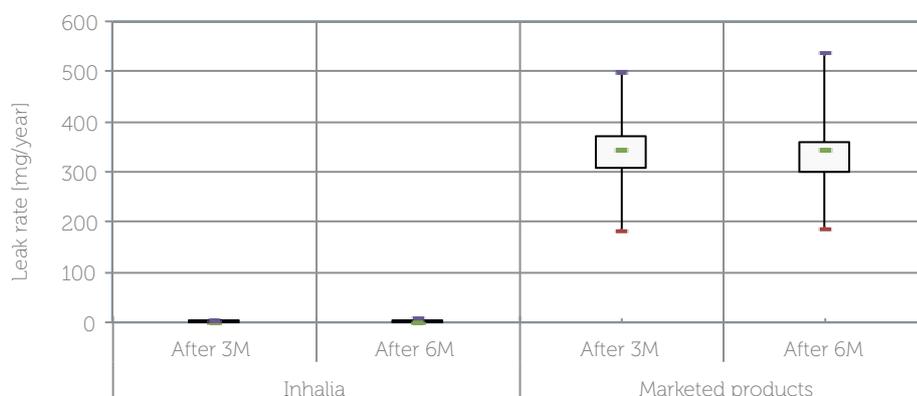


Figure 3: Leakage rate (T3 and T6 months) at 40°C and 75% relative humidity.

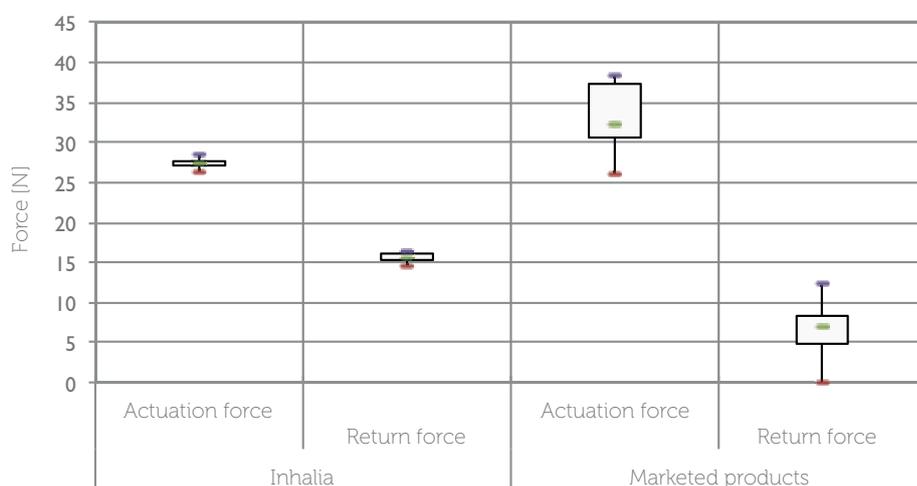


Figure 4: Actuation and return force measured at a speed of 250 mm/min. Return force measured at 0.5 mm before rest position.

tion forces were found to be above 32N and return forces around 7N.

With a dedicated spring profile and design that minimise friction between gas-kets and stem, the Inhalia valve has been designed to be patient friendly. The design reduces the actuation force to below 30N while keeping the return force high until the end of the stroke, to ensure that the dose counter mechanism can reset without blocking the valve.

A PRODUCT DEVELOPED AT NEMERA'S INNOVATION CENTRE

Innovating for patients is at the heart of Nemera's mission. Inhalia was designed as a next-generation platform to address the market's unmet needs and stringent regulatory requirements for pulmonary drug delivery in place today. Consistent dose delivery performance, long prime retention and low leakage are key benefits for patients. In addition, low leakage rates also avoid costly overfilling of formulation for the pharmaceutical company. As shown, the design has been optimised to accommodate dose counter mechanisms which are an increasing requirement in many markets today.

Inhalia is available in a variety of configurations and doses to meet a wide range of market requirements.

ABOUT NEMERA

Nemera is a world leader in the design, development and manufacturing of drug delivery solutions. Its expertise covers all five modes of delivery:

- pulmonary (MDIs & DPIs)
- nasal, buccal, auricular (pumps & valves)
- dermal and transdermal (airless & atmospheric dispensers)
- ophthalmic (multidose, preservative-free eyedroppers)
- parenteral (auto-injectors, pens, safety devices & implanters).

Nemera provides solutions for the pharmaceutical, biotechnology and generics industries, including standard innovative products ("off-the-shelf") and the development of custom devices and contract manufacturing. For more information, please visit: www.nemera.net.

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EDINBURGH INTERNATIONAL CONFERENCE CENTRE Wednesday 9th – Friday 11th December 2015

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- **DDL** provides an annual forum for scientists, academics, clinicians, regulatory and industry specialists involved in developing medicines for inhalation.
- **DDL** attracts a diverse and extensive selection of posters, presentations. Our Exhibition attracts the leading players from the Pharmaceutical Industry, Suppliers, Instrument Manufacturers and Contract Research Organisations.



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DDL26 will have 5 themed sessions each with a combination of invited and submitted lectures given by experts in the field of inhalation and students working to advance respiratory science.

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- Advances in formulation and analytical science
- Nasal, Buccal and upper airways delivery
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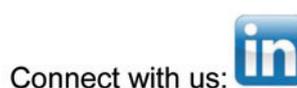
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the Lungs (DDL26) conference to be held on December 9-11, 2015, in Edinburgh, Scotland. This will include the introduction of a new COCe sealing gasket. COCe is a novel elastomeric material with multiple advantages:

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



Figure 1: DF30 metering valve (Image Courtesy Aptar Pharma).

Aptar Pharma

36, rue de la Princesse
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F: +33 1 39 58 12 98
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Partnerships Built on Innovation

HUMAN-CENTRED DESIGN & INHALATION DEVICE DEVELOPMENT

In this piece, Bill Welch, Chief Technology Officer, Phillips-Medisize, explains how the term “smaller and smarter” applies in the development of inhalation devices, and describes how his company’s human-centred design approach, integrated with design-for-manufacturability and design-for-assembly principles, is perfectly positioned for producing the next-generation of smaller, smarter inhalers.

THE NEED FOR HUMAN-CENTRED DESIGN OF INHALATION DEVICES

Numerous studies have shown patient issues with both the use of and adherence to prescribed inhaled therapies for asthma and COPD, whether maintenance or rescue inhalers. A simple web search will produce evidence of multiple studies indicating that greater than 30%, and in some cases up to 80%, of patients do not use their inhalation devices correctly. Additional studies report similar percentages in adherence to inhaled therapy.

Compromised adherence means the patient is not receiving the desired pharmacological benefit of their medication despite an effort to do so. Adherence may be negatively impacted by confusion, frustration, inconvenience, embarrassment, or a variety of other usability issues. Conversely, compliance can be maximised by providing the patient with an easy-to-use device and monitoring tools that promote the prescribed inhalation regimen.

In order to minimise the opportunity for misuse and improve adherence, an inhaler must be intuitive, usable, and desirable. This is the objective of the newest generation of “smaller and smarter”, patient-administered inhalation devices, developed following what is known as the “human-centred design” approach.

WHAT IS HUMAN-CENTRED DESIGN?

Phillips-Medisize’s integrated product development process combines human-centred design principles with a solid design-for-manufacturing / design-for-assembly (DFM / DFA) philosophy. It addresses design research, industrial design and human factors

engineering (HFE) – simultaneously addressing a product’s usefulness, usability, desirability, and manufacturability (see Figure 1).

The key benefits of this are: product adoption and compliance; predictable processing; overall product quality improvement; development time reduction; and stakeholder satisfaction.

The human-centred approach is not limited to a single phase nor is it a stand-alone module that can simply be attached to the front-end of a product development program. It needs to be embedded into the cultural fabric of an organisation in order to be effective.

HUMAN-CENTRED DESIGN PRINCIPLES

Design Research

Design research activities are typically conducted at the front-end of a development cycle in order to establish a firm foundation for future design work. This is required to determine the needs of end users, uncovering attributes that will resonate with them on an emotional level. Common design research methods include targeted interviews, contextual observation (i.e. witnessing a surgical procedure in an operating room or shadowing a diabetic patient through their daily testing and insulin injection routine in the home), participatory workshops, analogous product benchmarking, and trend tracking. These processes allow a cross-functional development team to appreciate circumstances, environmental conditions, and user expectations in an effort to identify design opportunities. Discoveries made through design research inform the development process, improving the likelihood of success upon market introduction.

Bill Welch

Chief Technology Officer
T: +1 715 386 4320
E: info@phillipsmedisize.com

Phillips-Medisize Corporation

1201 Hanley Rd
Hudson
WI 54555-5401
United States

European Headquarters:

Phillips-Medisize
Edisonstraat 1
2181 AB Hillegom
The Netherlands

T: +31 252 576 888
E: eu_sales@phillipsmedisize.com

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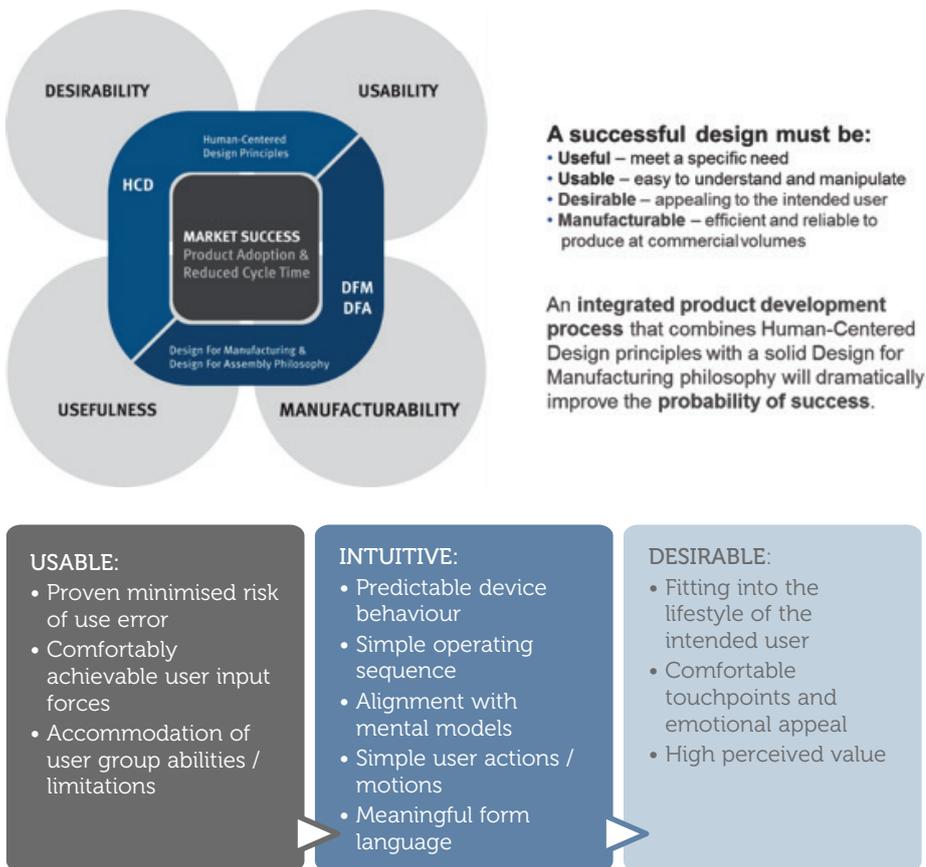


Figure 1: Summary of criteria for Human-Centred Design.

Industrial Design

Industrial designers build upon the foundation of design research, translating discoveries, product performance goals and marketing objectives into tangible concept directions. Product form, user interface, ergonomics, aesthetic detail treatment, material selection, and manufacturing approaches are all considered during this phase. Collaborative brainstorming with a cross-functional team helps to ensure consideration of multiple viewpoints. Industrial designers produce illustrations, preliminary CAD models, and physical prototypes to define conceptual directions. Through co-operation with their engineering peers, industrial designers strive to narrow the focus to a single concept direction that can be carried forward into subsequent development phases.

Human Factors Engineering (HFE)

The objective of HFE is to minimise use-related risks and to ensure safe and effective device use. HFE activities may include product handling studies, usability testing with representative users, and final verification / validation studies to satisfy regulatory expectations. HFE methods are applied throughout the development cycle to mitigate product-related safety risks and justify design decisions. HFE begins early in a design cycle and should be included as

an integral part of the development process. Design inputs such as user profiles, use environment, and other contextual influences must be considered as early as possible. Proper planning, execution and documentation of HFE activities throughout the development process should streamline the submission process for regulatory approval.

In classic models of human-centred design, the focus is on useful, desirable, and usable products. However, in the realm of drug delivery devices, including inhalation, the concept of manufacturability must receive equal emphasis. Manufacturability encompasses the healthcare market demands for quality and cost effectiveness, both of which must be aligned with the competitive landscape in order to achieve clinical and market success. To gain market acceptance, the next-generation inhalation devices must compete with the existing standard of care for overall cost of treatment. Expected benefits include eliminating unnecessary hospitalisations, emergency room visits, and office visits.

“SMALLER AND SMARTER”

The term “smaller and smarter” is regularly applied to describe next-generation, patient-administered devices, including inhalation devices.

Smaller

“Smaller” refers to the patient expectation of inhalation devices engineered to be compact and portable, in order to allow discreet usage and improve adherence. For example, the Exubera dry powder insulin device was considered very large and bulky. After the system failed to gain acceptance among patients and physicians, it was discontinued after less than a year on the market. Meanwhile, the mechatronic liquid insulin inhaler from Dance Biopharm, Inc (Brisbane, CA, US), is about the size of a deck of playing cards. The Dance inhaler, known as Dance-501 (see Figure 2), is in clinical trials today and, while a smaller device does not guarantee clinical, regulatory, or market success for the entire system, the form factor selected is similar in size to mobile phones that have proven consumer acceptance.

Smarter

Smarter, on the other hand, has multiple dimensions to be optimised based on the device and user needs.

The first dimension of smarter is the creation of more intuitive devices, thereby decreasing patient errors while increasing adherence and desirability of the therapy.

The second dimension of smarter is to improve on its primary intended function: more effective, targeted delivery of the drug, and greater efficiency of delivery such that less drug product is required to produce the desired benefit. This dimension provides a potential cost savings that will support improvements in other parts of the system, such as inclusion of electronics and software.

A third dimension of smarter is the integration of electronics to improve functionality via a mechatronic delivery system. Dance’s Dance-501 and the Tidal inhaler from Teva (Petach Tikva, Israel) (acquired as part of the MicroDose Therapeutx acquisition in 2013) are both examples of next-generation inhalers using novel mechatronic systems and the patient’s tidal breathing potentially to gain increased delivery effectiveness while reducing device misuse.

The final dimension of smarter is wireless connectivity to communicate with smartphone apps and/or cloud databases that can share information with both the patient and caregivers to improve adherence. CareTrx from Gecko Health Innovations (also acquired by Teva), and Propeller Health’s (Madison, WI, US) system, are examples of device add-ons and software systems specifically targeting this facet of smarter inhalation systems.



Figure 2: The Dance-501 inhaler from Dance Biopharm is an example of a smaller, smarter inhaler.

In evaluating the landscape of next-generation inhalation devices, there are devices that will accomplish most or all of the above

elements of “smaller and smarter”. Those inhalation devices that successfully achieve a smaller and smarter patient solution are

excellent examples of applied human-centred design principles, creating more usable, intuitive, and desirable devices for patients.

SUMMARY

The human-centred design approach has been driving the trend toward development of smaller and smarter, next-generation inhalation devices. When successfully executed, the process will produce devices that are more useful, usable, and desirable than current-generation devices. Through application of the design research, industrial design, and human factors disciplines in concert with DFM/DFA philosophies, the patient will receive an inhalation device that minimises opportunities for error and promotes greater adherence to the prescribed therapy.

THE WIRELESS CONNECTED INHALATION DEVICE

The primary demand for wireless, connected inhalation devices is to provide a technology solution for improved monitoring and adherence tracking, both for patients and caregivers. A commonly requested system is one which provides dose history transmission to a local device, such as a smartphone, and then to a database for caregiver access, if desired.

A key enabler for connected inhalation devices is the increasing availability and lower costs of wireless communications. One option, known as Bluetooth Low Energy, also known Bluetooth LE, BLE or Bluetooth Smart, can give patients and caregivers tools to manage adherence using familiar mobile phone technology and user interfaces, as well as compatibility with healthcare data exchange standards.

Why Bluetooth Low Energy?

BLE was created in 2010 on the release of the Bluetooth Core Standard 4.0. This wireless technology is perfect for low power consumption, small size, and high compatibility to smartphones.

The iPhone 4S was the first smartphone to offer Bluetooth 4.0 compatibility, with adoption now essentially universal in smartphones. BLE radio hardware to be placed in the drug delivery device can be extremely compact, with applications that include hearing aids and other microelectronic devices.

The BLE protocol is optimised to carry small data payloads at infrequent time intervals. Examples of good uses include continuous glucose monitoring, infant temperature monitoring, and drug delivery device dose history, whether for inhalers or other device types. In all of these cases, only small amounts of data are required to be transferred, the data transfer need not be continuous, and therefore the BLE radio will be on < 0.1% of the time.

How Does BLE Reduce Power Consumption?

The key principal is to connect the sending device to the receiving device at periodic intervals – the connection interval – to exchange data and then put the devices’ radios to sleep until the next exchange time. By limiting the “awake” time of the radios, power usage is reduced. Further, the BLE radio architecture uses relaxed frequency channel characteristics to further reduce power consumption.

However, this mostly-off operation imposes a significant overhead on data transfer, so if large amounts of data have to be sent, it has to be chopped up into small segments and a part sent every connection interval.

By contrast, Bluetooth “Classic” protocol allows a data transmission to have variable length that can be chosen to suit

the size of the data transfer. Bluetooth “Classic” is better suited than BLE for applications requiring data streaming for large amounts of data, with the trade-off of increased power needs.

BLE Compatibility with ISO 11073

The ISO 11073 Standard for Medical Devices creates a mechanism to exchange health care data between devices and users of the data, such as electronic medical record software. The standard describes a method to send the information about data formatting along with the data so the receiving end can parse the data without prior knowledge of its formatting. The standard is independent of the data transport system – it applies equally to any wired or wireless protocol.

Since most BLE usage for medical devices require a gateway device such as a smartphone, it is common to use the smartphone app to ‘transcode’ the device data into 11073-compatible data format before it is pushed to the cloud and other devices with which it needs to be compatible. For reference, see: “Personal Health Devices Transcoding White Paper”. Bluetooth Special Interest Group, Oct 21, 2014.

Summary

BLE, with its low power, small size, and near-universal compatibility, is an enabling technology for wireless dose history transmission, for use both by patients and caregivers, for application with small data size and modest transmission speeds.

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PATIENT PREFERENCE IN RESPIRATORY DEVICE TRAINING & EDUCATIONAL TOOLS

Here, Paul Sullivan, Associate Director, Business Development, and Craig Baker, Executive Vice-President, both of Noble, provide data from recent patient studies to emphasise the importance of training devices in improving adherence to, and compliance with, inhaled therapeutics.

Pulmonary drug delivery is an effective route of administration for localised and systematic uptake of pharmaceutical products. As a result, pulmonary administration is a viable alternative to more invasive routes, with future growth potential across new therapeutic areas. These products are often marketed as combination therapies, consisting of formulation with active pharmaceutical ingredients, and drug delivery devices.

When properly used by patients, inhalers administer the prescribed dose to the lungs. Over the years, the use of pulmonary drug administration has continued to grow, with more patients being introduced to pulmonary delivery devices such as metered-dose inhalers (MDIs), dry-powder inhalers (DPIs) and nebulisers. Healthcare professionals receive professional training on the correct ways to use delivery devices, but when the patient, who has limited or no experience, receives in-office training on how to use the device, it's often not memorable or fully understood, resulting in misuse at home. According to a recent study published by the American College of Allergy, Asthma and Immunology, only 7% of inhaler patients follow the proper technique when using their devices.

“Recent publications have confirmed that most patients with asthma do not use their inhaler properly. In addition to only 7% of users demonstrating perfect technique, 63% failed to complete three or more steps. This is a good reason for much needed education, both verbally and visually, to be administered by physicians and asthma educators,” said Dr Sam Pejham, Associate Clinical Professor at UCSF School of Medicine (San Francisco, CA, US). “Also the availability of trainers for patients to demonstrate in front of their provider how they use their inhaler is crucial to ensure proper technique. Currently, asthma patients’ poor inhaler

technique is causing them to have diminished drug delivery which could lead to poor asthma management.”

One important factor for recognising patient centricity is the first 30, 60, or 90 days after diagnosis, commonly called “onboarding”. This is the time when patients are first introduced and trained on how to use drug delivery devices. In-office training is undoubtedly vital and beneficial. However, inconsistencies in training technique and various environmental conditions can affect this training and cause deviations within patient groups.

Improving the training process for pulmonary drug administration is a key opportunity for pharmaceutical brands. Noble identified deviations and inconsistencies as an unmet clinical and market need. The company conducted an in-depth analysis of secondary literature to understand causes of product misuse and developed strategies that could be implemented to improve patient adherence and outcomes. Another study was conducted to understand the impact of various forms of training materials and devices on patient performance.

Identifying user error as a significant risk factor, a review of commercial device platforms and instructions for use (IFU) was conducted to understand common usage steps and the source of errors during the administration sequence. Figure 1 is a summary of common tasks associated with the use of an MDI. Included is a preliminary risk level assessment correlating the severity, detectability and probability of errors in common usage steps.

Through this analysis and initial review, training and education was identified as a significant treatment barrier and control for preventing errors and improving technique. Multisensory training technology has the potential for major impact as it stimulates



Paul Sullivan
Associate Director,
Business Development
T: +1 888 933 5646



Craig Baker
Executive Vice-President

Noble
121 South Orange Avenue
Suite 1070 North
Orlando
FL 32801
United States

the senses to enhance memory recall through audio, visual and tactile features.

In one study, five training methods were analysed:

- Instructions for use (IFU) document: Traditional 12-step IFU, based on common themes and steps of currently marketed respiratory devices
- Mechanical training device and IFU: Mechanical simulator of currently marketed respiratory device. All forces, feedback and behaviour were accurately simulated
- Training device calibrated whistle and IFU: Training device with a mechanical whistle calibrated to respiratory flow rate requirements of common inhalers
- Training device with auditory instructions and IFU: Training device with auditory instructions walks patients through the IFU in a predetermined sequence
- Smart training device for detecting errors and IFU: Training device with sensors and adaptive algorithms to detect and teach patients how to prevent errors.

As shown in Figure 2, the study found that users are most confident when training and on-boarding with smart training devices that detect and teach them how to prevent errors. Patient confidence is a significant driver of compliance and patient adherence. In light of the importance of confidence during on-boarding, training device configurations were evaluated to determine how each affected patient confidence. Based on participants' feedback, 82% of users would feel most confident when training with a device that detects and corrects errors. Across all configurations, training devices increased confidence by 41%, which is consistent with other device-related studies.

"For us, usability and human factors go hand-in-hand with effectively training patients to use our drug delivery systems," said Chris Evans, Vice-President, Research & Innovation, West Pharmaceutical Services (Exton, PA, US). "By instilling confidence with good training, fear or anxiety is diminished ... It also minimises some major barriers to adherence and compliance."

Similar to confidence, anxiety can result in stress and avoidance behaviours that adversely affect patients' adherence to therapy. Based on participant feedback, 76% of users prefer error detection technologies to overcome anxiety when on-boarding to device-delivered therapies. Patient anxiety decreased by 18% across all training methods evaluated during this study (Figure 3).

STEP	DESCRIPTION	RISK OF ERROR	FREQUENCY OF ERROR
1	Prepare device	Low	Low
2	Remove mouthpiece	Low	Low
3	Inspect mouthpiece and device	Medium	High
4	Prepare device and dose (i.e. shake, prime, etc.)	High	High
5	Exhale fully	High	High
6	Place and properly orient device in mouth	Medium	Medium
7	Actuate device to deliver medication	High	Medium
8	Inhale with the appropriate force	High	High
9	Inhale at the appropriate sequence and duration	High	High
10	Hold breath for appropriate duration	High	Medium
11	Repeat as prescribed	High	Medium
12	Clean and store device as prescribed	Low	Medium

Figure 1: Common MDI instructions for use (IFU) Steps. The most common errors are failure to prime, exhale, and coordinate actuation with the necessary timing, force, and duration of the patient's inhalation. These factors commonly correlate with successful delivery, deposition and absorption of medication.

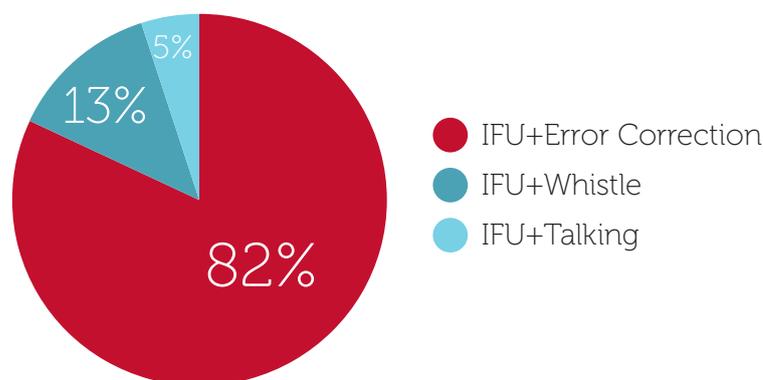


Figure 2: Preference (%) related to confidence when on-boarding with specific training device configurations.

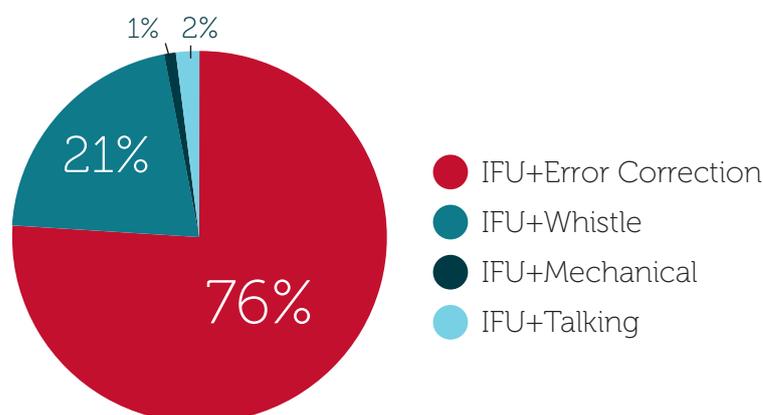


Figure 3: Preference (%) related to anxiety when on-boarding with specific training device configurations.

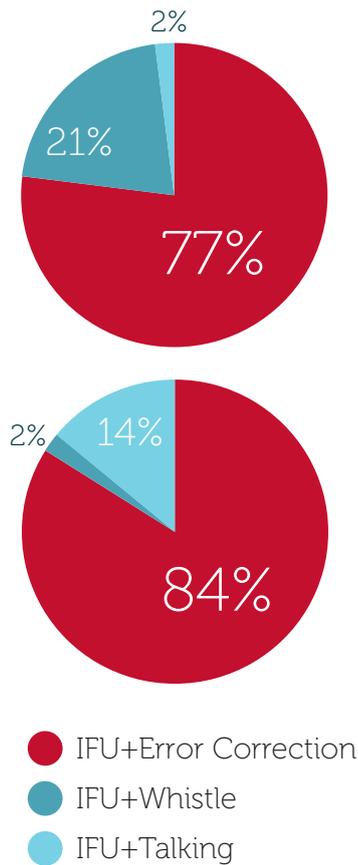


Figure 4: Top: Users would make the fewest errors after being trained with error-detecting technologies. Bottom: Users prefer error-correcting training when on-boarding to pulmonary delivery devices.

Smart training devices with error-detecting technologies are preferred methods in overcoming anxiety and preventing errors.

In addition to evaluating the effects of training on confidence and anxiety, the study sought to understand the patients' overall training preferences and how these factors would relate to their ability to safely and effectively use a pulmonary delivery device. Figure 4 is a summary of these findings related to overall preferences and expected delivery outcomes. Users trained with smart, error-detecting

“According to a recent study published by the American College of Allergy, Asthma and Immunology, only 7% of inhaler patients follow the proper technique when using their devices”

technologies would make the fewest errors when administering with pulmonary delivery devices.

Based on a review of secondary literature, errors and technique are significant adherence barriers for patients using pulmonary delivery devices. The findings of this user study suggest that training devices could be effective tools to increase patient confidence and decrease anxiety, two variables that are closely associated with adherence and patient outcomes. Though the findings were robust and insightful, follow-up research is recommended to evaluate the effect of device training on actual patient errors and long-term outcomes further.

“With increasing self-administration of injectable medications, it is critical that we recognise the best drug and delivery system is only effective if the patient delivers the dose correctly, and in accordance with the appropriate treatment regimen,” explained Graham Reynolds, Vice-President of Marketing and Communications, Pharmaceutical Delivery Systems, at West. “While manufacturers continually work to better understand user needs and design drug delivery systems for affinity, it is also imperative that we spend more time on effective training and on-boarding for patients – with the aim of improving patient adherence and outcomes over the long run.” What Mr Reynolds says in the context of injectables here also holds true for inhaled medications of course, as these are even more commonly self-administered.

As pulmonary delivery markets continue to evolve, patients and industry stakehold-

ers will continue searching for value and differentiation. At its core, the goal of device training is to fulfil such needs and support patients in the successful management of their treatments.

ABOUT THE AUTHORS

Paul Sullivan

Paul Sullivan is the Associate Director of Business Development at Noble®, a product development company with a focus in designing and manufacturing drug delivery training and patient on-boarding solutions. Prior to Noble, Paul worked at Informed Medical Communications, as a Director of Business Development and Client Service. His primary role was to train Physician and Nurse Key Opinion Leaders on the skills of peer-to-peer influence and round-table moderating. In 2003, started his career in the pharmaceutical industry as a pharmaceutical sales representative with Procter & Gamble Pharmaceuticals, and holds a Kinesiology degree with honours from the University of Western Ontario.

Craig Baker

Joining Noble® just a few years after its creation, Craig is the company's Executive Vice-President. He holds an undergraduate degree from the University of Iowa and a masters degree from University of South Carolina. In addition, he has ten years of management experience in the marketing industry, and the pharmaceutical and healthcare fields. This unique insight into both industries is an important advantage for the future growth of Noble.



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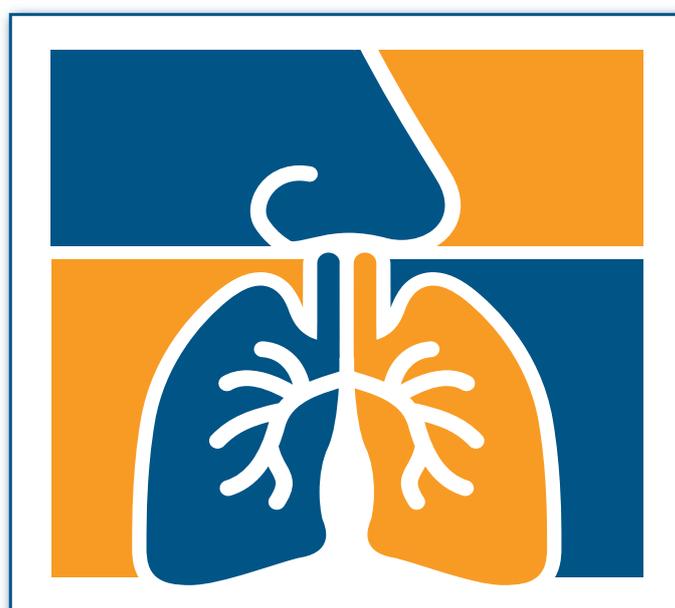
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PRESSPART

IMPROVING DRUG STABILITY & DRUG DELIVERY BY MODIFICATION OF MDI CANISTER SURFACES

In recent years, a number of surface coatings have been developed that can be applied to metered-dose inhaler (MDI) canisters and valve components, to protect the contents from deposition and degradation. More recently, plasma processes have been developed to modify and improve the surface energy performance of a MDI canister. This approach has a number of advantages to alternative coatings but requires careful optimisation to ensure the highest quality finish and MDI performance. Richard Turner, Business Development Director, Presspart Manufacturing, explains.

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

MDIs are commonly used to deliver drugs for treating respiratory and nasal disorders. The drugs are administered by aerosol, in suspension or solution, with a liquefied gas propellant. For more than 50 years, chlorofluorocarbons (CFCs) were the propellants of choice, but these have now largely been phased out, in line with the Montreal Protocol.

Replacement propellants have been developed over the past two decades based on hydrofluoroalkanes (HFA), specifically HFA 227 and HFA 134a. These substances are not ozone-depleting, they are also non-flammable and chemically inert, making them ideal candidates for use in medical products. However, some properties of these compounds are substantially different from those of the CFCs traditionally used in MDIs.

When HFA-MDI drug formulations are in suspension, interactions with the canister substrate can cause deposition of the drug on the canister walls or on exposed surfaces of the valve components. Interactions with solutions more commonly cause degrada-

tion, 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.

RANGE OF COATINGS

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

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

Fluorocarbon polymers are commonly used to coat the interior canister surfaces



Mr Richard Turner
Business Development Director
Pharmaceutical
T: +44 1254 582233
F: +44 1254 584100

Presspart Manufacturing Ltd
Whitebirk Industrial Estate
Blackburn
BB1 5RF
United Kingdom

www.presspart.com

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

COATING TECHNIQUES

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

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

PLASMA PROCESSING TECHNOLOGIES

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

The process creates an ultra-thin layer that protects against degradation, deposi-



Figure 1: Aluminium MDI cans.

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

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

OPTIMISING THE PLASMA PROCESS

Plasma processing of MDI canisters can bring multiple benefits to the MDI performance, helping to reduce drug deposition and also to improve the stability of formulations where interactions with the aluminium

substrate would lead to product degradation and reduced shelf life. However, plasma processing for MDI canisters needs to be highly controlled to ensure complete consistency of treatment and uniformity of coating to the internal walls of the canisters.

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

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

It is critical that plasma processing achieves complete and consistent coating across the entire surface of the inside of the canister. Traditional plasma processes, RF or microwave, are particularly difficult to control when internal surfaces are to be treated. Poor penetration of plasma ions with low energy results in non-uniform, thin or porous coatings with poor performance. Increased ion energy to aid depth of can penetration gives rise to ion etching at the can neck and a more “line-of-sight” process.

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

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

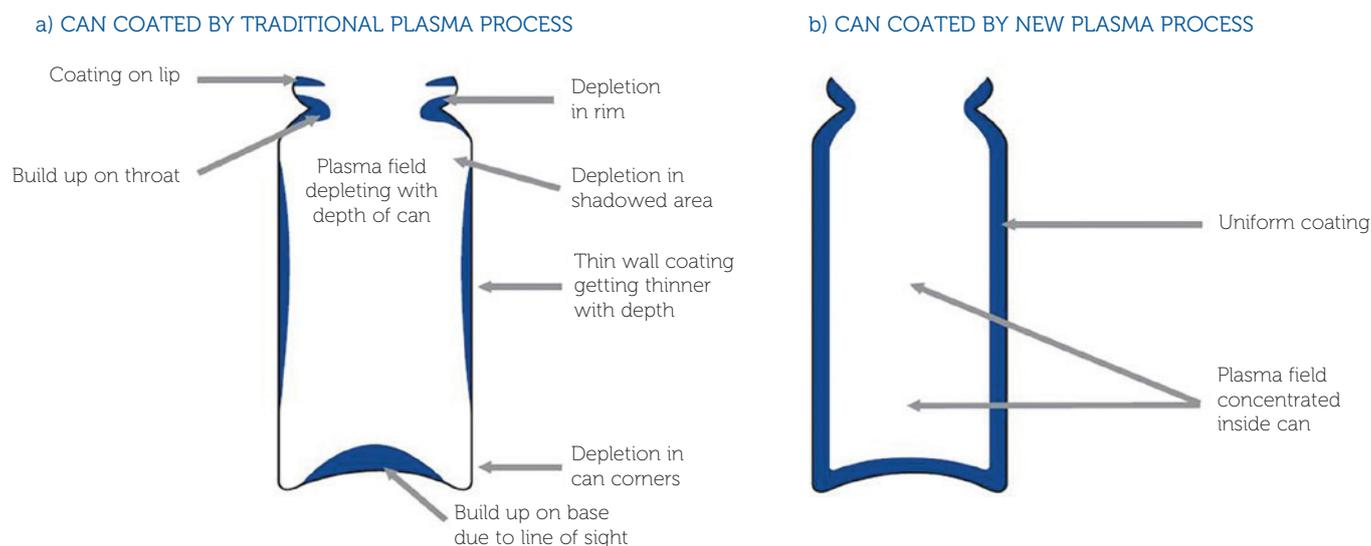


Figure 2: Traditional plasma processing (a) does not ensure a uniform coating to internal wall of the canister whereas the new plasma process (b) gives a uniform coating to canisters.

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 MDI world market.

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

CONCLUSIONS

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

LOOKING FORWARD

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