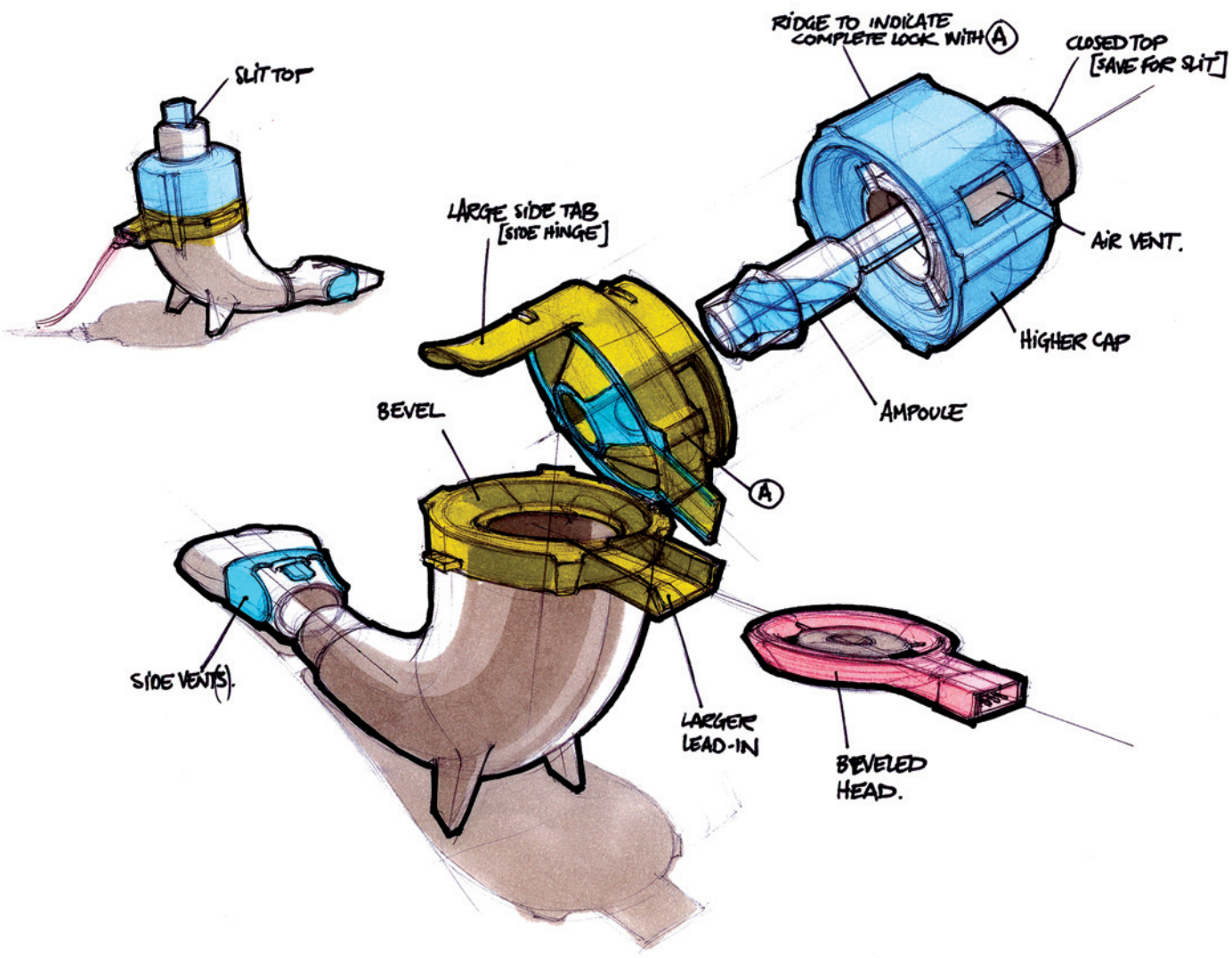
# PULMONARY & NASAL DRUG DELIVERY

ON drugDELIVERY




JUNE 19TH, 2014 • ISSUE N° 50

ONdrugDelivery Issue N° 50, June 19th, 2014

## Pulmonary & Nasal Drug Delivery

This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

### EDITORIAL CALENDAR 2014/15

July: Novel Oral Delivery Systems
Sep: Prefilled Syringes
Oct: Drug Formulation & Delivery Solutions & Services
Nov: Pulmonary & Nasal Drug Delivery
Dec: Delivering Biotherapeutics
Jan: Ophthalmic Drug Delivery
Feb: Prefilled Syringes
March: Transdermal Delivery, Microneedles & Needle-Free Injection
April: Pulmonary & Nasal Drug Delivery
May: Injectable Drug Delivery: Devices Focus

### SUBSCRIPTIONS:

To arrange your **FREE** subscription (pdf or print) to ONdrugDelivery Magazine:
E: subscriptions@ondrugdelivery.com

### SPONSORSHIP/ADVERTISING:

Contact: Guy Furness, Proprietor & Publisher
T: +44 (0) 1273 78 24 24
E: guy.furness@ondrugdelivery.com

### MAILING ADDRESS:

Frederick Furness Publishing Ltd
The Candlemakers, West Street, Lewes,
East Sussex, BN7 2NZ, United Kingdom

ONdrugDelivery Magazine is published by Frederick Furness Publishing Ltd. Registered Office: The Candlemakers, West Street, Lewes, East Sussex, BN7 2NZ, United Kingdom.
Registered in England: No 8348388.
VAT Registration No: GB 153 0432 49.
ISSN 2049-145X print
ISSN 2049-1468 pdf



ONdrugDELIVERY



Front cover image, "Design Concept Drawing by Cambridge Consultants for PARI's eFlow® CS nebuliser", provided by PARI Pharma GmbH (see this issue, page 13). Reproduced with kind permission.

# CONTENTS

HOVIONE

# SCALE-UP & QBD APPROACHES FOR SPRAY-DRIED INHALATION FORMULATIONS

Here, Eunice Costa, PhD, Scientist, Drug Product Development; Filipe Neves, PhD, Senior Scientist, Group Leader, Drug Product Development; Gonçalo Andrade, PhD, Business Development Manager; and Conrad Winters, PhD, Director, Drug Product Development, all of Hovione, describe the strong position of inhalable products in preclinical and clinical pipelines and make the case for formulation-based approaches to enable and enhance pulmonary product development. Spray-drying technology in particular is highlighted as a highly favourable, scalable manufacturing technique for inhalable composite particles.

## INHALED DRUG DELIVERY

Inhaled drug delivery is a growing niche market within the pharmaceutical industry. Pulmonary drug delivery accounted for US$19.6 billion (£11.6 billion) in revenues in 2010[1] and represented approximately 15% of the drug delivery market.[2] Inhalation is emerging as an alternate drug delivery route, expected to reach $44 billion by 2016 [1] and representing approximately 20% of the drug delivery market by 2017.[2] This growth will be driven by new drug product launches for unmet clinical needs, novel drug product combinations and products for improving patient compliance, where pressurised metered-dose inhalers (pMDIs) and dry-powder inhalers (DPIs) are expected to be the major contributors (15.7% CAGR and 12.3% CAGR, respectively).[1]

## MARKET TRENDS

Pulmonary drug delivery can offer significant advantages over other administration routes. Compared with parenteral administration, it is a convenient and less intrusive alternative, reducing the need for medically trained staff during administration. Also, compared with parenteral formulations, DPIs may not require the refrigeration often necessary for vaccines and, when compared with the oral route, lower doses can be used with the potential for reduced side effects.

For drug molecules that have a pronounced food effect, extensive first-pass metabolism, or are subject to efflux or low aqueous solubility, pulmonary delivery offers a viable route where oral delivery would be extremely challenging.

This high number of projects presently in clinical development (Figure 1) reflects different development strategies, ranging from lifecycle management strategies related to inhaler redesign, such as AstraZeneca's ongoing Symbicort (budesonide + formoterol) programme, to new chemical entities for inhaled delivery (e.g. Aesica's development programmes). The majority of these clinical programmes are aimed at treating respiratory based illnesses such as asthma and chronic obstructive pulmonary disease (COPD), cystic fibrosis and pneumonia. However, there have been an

| | Preclinical | Phase I | Phase II | Phase III |
|---|---|---|---|---|
| Number of projects | 196 | 28 | 2 | 1 |

Figure 1: Dry-powder inhalation products in clinical development (Source: PharmaCircle, May 2013).

**Dr Eunice Costa**
Scientist, Drug Product Development

**Dr Filipe Neves**
Senior Scientist, Group Leader,
Drug Product Development

**Dr Gonçalo Andrade**
Business Development Manager

**Dr Conrad Winters**
Director, Drug Product Development

T: +351 21 982 9000
F: +351 21 982 9388

**Hovione**
Sete Casas 2674-506
Loures
Portugal

**www.hovione.com**

increasing number of DPI products in clinical development that target non-respiratory indications. For example, in Type II diabetes, MannKind Corporation has filed a US NDA for Afrezza (inhalable insulin).

One other major driver for DPI formulation development is compliance with the Montreal Protocol, which establishes a control over ozone-depleting gases and led to the replacement of the original CFCs in metered dose inhalers for HFAs (and HFCs).[3,4] But the latter still constitute an environmental threat since both HFAs and HFCs are greenhouse gases and environmental concerns may lead to a phase down/phaseout in pMDIs [4] and drive their conversion to DPI formulations, also contributing to the results of Figure 1.

## TECHNOLOGY TRENDS

Innovation in inhalation drug delivery has primarily been focused on two parallel pathways: the development of novel inhaler devices, and the improvement of powder formulations.[5] Although pulmonary delivery can be enhanced by designing more sophisticated inhalers (e.g. electronic synchronisation), such devices tend to be complex and costly, and their practicality has been questioned. On the other hand, superior delivery efficiency may be achieved more cost-effectively by developing optimised formulations, in physical blends with carriers or as composite particles, for use with simple and user-friendly inhalers.[6] The latter is broadly known as particle engineering.

Among several attributes of a DPI formulation, particle size is one of the most important design variables; particle size relates to the aerodynamic diameter and this, for most inhalation drugs, needs to be in the 1–5 µm aerodynamic range.[7] Jet milling is still the most common size-reduction method in the pharmaceutical industry. However, and in spite of being cost-effective and of easy operation, there may be disadvantages such as lack of control over size, amorphous content and surface properties of the milled particles.[8] In order to overcome some of these challenges, methods that consider the active ingredient suspended in a liquid media have been gaining significant momentum.[9] However, the use of an anti-solvent system, and the potential for residual solubilisation, may pose challenges from a chemical and physical stability perspective, whereas the need of a final isolation step may also be considered a drawback.

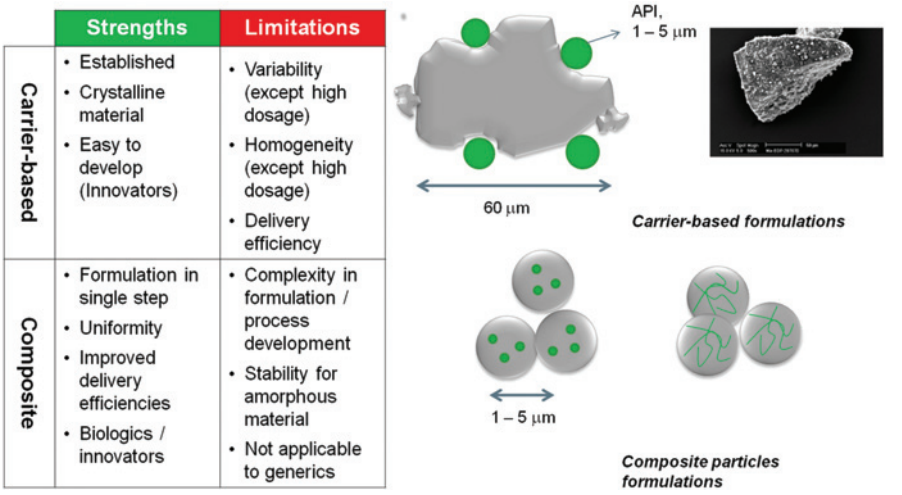



Figure 2: Carrier-based versus composite particle approaches: strengths and limitations.

Other techniques for making micron-sized particles involve direct particle formation from solution. In this field, spray drying (SD) has emerged as a noteworthy approach for achieving the desired aerodynamic size, morphology and, ultimately, powder flow.[10] This technique is distinctly different from milling, as particles are built up by spraying the drug and excipients from a solution or emulsion into fine droplets that are afterwards dried in a chamber. Compared with milling, SD can produce more spherical particles that tend to be amorphous, conferring enhanced solubility of poorly soluble drugs.

Spray drying has been extensively used for the generation of inhaled composite platforms, namely Pulmosol (Pfizer), Pulmospheres (Novartis) or iSperse (Pulmatrix). This technology has been applied to a diverse array of molecules, from small molecules for respiratory disease treatment to biomacromolecules for systemic delivery. For example, insulin was engineered in order to yield particles with a corrugated surface that improved dispersibility (Exubera DPI from Pfizer). More recently, Pulmospheres, based on solid foam particles prepared by SD of an emulsion, have been employed for a DPI formulation of tobramycin (TOBI Podhaler).

As summarised in Figure 2, these platforms are challenging to develop given the simultaneous requirements of physical stability and optimal aerodynamic performance. Conversely, the particle engineering and formulation are done in a single step, overcoming potential uniformity issues of traditional lactose-based DPI approaches and enabling the delivery of higher fine-particle fractions (FPFs).[10]

The following paragraphs address spray-drying technology as a manufacturing technique for inhalable composite particles, starting by focusing on the scale-up procedure, typical challenges and ways to overcome them, and finishing by showing how systematic methodologies and scientific understanding can be used to conduct the process development based on QbD principles.[11]

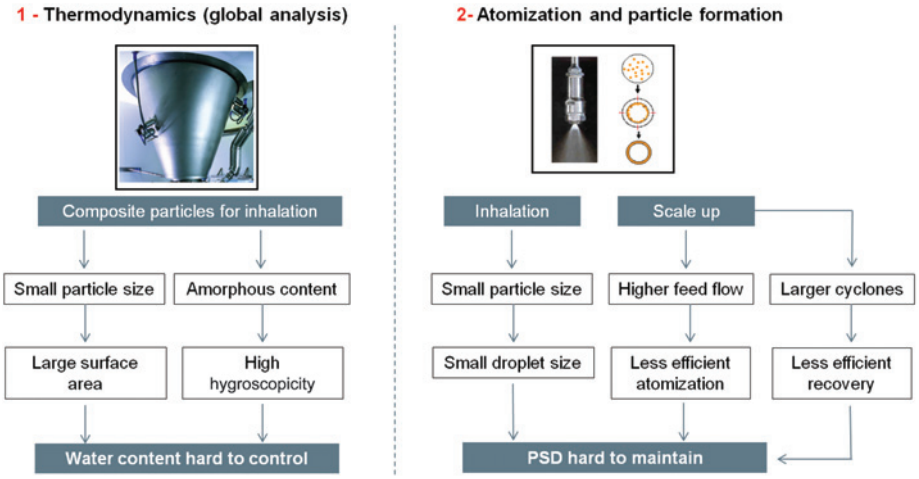



Figure 3: Main difficulties during development and scale-up of spray-dried inhalation products.

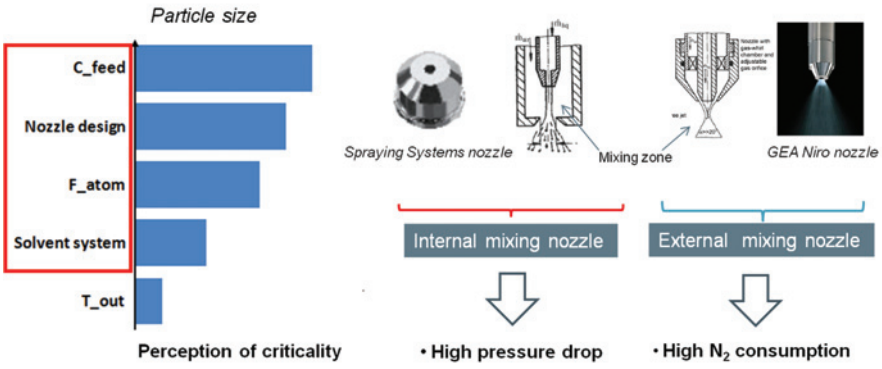



Figure 4: Main critical parameters and challenges during the atomisation step. C_feed = solids feed concentration, F_atom = flowrate of atomisation gas, and T_out = outlet drying gas temperature (Nozzle schemes adapted from Hede et al, 2008.)

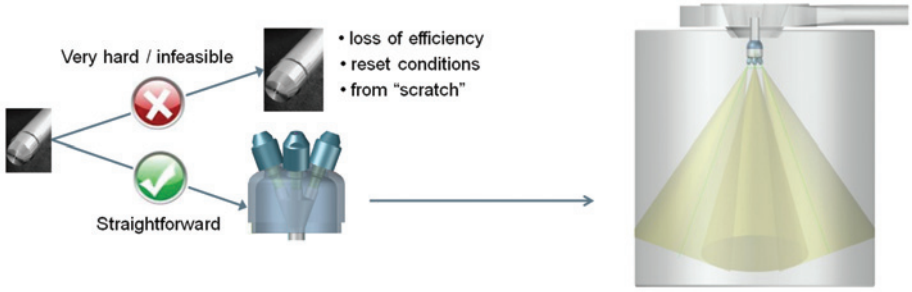



Figure 5: Multi-nozzle approach for expediting scale-up of atomisation (Hovione's apparatus).[12]

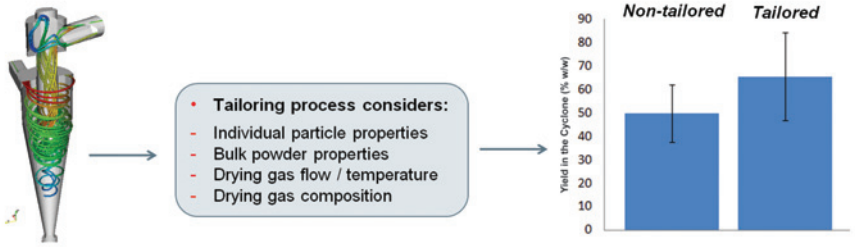



Figure 6: Tailoring process of cyclones for improved recovery of inhalation powders during scale-up.

## SPRAY DRYING SCALE-UP APPROACH

The manufacturing of spray-dried inhalation powders involves two main challenges: particle size and residual moisture control (Figure 3). Firstly, a very small particle size is required, and this should not increase during process scale-up. By itself, this poses significant problems during the droplet formation (atomisation efficiency decreases for higher feed flow-rates) and particle recovery (cyclone efficiency decreases in larger units) steps. Secondly, due to the small size of the particles, the total surface area of the bulk powder is significantly high which, when combined with the increased hygroscopicity of amorphous phases, leads to challenges in moisture control.

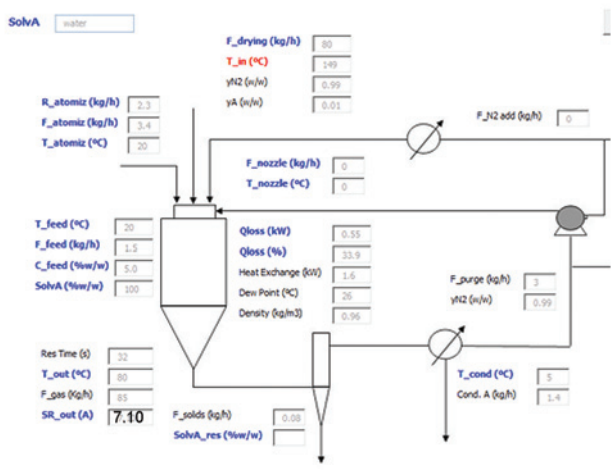
With regards to particle size control, as introduced before, most of the difficulties during development result from the loss of efficiency of current off-the-shelf atomisation systems, when managing increased throughputs during scale-up.

Such loss of efficiency is translated by a higher demand of atomisation gas flow and this will lead to different bottlenecks depending on the type of atomisation systems (Figure 4):

a) For external two-fluid nozzles (high consumers of atomisation gas at low pressures), the flow of atomisation gas may increase so much that the drying chamber will be incapable of dealing with it (atomisation gas flow can grow to a demand of 30-50% of the drying gas flow).

b) For internal two-fluid nozzles (lower consumers of atomisation gas but at higher pressures), the increase of atomisation gas may promote such a high pressure

A)




B)

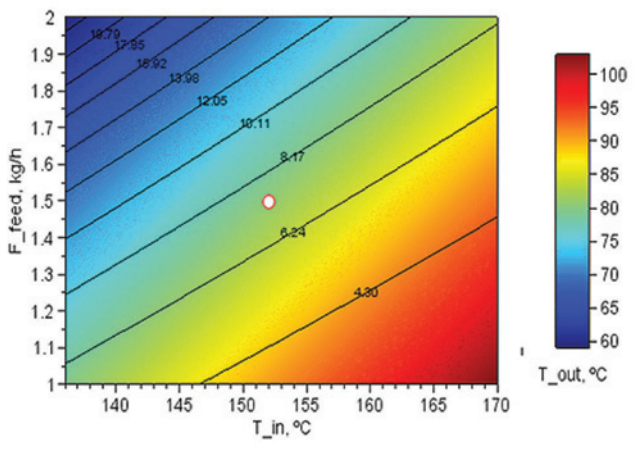



Figure 7: Use of thermodynamic simulations for relative humidity / saturation space mapping: (A) operating parameters and (B) design space.

drop on the nozzle that the pressure of the gas-feed lines may often require very complex / expensive upgrades.

In this constraining reality, as shown in Figure 4, nozzle design and atomisation gas flow are the main process parameters that can typically be used to control particle size. Solids concentration is another one, but minimising particle size via C_feed decrease is not recommended, given the corresponding penalty on process throughput.

Regardless, even when these constraints can be overcome, it is not guaranteed that droplet size can be maintained during scale-up. During this process, nozzle operating ranges are often exceeded and time-consuming testing needs to take place in order to select a new nozzle. As there are physical limitations on the atomisation of large liquid flow rates into very small droplets, this is not always successful.

Under the above scenario, the use of multi-nozzle apparatuses comprising several low-throughput nozzles (as opposed to a single high-throughput nozzle) becomes appealing. By using this approach, the ratios between liquid and atomisation gas flow can be maintained (in each nozzle), avoiding some of the constraints described earlier and enabling a smooth scale-up (as operating conditions do not need to be changed, since each nozzle is always performing the same "work").[13]

However, this approach requires some special care during the engineering of the SD units, as: i) distribution of the liquid feed and atomisation gas flows needs to be homogeneous, ii) apparatus size / positioning cannot impact the drying gas flow pattern, and, iii) the apparatus needs to enable spray-drying angles in a way that no overlapping occurs nor spray shape is impacted by the drying gas flow (in order to avoid secondary atomisation).

Nonetheless, when successfully accomplished, the only scale-up action (during product development) will be the increase of the number of nozzles used, proportionally to the scale of the unit (see Figure 5).

Regardless of the many advantages of a multi-nozzle apparatus, its use – by itself – does not guarantee successful particle size control during scale-up. The reason is the typical loss of recovery efficiency when moving to larger cyclones. As smaller particles tend to escape to a greater extent (when compared with larger particles), if significant losses are experienced this will impact on the particle size distribution (PSD) of the recovered product. One successful way of overcoming this serious hurdle is tailoring the cyclone to the product's characteristics (Figure 6).

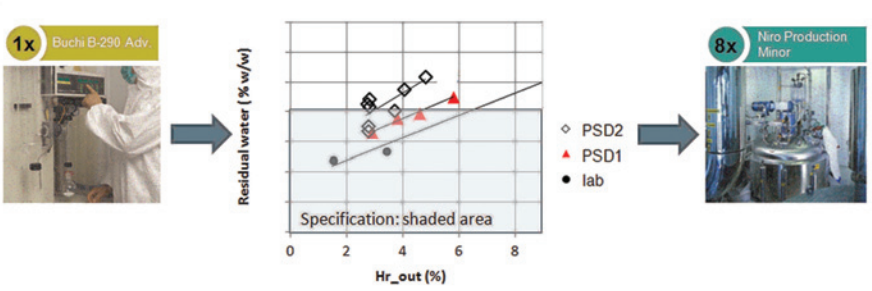



Figure 8: Typical challenges of moisture control during scale-up of spray drying processes: lab scale (black circles); pilot scale (red triangles); and manufacturing scale (open diamonds).

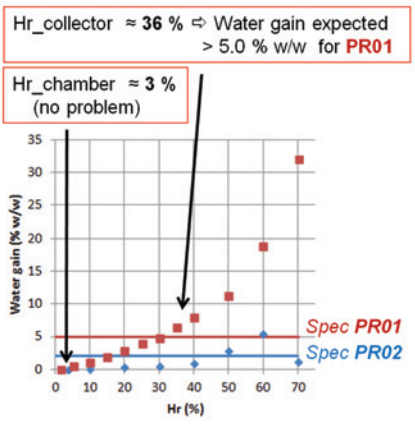
This tailoring process considers the specific attributes of the particles and of the SD process (e.g. particle density and drying gas composition) in order to yield a product-specific design, capable of maximising recovery. The costs involved in tailoring a new cyclone are typically low and quickly recovered, considering the high value of the products and the advantages of a superior control.

Another critical point for SD process development and scale-up is controlling the residual moisture levels to control microbiological and physiochemical stability, considering that aqueous feed solutions are usually employed and that (partially) amorphous materials are obtained. In addition, materials are sticky in a glassy state, so it is important to process them at temperatures and relative humidity (RH) below the glass transition. Hence, in order to obtain material compliant with the target moisture content, while ensuring a good process yield, understanding thermodynamics is key.

The SD scale-up methodology should integrate mechanistic modelling (e.g. heat and mass balances) in order to determine a thermodynamic design space for a given process and scale. Typically the RH inside the SD chamber is critical in determining the moisture content of the product. Additional knowledge, such as dynamic vapour sorption behaviour, is also important to determine product sensitivity to RH. Given the product specification, an operating range is obtained for key process parameters – such as temperature profile (T_in / T_out) and feed flow (F_feed) – that determine the target RH (Figure 7).

Usually, during SD process scale-up, operating parameters are selected so that RH is maintained across scales and hence the resulting product moisture content is kept constant. This can be referred as a conservative scale-up approach, since increased residence time in a larger dryer should favour a reduction in product moisture content. However, for some products, an increase in water content is observed upon scale-up even when pursuing this conservative approach, as shown in Figure 8. These deviations are often due to water uptake at the cyclone discharge, given the typical high hygroscopicity of the material produced by spray drying.

Indeed, the collector at the cyclone discharge is at a lower temperature than the outlet of the SD chamber which, for a constant absolute humidity, results in




| | Pros | Cons |
|---|---|---|
| ***Heated vessels*** | - Predictability<br>- Control | - Lack of scalability<br>- Thermal degradation<br>- Crystalization for amorphous compounds |
| ***Nitrogen sweep*** | - Scalable<br>- Enables lower Hr | - Controlability<br>- Potential back flow of fine material |

Figure 9: Challenges with moisture uptake (left) and ways to prevent these (right).


Figure 10: Overview (main steps) of the general QbD approach followed at Hovione.

an increased RH inside the collector (see Figure 9). For preventing water uptake during collection of highly hygroscopic materials, two different engineering strategies can be followed; namely either heating the collectors or introducing a nitrogen stream. The first approach enables more control with a predictable impact on the final properties. However, it is not a scalable approach and cannot be adopted for all molecules. Conversely, a nitrogen sweep, preventing the "wet" drying gas to contact with the collected product, enables lower RH levels and is readily scalable, thus addressing some of the challenges of the former strategy.

Despite the overall challenges in establishing and scaling-up a spray drying process for manufacturing an inhalation drug product, the issues are well-known and can be overcome through an integrated process understanding and implementation of science-based solutions, thus ultimately enabling a development under QbD principles.

## SPRAY DRYING DEVELOPMENT UNDER QBD

The QbD approach followed at Hovione is shown in Figure 10, while its application to the spray drying process of an inhalation powder is illustrated in Figure 11.

The critical quality attributes (CQAs) are defined based on the target product profile. These translate the properties of the drug that need to be kept within an appropriate limit or range in order to assure the desired product quality, for example, purity, solid state and particle size. For the sake of simplicity, only particle size is considered in Figure 11.

During the first risk assessment, and for each CQA, an analysis of the potential critical process parameters (pCPPs) and potential critical material attributes (pCMAs) is conducted. The aim is to evaluate, in each process step, which operating parameters / raw materials have the potential to impact a CQA (within the known ranges) and, therefore, should be monitored or controlled. Since the number of parameters is usually high, this risk-assessment (based on prior knowledge of product/process) is used to rank the parameters in terms of perception of criticality. The ultimate goal is to keep the development process as lean as possible, by focusing the studies on those parameters with higher likelihood of being critical (atomisation ratio, feed concentration and drying temperature, in Figure 11).

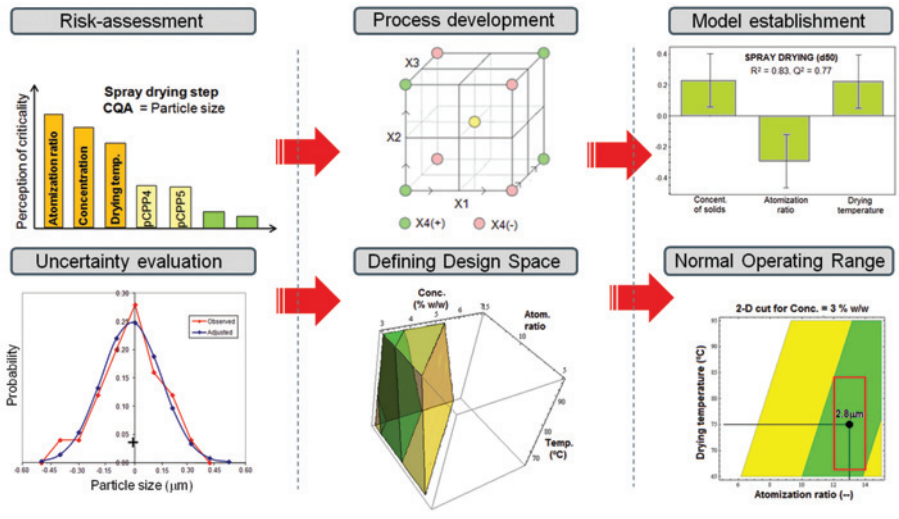



Figure 11: Application (main steps) of the general QbD approach to a spray drying process of an inhalation powder.

The output of the previous risk assessment is a qualitative match between CQAs and pCPPs and pCMAs. To confirm the dependences and quantify the effects, a process development stage is conducted. Often a statistical approach is followed through a sequence of Designs of Experiment (DoE) with different objectives such as screening/optimisation and robustness studies. This development stage constitutes the core of the QbD methodology since most of the process knowledge is generated here and, although not mandatory, a statistical and/or mechanistic model is a usual outcome of this step.

Once the impact of the pCPPs/pCMAs is quantified on the CQAs, a feasible operating space can be defined. This space, also known as design space, will consider the interactions between operating parameters and material attributes and will often be a multi-dimensional space (see Figure 11). Within the design space, the normal operating range (NOR) is established. This is the part of the design space where the process typically operates. When setting both these spaces, the error distributions that are associated to each prediction model should be considered in order to define statistical confidence levels. So, in Figure 11, the yellow shaded regions consider 90% of the error distribution, while green shaded ones correspond to 95%, the latter being more constrained but also more reliable.

The remaining steps of the methodology are not illustrated in Figure 11, but will be briefly described given their importance. After defining the design space and NOR, an exhaustive analysis of the process is conducted at the manufacturing scale. In this study – a Failure Mode Effect Analysis – all manufacturing aspects are reviewed, evaluating the equipment characteristics and the operating procedures against the process knowledge that was gathered to date.

The purpose of this study is to understand and quantify the risk and to define actions to minimise failures. By knowing the feasible operating regions (the design space) and after evaluating the equipment/procedures at the manufacturing scale (directly linked to the practical NORs), a final criticality analysis takes place in order to identify CPPs/CMAs that will require tighter monitoring or control, for example, all those for which the corresponding NORs are close to the boundaries of the design space. Finally, once the criticality around a process parameter and/or raw material attribute is confirmed, appropriate control

strategies will be set in place. The ultimate goal is to assure that operation is taking place within the design space, therefore assuring product quality.

## CONCLUSIONS

Although carrier-based formulations still represent the vast majority of the products on the market and under development, approaches based on composite particles are gaining momentum due to a number of important advantages. Spray drying is a key technology for the manufacturing of such particles and, although some challenges can be recognised during scale-up, these can be overcome through an integrated process understanding and implementation of science-based principles, ultimately resulting in highly capable manufacturing processes.

## REFERENCES


1. *Nagavarapu U, "Pulmonary Drug Delivery Systems: Technologies and Global Markets", BCC Research report, January 2012.*
2. *"North American Drug Delivery Technologies Market (Metered-Dose Inhalers, Needle-Free Injectors, Auto-Injectors, Nasal Sprays, Transdermal Patches, Nebulizers, Infusion Pumps, Drug Eluting Stents, Sustained Release, Ocular Implants) – Forecasts To 2017". Markets and Markets report, July 2013.*
3. *Price DB, Valovirta E, Fischer J, "The importance of preserving choice in inhalation therapy: the CFC transition and beyond". J Drug Assessment, 2004, Vol 7(2), pp 45.*
4. *IPAC Position Statements and Meeting Minutes, 2012 and 2013.*
5. *Newman, Busse, "Evolution of dry powder inhaler design, formulation, and performance". Respiratory Med, 2002, Vol 96, pp 293-304.*
6. *Chow A, et al, "Particle Engineering for Pulmonary Drug Delivery". Pharm Res, 2007, Vol 24(3), pp 411-436.*
7. *Bates D, et al, "Deposition and retention models for internal dosimetry of the human respiratory tract". Health Physics, 1966, Vol 12(2), pp 173–207.*
8. *Snow R, et al, "Size reduction and size enlargement" in: Perry R, Green D, "Perry's Chemical Engineer's Handbook", Publ by McGraw Hill, New York (1984).*
9. *Cacela C, Gil M, Temtem M, "Advances in Size Reduction Process for Mometasone Furoate Monohydrate". Respiratory Drug delivery, 2012, Vol 2, pp 535-538.*
10. *Vehring R, "Pharmaceutical Particle Engineering via Spray Drying". Pharm Res, 2007, Vol 25(5), pp 999-1022.*
11. *ICH (2009), Pharmaceutical Development Q8 (R2), available at http://www.ich.org/ fileadmin/ Public_Web_Site/ICH_Products/ Guidelines/Quality/Q8_R1/Step4/ Q8_R2_Guideline.pdf.*
12. *Hede, PD, Bach P, Jensen AD, "Two-Fluid Spray Atomization and Pneumatic Nozzles for Fluid Bed Coating / Agglomeration Purposes: A Review". Chem Eng Sci, 2008, Vol 63, pp 3821-3842.*
13. *Neves F, Santos J, Olival L, "Multi-Nozzle Concept for Expedite Scale-Up of Spray Dried Inhalation Powders". Provisional patent filed in Portugal (2014).*

# EVERYTHING FOR INHALATION

## API PARTICLE REDUCTION

- Jet milling
- Wet polishing
- Composite particles
- Nanocoating
- Microencapsulation
- Spray drying

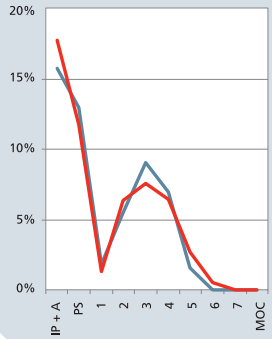
## FORMULATION

- Pure API
- Carrier based
  - Lactose based
  - Leucine based
  - Mannitol based
  - Custom excipients

## CAPSULE FILLING

- Phase I clinical trials (Fill gun)
- Phase II clinical trials up to low volume commercial - automated capsule filling (100% net weight unit verification)
- Blistering and packaging

## MATCHING INNOVATOR DEPOSITION PROFILES




# Integrated Development and API Supply

Budesonide, fluticasone, formoterol, mometasone, salmeterol, tiotropium



Inhalation at Hovione
+351 21 982 9360
inhale@hovione.com | www.hovione.com/inhale

HOVIONE

# PRODUCT PROFILE: TEAMED: FOR DRUG DELIVERY DEVICE PRODUCTS

team technik
PRODUCTION TECHNOLOGY

## PROFITABLE ASSEMBLY & FUNCTIONAL-TEST AUTOMATION VIA STANDARDISED PLATFORMS

There is increasing demand for new solutions to automate the manufacturing of medical products from Phase I clinical trials through to a successful high-volume production programme. Teamtechnik Group is a leading supplier in the development and implementation of turnkey production systems for medical devices.

## THE TEAMED PLATFORM

With its *TEAMED* platform, teamtechnik offers a scalable linear production system for both automated assembly and testing of devices. *TEAMED* is a multi-purpose automation platform, which has been specifically developed to address the particular challenges associated with the assembly of medical devices. This platform is designed to meet the needs of pharmaceutical production systems.

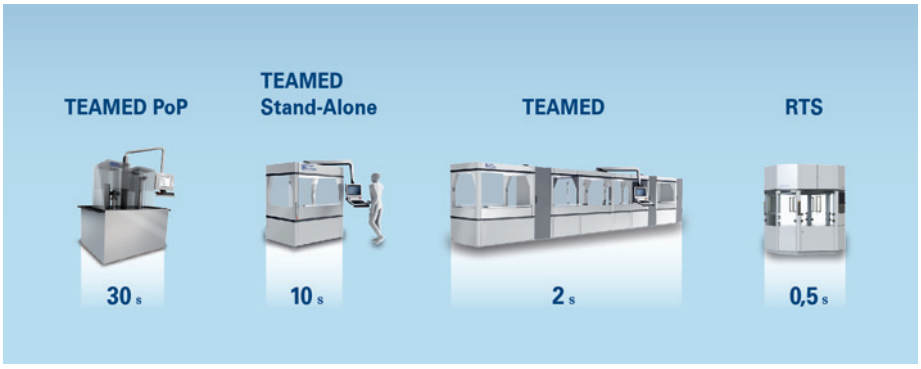



Figure 1: Modular platforms for assembly and function test.

Figure 2: Assembly system at TEAMED platform.

Figure 3: Counter window for welding process integrated in platform TEAMED.

The *TEAMED* platform enables the integration of a sophisticated assembly processes with up to 100% end-of-line testing. It also facilitates production that is compliant with global standards such as cGMP, US FDA and CE - and is certified to Class 6 Clean Room specifications. The *TEAMED* platform incorporates processes from prototype production directly into series manufacturing, thus verifying critical process steps at the earliest possible stage, providing reassurance for future series production from the outset.

The *TEAMED* platform has been developed for proof-of-principle applications as well as for high-speed industrialisation. Drawing upon teamtechnik's comprehensive library of processes, the *TEAMED* solution optimises assembly processes and reduces time to commercialisation for new products.

**A typical device project development and commercialisation cycle for a new inhaler device, utilising the TEAMED platform, is described below.**

## "TEAMED POP" FOR PROTOTYPE PRODUCTION

### Phase I Clinical Trials

Inhaler device assembly involves many complicated processes, which must either be monitored in-process, or results verified after the process. Ideally, in order to minimise time to market, a device design and assembly process would be completely defined from the outset of Phase I. For reasons of cost, risk and design evolution, this ideal is not generally possible and teamtechnik's *TEAMED PoP* (proof-of-principle) platform provides a solution for such a challenge.

Incorporating both automated and manual elements, *TEAMED PoP* offers the ability to perform and monitor critical assembly processes with automatic solutions at a very early stage in a project, whether or not a device design has been fully defined at that point. Able to accommodate up to five process operators working at the machine, it is often the case that a customer will engage with teamtechnik and utilise *TEAMED PoP*, while a device is still under development.

*Continued on Page 12...*

# FOR YOUR DEVICE.
# **FOR YOUR SUCCESS.**






## Proven production systems

- Assembly and functional test
- Excellent product and process expertise
- From start-up to high-speed
- Solutions for proof of principle and prototype production

Get inspired for the future. **www.teamtechnik.com**

team technik
PRODUCTION TECHNOLOGY

# PRODUCT PROFILE: TEAMED: FOR DRUG DELIVERY DEVICE PRODUCTS

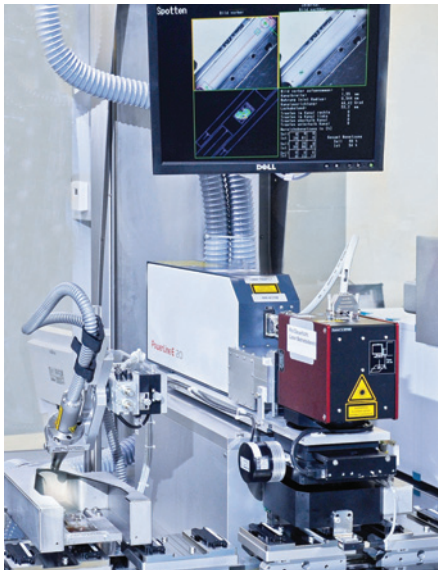


Figure 4: Laser process for radiation, integrated in TEAMED platform.

... *Continued from Page 10*

## "TEAMED STAND-ALONE" FOR SMALL-VOLUME PRODUCTION

**Phase III Clinical Trials**

Providing continuity from the Phase I experience utilising *TEAMED PoP*, the same process units can then be integrated into a *TEAMED Stand-Alone* machine for small-volume production to support Phase III clinical trials.

*TEAMED Stand-Alone* is a semi-automated assembly line with process materials being fed by operators, and with process stations being linked by a carrier transport system. The carrier features have the same design as in the corresponding *TEAMED PoP* machine, although typically incorporating additional nests for manually pre-loaded parts. Although most of the assembly operations will be performed automatically, the refined process stations are based on similar technologies to those on the precursor *TEAMED PoP* system.

## "TEAMED" FOR INDUSTRIALISATION

**Commercial Scale**

For high-volume, commercial-scale production, teamtechnik provides a fully-automated *TEAMED* line with all device components being delivered by bowl feeders or palletising systems. The carrier design is ideally based on the same concept as used for the earlier *TEAMED PoP* and *TEAMED Stand-Alone* machines.

A number of critical processes - such as dosing, gluing or welding (ultrasonic or laser) - will typically have been refined and validated with the *TEAMED PoP* and *TEAMED Stand-Alone* systems, and are continued through in the design of the high-volume manufacturing line. The simple replication of validated processes can significantly reduce time to market for a new device, thereby improving return on investment. This benefit can be realised by means of the modular design of the *TEAMED* system, using individually customised processes and a machine concept which combines the flexibility and operational efficiency of pre-validated servo-actuated motions and cam-driven units.

## "RTS" CAM-DRIVEN PLATFORM FOR HIGH-SPEED PRODUCTION

Drawing on the considerable experience and expertise of teamtechnik's Pfuderer division, RTS is the company's high-speed automation platform. Typically operating at up to 120 cycles per minute, RTS offers a cam-driven ring transfer system, providing between eight and 32 individual stations, and is designed for processes which require the highest outputs.

## MARKET LEADERS TRUST IN TEAMTECHNIK

Customers rightly expect robust, reliable and cost-effective production systems for their medical device products. Providing the foundation for long-lasting customer relationships, teamtechnik's engineers are well-versed in the design and building of process technologies which offer sophisticated assembly and functional testing for a wide range of production applications.

## ABOUT TEAMTECHNIK GROUP

Based in Freiberg, Germany, teamtechnik Group is an international leader in highly flexible automation technology and has been providing intelligent and reliable automation solutions for medical, pharmaceutical, diagnostic and other industries for several decades.

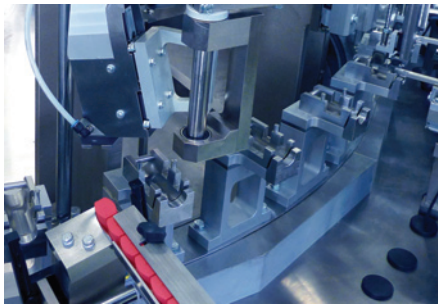


Figure 5: Mouth piece cover fitting process integrated in platform RTS.

With 850 employees throughout the world, and annual revenues of more than €150 million, teamtechnik supports customers from sites in Germany, Poland, France, China, Korea and the US.

To ensure that customers have access to relevant expertise during post-installation and ramp-up phases of their projects, teamtechnik provides resident engineers – based locally and available on-site – during this critical phase of a programme. Through its global service network, teamtechnik also ensures that production equipment is available around the clock, providing customers with dedicated service team contacts, each with comprehensive knowledge of a particular customer's manufacturing system.

**Reiner Zeidler**
Sales Manager, Medical Systems
T: +49 7141 7003 179
E: reiner.zeidler@teamtechnik.com

**Teamtechnik Group**
Planckstraße 40
D-71691 Freiberg am Neckar
Germany

**www.teamtechnik.com**

PARI Pharma
Advancing Aerosol Therapies

# THE eFLOW "CLOSED SYSTEM" (CS) – A NOVEL DEVICE PLATFORM FOR LIQUID AEROSOL DRUG-DEVICE COMBINATIONS

Thomas Gallem, Director, eFlow Product Design & Lifecycle Management, PARI Pharma, describes the design and development stages, including the incorporation of human-factors engineering and optimisation for elderly patients, of the company's eFlow CS nebuliser, which uses a proprietary single-dose drug ampoule as an integral part of the nebuliser handset.

## INTRODUCTION

Inhalation systems based on eFlow® Technology provide the benefit of short nebulisation time, silent operation and mobility for patients relying on frequent aerosol therapies. The eFlow CS device combines PARI Pharma's perforated, vibrating membrane technology [1] to generate liquid aerosols of controlled droplet sizes, with a proprietary blow-fill-seal (BFS) ampoule which can be opened solely in the device. Use of this single dose drug ampoule optimises dose uniformity, [2] simplifies medication dispensing from the drug vial into the nebuliser and minimises potential for misuse, such as taking the wrong medication or the wrong dose.

In the first development stage, a functional prototype was built to evaluate the device performance *in vitro*, to draw interest from potential pharmaceutical partners, and to enable use of the eFlow CS (not customised at that stage) in clinical studies with their drug of interest. In the second stage, the device was further optimised to the specific requirements of the target user population of elderly COPD patients. Several usability studies have been performed which resulted in an iterative optimisation process to ensure that the target population is able to use the device safely and effectively.

## DRIVERS FOR THE DEVELOPMENT OF eFLOW CS

The eFlow aerosol delivery platform [3] was established to meet the versatile needs of patients and caregivers. Currently, as part of this platform, PARI Pharma offers two different categories of devices based on the eFlow technology for commercial use:

1. The open system platform for general use (eFlow® *rapid* in the EU, eRapid® in the US) consists of devices which received market clearance in the US via a 510(k) premarket notification (CDRH Guideline 784) and in the EU by CE marking. Similar in performance to traditional jet nebulisers but with significantly reduced nebulisation times, the intended use of these nebuliser systems comprises the administration of standard medications for inhalation as prescribed by the physician.
2. The drug-specific eFlow devices (e.g. the Altera® nebuliser for Gilead's inhaled antibiotic, Cayston® (aztreonam) for use in cystic fibrosis), which require a drug-specific 510(k) approval in US with an intended use restricted only to medications for inhalation that have been approved with the specific device.

For the latter, to indicate that the drug-specific device has to be operated with a particular drug, a mutually conforming branding and labelling concept was introduced. This comprises branding and labelling of the nebuliser system including the nebuliser handset and aerosol head (Figure 1) with a clear statement about the intended use on the packaging and in the instructions for use (IFU).

Although this branding concept has been successfully implemented, the fact that the

**Mr Thomas Gallem**
Director, eFlow Product Design & Lifecycle Management

T: +49 89 742846 - 11
F: +49 8151 279 - 6311
E: t.gallem@pari.de

**PARI Pharma GmbH**
Lochhamer Schlag 21
82166 Gräfelfing
Germany

**www.paripharma.com**

nebuliser handset provides an open medication reservoir still leaves room for misuse. It was therefore the next logical step to develop a forward-looking device concept that would address this issue, adding value for PARI Pharma's licensing partners.

A closer look at the handling procedures for existing nebulisers, which a patient needs to follow in order to take his/her daily inhalation therapy, revealed that many steps can impact successful therapy. Dose uniformity, for example, is influenced by the special care which a patient takes when dispensing his medication from the drug vial into the nebuliser reservoir. In addition, there are no lockout mechanisms in the nebulisers that can prevent the patient from choosing the wrong medication or dose. This might affect treatment safety, especially with advanced, highly efficient nebuliser systems.

To address this unmet need, the eFlow® CS device has been developed. It uses a proprietary single-dose drug ampoule as an integral part of the nebuliser handset. This specific ampoule is required to interface with the aerosol-generating membrane of the nebuliser handset during use. Opening the ampoule is possible only when the ampoule is inserted into and mated with the nebuliser handset.

## FUNCTIONAL PRINCIPLES OF THE eFLOW CS DEVICE

### The eFlow CS Ampoule

Besides its function as the primary packaging container for the liquid drug formulation, the ampoule of the eFlow CS is designed as an integral component of the nebuliser-handset assembly, enabling a unique drug-device interface. This defines a number of additional requirements, such as sufficient mechanical stability, precise ampoule geometry (particularly in the areas of the ampoule-nebuliser interface), and the ability to be produced in a large-scale manufacturing process.

A blow-fill-seal (BFS) process 7 was found to be best suited for this purpose and was finally chosen from the available options for production of the eFlow CS ampoule. A low-density polyethylene (LDPE) material was selected as it provides the required mechanical properties and, in addition, LDPE is widely-used for packaging of liquid medications for inhalation.

The specific design elements of the eFlow CS ampoule are described in Figure 2.

The full cross-sectional view (Figure 2, right) visualises the closure plate (b) with the circular predetermined breaking line. This part of the ampoule is designed to break off along the edge of the plate, flip aside and rest in a defined vertical end position when the opening collar (Figure 3) and the ampoule are fully engaged. The protection rim (Figure 2, (a)) will prevent the ampoule from unintended opening. The chamber of the ampoule can hold fill volumes of 0.8-2.5 ml. The shell of the ampoule has a ring-shaped groove to mount the ampoule inside the medication cap or similar holding feature. When the ampoule is inserted into the nebuliser, a labelling tag remains visible so that the patient always knows which medication is filled (Figure 4).

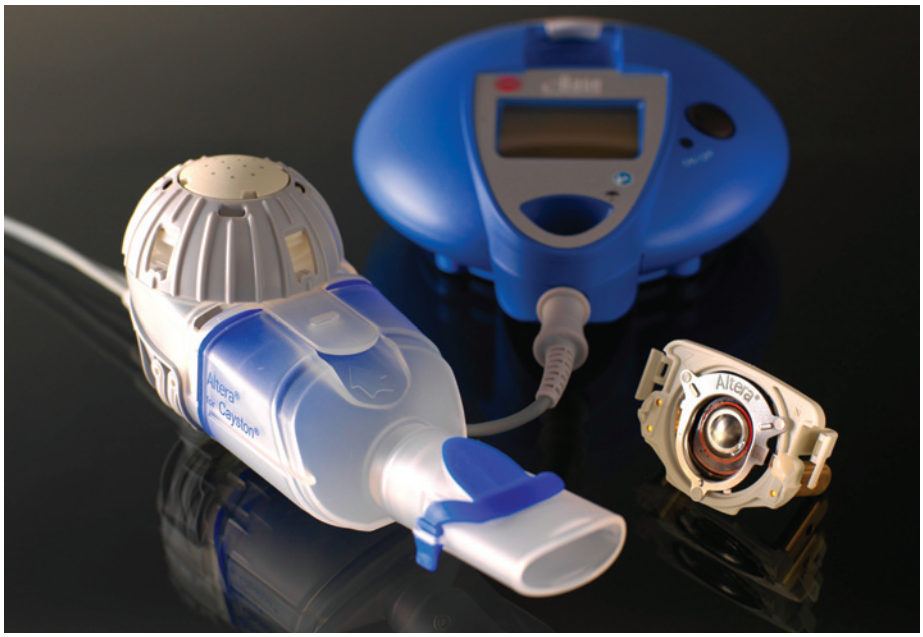



Figure 1: Altera® Nebuliser System with labelling on nebuliser handset and aerosol head indicating drug specific use.

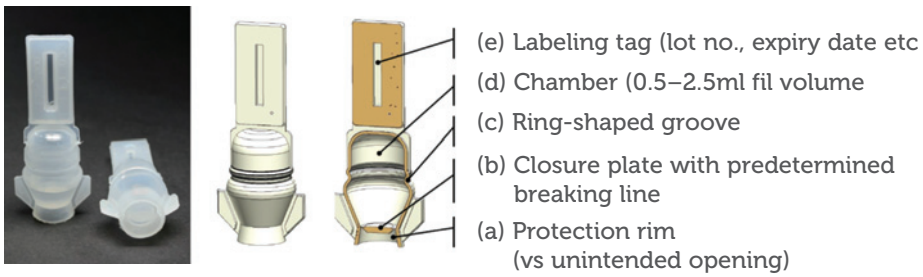



Figure 2: Specific design elements of the eFlow® CS ampoule.

### Drug-Device Interface of the eFlow CS

The concept drawing in Figure 3 visualises the eFlow CS nebuliser handset (left) and the operating principle of the ampoule opening and medication feeding mechanism, including the eFlow CS aerosol head (1), the opening collar (2) and the ampoule (3).

The core component for aerosol generation, the eFlow CS aerosol head (1), is similar to the one used in the commercially available eFlow devices (e.g. Altera®). Its

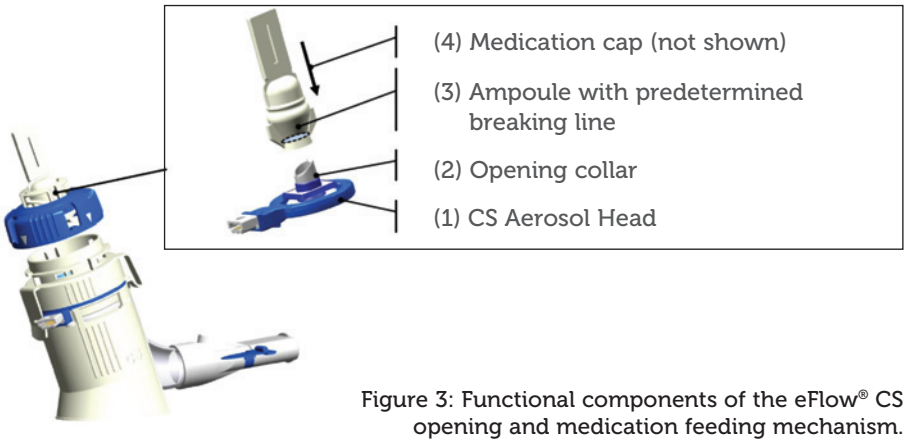



Figure 3: Functional components of the eFlow® CS opening and medication feeding mechanism.

Figure 4: Functional prototype of the eFlow® CS nebuliser (before customisation).

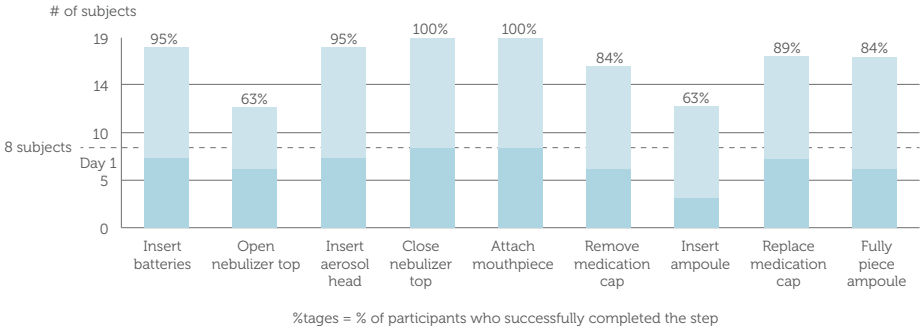



Figure 5: Critical handling steps identified in an early user study in elderly COPD patients.

peripheral portion (the blue ring-shaped part in Figure 3) was adapted to the requirements of the eFlow CS nebuliser handset whereas the vibrating centre portion remained unchanged. The opening collar (2) is essential for a reproducible ampoule opening and medication feeding process. It punches and opens the ampoule when both parts are fully engaged. The opening collar is integrated within the top of handset assembly. Upon opening of the closure plate the medication flows from the ampoule (3) through the lumen of the opening collar and comes into contact with the perforated membrane of the aerosol head from where it can be nebulised following activation.

The medication cap integrates the ampoule into the nebuliser. This cap interacts with the top of the handset part and enables drug loading and liquid feeding in two steps. First, the ampoule is inserted into the medication cap which then is attached to the nebuliser. While turning and closing the medication cap, integrated threads transfer the rotation into a linear motion of the ampoule relative to the opening collar. When the end position is reached, the system is primed for starting nebulisation.

For improved delivery efficiency during continuous nebulisation, the eFlow CS nebuliser handset also features a flow-optimised aerosol chamber with valves.[5,6] Upon inspiration by the patient the inspiratory valve in the top of the handset opens allowing the inspiratory flow to entrain the aerosol generated into the chamber. Upon expiration the inspiratory valve closes and the expiration flow is diverted via the expiratory valve at the mouthpiece. During the expiratory phase, aerosol is continuously generated and collected in the chamber for delivery in the next inspiratory phase. Thus, aerosol losses are minimised and the delivery rate maximised.

To verify the performance of the novel device concept, a functional prototype (Figure 4) was built and tested *in vitro*. In order to retain flexibility with respect to subsequent optimisation and customisation for various clinical programmes, a modular preproduction tool for the eFlow CS ampoule was built for aseptic filling of investigational drug products suitable for fill volumes between 0.8-2.5 ml (HOLOPACK GmbH [7]).

The results of the design verification test exceeded most expectations.[2] The residual volume remaining in the ampoule and opening collar at the end of a treatment is about 0.15 ml and virtually independent of the fill volume. Varying the holding angle of the eFlow CS nebuliser handset in a range of 20° forwards to 40° backwards from a horizontal oriented mouthpiece axis had no significant effect on the drainage properties and the total output, using isotonic saline.[4] This was an important prerequisite for the required delivered dose consistency under typical handling conditions.

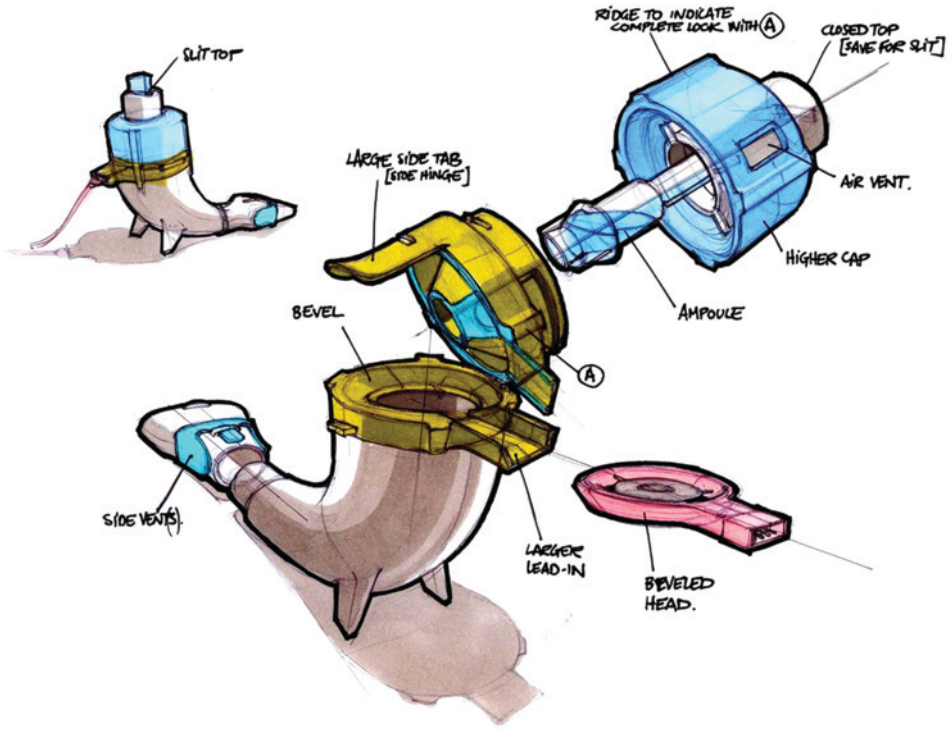



Figure 6: Design concept of an optimised eFlow® CS device for elderly COPD patients.

## CUSTOMISING THE eFLOW CS FOR ELDERLY USERS (65+)

The first use of the eFlow CS functional prototype in a clinical study was in the third quarter of 2012. The preparation of the study devices made clear that some of the elderly COPD patients, especially those with age-related handicaps (e. g. visual, hearing and dexterity impairments), may struggle with using the device according to the IFU. Therefore, a series of user studies was planned and performed in order firstly to identify the use-related risks and secondly to optimise the device for the intended user population.

Following common best-practice rules for human factors engineering,[9] this process started at an early stage of the device customisation by defining users, uses and use environments. The focus of the user studies was on use-related

hazards and understanding the risks associated with them, and it followed a coherent plan to identify and address any human-factors issue. The IFU and the accompanying documents including the packaging were regarded as part of the user interface and therefore tested as thoroughly as any other part.

In alignment with the regulatory requirements as described in the Draft US FDA Guidance for Human Factors Engineering (HFE) and the International Standards ANSI/AAMI/IEC 62366 & ANSI/AAMI/ISO 14971, an HFE file was created to document the user-study results and the iterative device improvements.

A first observational user study in the target population of elderly COPD patients aged between 65 and 80 revealed the most critical handling steps with the device. Due to the restricted physical and mental capabilities of the target population, even fairly simple handling steps like "open nebuliser top", "remove medication cap" and "insert ampoule" could not be successfully finished by all participants (Figure 5). In addition, the rough handling observed during the user studies called for further improvement of the robustness of the device.

Based on these findings, new design concepts were developed supporting more intuitive handling. In this device optimisation process all design elements that are relevant to the aerosol performance of the eFlow CS nebuliser handset, such as the medication feeding mechanism (Figure 3), the valves, the aerosol chamber and the aerosol head, had to remain unchanged.

Several design concepts have been developed and evaluated and the one that best fulfils the new user-related requirements is depicted in Figure 6. Its main design features are:

- An improved ampoule that can only be inserted into the nebuliser in one way
- An enlarged and simplified medication cap that reduces the ampoule opening torque and provides a better grip
- A sideways nebuliser opening for improved aerosol-head accessibility and assembly
- A more robust interface for the connection cord adapter.

This design concept was transferred into a new eFlow CS device (Figure 7) which will be ready for use in a large, multicentre Phase III clinical study later in 2014. The robustness and ease of handling of the new design has been demonstrated by several usability studies and iterative design optimisation including intense design verification testing. The results of the pre-summative user study confirm that the issues identified in Figure 5 have been successfully addressed. External HFE specialists [10] were involved in planning and conducting the user studies for the device optimisation process. Their support covered the whole range of HF activities including the recruitment of study participants to the point of the creation of the summative HF study report. In addition, most HF service providers offer access to an infrastructure to execute the user studies in a real life environment.

Figure 7: eFlow® CS for elderly COPD patients (after customisation).

## SUMMARY

The novel eFlow CS inhalation device, an advanced, highly efficient nebuliser system, has been developed to improve treatment safety. It features an integrated, single-dose BFS drug ampoule combined with a unique opening mechanism. Since the specific ampoule is required to operate the device, potential misuse, like choosing the wrong medication or filling the wrong dose, is minimised.

The integration of the ampoule with the device removes human errors from improperly adding the drug solution into the nebuliser while improving dose-uniformity and hygiene requirements.

Supported by a series of user studies, the design was optimised for the target user population of elderly COPD patients. The new design has been demonstrated to fulfil the technical requirements and to support intuitive handling.

## REFERENCES

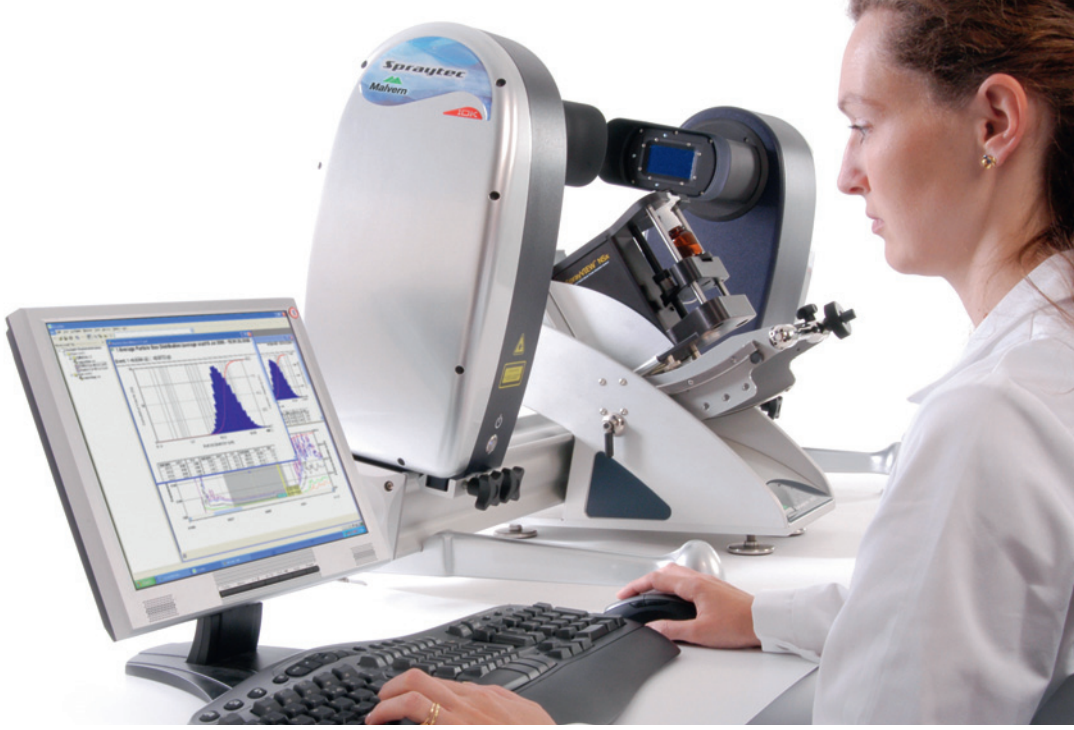

1. *Knoch M, Keller M, "The Customized Electronic Nebulizer: a New Category of Liquid Aerosol Drug Delivery Systems". Expert Opin Drug Del, 2005, Vol 2(2), pp 377-390.*
2. *Gallem T, Tservistas M, Uhlig M, Waldner R, Seemann S, Keller M, Knoch M, "Evaluation of an Ampoule-Based Nebuliser System Intended to Facilitate Accurate Dosing", Proc Respiratory Drug Del Eur (RDD Europe), 2009, pp 341-244.*
3. *Keller M, Knoch M, "Optimising Drug & Device Together for Novel Aerosol Therapies", ONdrugDelivery, March 2010, pp 12-16. (www.ondrugdelivery.com)*
4. *Gallem T, Tservistas M, Waldner R, Loenner M, Knoch M, Keller M, "Assessment of the Influence of the Holding Angle on Drainage and Output Properties of a new Ampoule-Based Nebuliser System". Proc Respiratory Drug Del (RDD), 2010, pp 713-718.*
5. *Borgschulte M, Germer M, Hug M, Keller M, Knoch M and Stangl R, "Means to Optimize Drug Delivery from a Novel Electronic Inhaler". Proc Respiratory Drug Del (RDD), 2004.*
6. *Patent family based on German patent: DE 199 53 317, e.g. US 6,962,151.*
7. *HOLOPACK Verpackungstechnik GmbH; www.holopack.de.*
8. *US FDA Draft Guidance, "Applying Human Factors and Usability Engineering to Optimize Medical Device Design". June 2011.*
9. *http://IPAC-RS HF Webinar 2012, slide 9 www.ipacrs.com.*
10. *Leslie E. Johnston, Senior Human Factors Engineer, Cambridge Consultants, Inc (Cambridge, MA, US). E: leslie.johnston@cambridgeconsultants.com. (www.cambridgeconsultants.com)*

# FROM **SPRAYS...**

**SPRAYTEC:**
**Dynamic particle and droplet sizing**

- Measures concentration and particle/ droplet size during device actuation
- Rapid screening and accelerated optimization of OINDP formulations and delivery device
- Complementary to other analysis methods such as cascade impaction
- Promotes a knowledge-based approach to product development advocated by QbD

**www.malvern.com/spraytec**



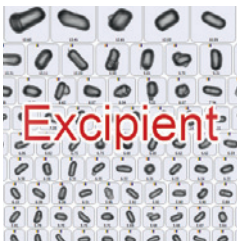

# CHARACTERIZE YOUR OINDP IN **DETAIL**

**www.malvern.com/g3id**

## ...TO **API SIZE**

**MORPHOLOGI G3-ID**
**Morphologically Directed Raman Spectroscopy**

- Component specific particle size and shape distribution measurements for OINDP formulations
- Simple SOP operation from sample dispersion through to size, shape and chemical analysis
- Provides supporting evidence for in-vitro bioequivalence and CMC studies for nasal sprays
- Aids the deformulation of OINDP formulations, promoting a QbD focused approach to ANDA submissions





Malvern | Material relationships

www.malvern.com

# ARTIFICIAL NEURAL NETWORKS & TISSUE MODELS FOR INHALED FORMULATION SCREENING, SELECTION & BIOEQUIVALENCE TESTING

In this article, MedPharm CSO and COO Professor Marc Brown, PhD, CChem, FRSC; Ms Jo Muddle, PhD Student, Kings College London and Scientist at MedPharm; and Professor Clive Page, PhD, Professor of Pharmacology at King's College London, and Head of Sackler Institute of Pulmonary Pharmacology, describe the use of artificial neural networks (ANNs) and novel tissue models as methods for formulation candidate screening, selection and characterisation and, in generic product development, for bioequivalence testing. As lower-cost alternatives to, for example, in vivo approaches, and potentially more informed alternatives to next-generation impactor studies, the authors argue that the ANN and tissue model methods presented here could be usefully employed early in the development process.

Pulmonary and nasal drug delivery is on the rise. Innovations from pharmaceutical companies and device developers alike are helping to drive innovation in drug delivery via the inhalation route. The pulmonary delivery market is projected to be worth US$44 billion (£26 billion) by 2016 with a CAGR estimated at 14.3% over the next two years until then (BCC Research, 2012).

There have been a number of new drug advances recently. For example GSK has received US FDA approval for its new COPD product, the dual bronchodilator Anoro Ellipta (umeclidinium + vilanterol). This is predicted to be a major blockbuster for the company with projected annual sales of $3 billion to 2019, according to Thomson Reuters. This is in addition to last year's FDA approval of Breo Ellipta (vilanterol + fluticasone furoate), another COPD product, which analysts believe will achieve $2.22 billion in annual sales by 2018 (Thomson Reuters). AstraZeneca is continuing to push the boundaries with the development of a nasal vaccine for four strains of the influenza virus for nasal delivery. It won EU approval for the product at the close of 2013. Finally, MannKind's efforts to bring an inhaled insulin product to the market have had those in the field sitting up and taking notice. The list of companies whose programmes were terminated in this area is a long one, and success for MannKind may re-invigorate research efforts despite the failure of Pfizer's Exubera.

For a long time, one of the challenges of delivering medicines by the inhalation route has been ensuring patient compliance. Incorrect inhaler techniques, sub-optimal devices, and over and under use of medications are all cited as major compliance problems. Only 40-60% of COPD patients are reported to stick to the correct dosing regimen and only 10% of asthma patients perform all steps correctly when using a pMDI.[1] To combat this, device developers and manufacturers have been steadily improving the design of delivery devices. For example, installing dose-counters on pMDIs allows patients to see when they need to ask for a new inhaler, whilst improved hand-held nebulisers benefit the end-user by providing a more user friendly and convenient device.

The growing healthcare burden in many developed countries is also encouraging growth in the inhalation generics field. With a number of patent expiries looming, initiatives are in place to boost the progress of these medications to market, through changes to regulatory requirements. Recently the FDA relaxed its stance on the need for lengthy clinical trials for generic versions of the GSK product Advair (fluticasone propionate + salmeterol xinafoate) in order to show bioequivalence; an often challenging hurdle for companies. Still, the cost of bring-

**Jo Muddle**
MedPharm & KCL PhD Student

**Professor Clive Page**
Professor of Pharmacology
Head of Sackler Institute of Pulmonary Pharmacology

**Professor Marc Brown**
Chief Scientific Officer & Chief Operating Officer
T: +44 1483 457580

**MedPharm Ltd**
R&D Centre
Unit 3 / Chancellor Court
50 Occam Road
Surrey Research Park
Guildford, GU2 7AB
United Kingdom

**www.medpharm.co.uk**

ing a generic to market may easily run into the tens of millions of dollars, thus innovations in research and development tools are required to reduce this financial burden and to encourage generic and NCE airway product development. Such innovations should also reduce the inherent risk within R&D work by mitigating the chance of later stage attrition.

## ARTIFICIAL NEURAL NETWORKS

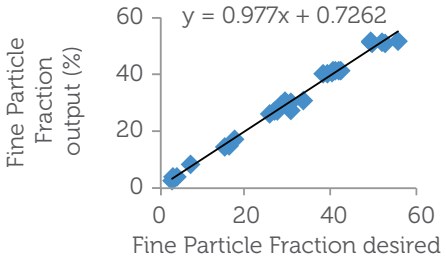
MedPharm is pioneering this effort and offers the full range of API characterisation and selection, device selection, biological testing, formulation development, *in vitro*, *in vivo*, preclinical and clinical testing services and GLP/GMP supplies to its clients to aid their developmental programmes.

Innovation in research techniques and tools is ongoing within the company and whilst techniques such as API and excipient characterisation, formulation development, and next-generation impactor (NGI) testing are routine for the company, new services are also made available to clients. For example, MedPharm has developed a new *in silico* model based on artificial neural networks (ANN) to enable early selection of the most promising APIs and formulations to take forward into testing, a technique that is already creating a stir at industry conferences.

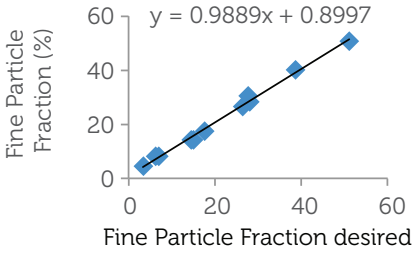
ANNs have been widely recognised as powerful pattern recognition tools in areas such as forecasting finance and medical diagnosis. In addition, ANNs have been shown to be beneficial when analysing drug delivery in the pharmaceutical science area. For example ANNs have been used to predict drug delivery to the lungs *in vivo*. Nazir and colleagues reported the use of ANNs in this context using a variety of input factors: different breathing patterns; particle size; mass median aerodynamic diameter (MMAD); and geometric standard deviation, to predict the aerosol particle deposition in the different regions of the lung.[2,3] De Matas and colleagues used ANNs to predict a variety of pharmacokinetic (PK) responses for delivering inhaled drug into human lungs using similar input variables as Nazir's studies.[4-6] Both groups showed the success of using ANNs to predict the pharmacodynamic (PD) and PK effects of delivering drug to the lungs, albeit with a dataset of limited size.

Although ANNs have been used to predict *in vivo* outcomes from *in vitro* data, ANNs have not yet been reported as a means of predicting impactor data, from an NGI for example, or the parameters that can be derived from these studies (i.e. MMAD, fine particle fraction (FPF) and emitted dose). Recently, MedPharm has been able to show the feasibility of using different formulation and device characteristics to predict drug deposition *in vitro* (Figure 1).[7] The next stage of assessing the viability of using ANNs to predict FPF will be to test a larger dataset with a variety of different DPIs and APIs.

A) Training set
Mean Squared Error – 2.300%
Normalised Mean Squared Error – 0.010%
Mean Abs Error – 1.133%
Min Abs Error – 0.044%
Max Abs Error – 4.091%
R - 0.995




B) Cross Validation set
Mean Squared Error – 1.763%
Normalised Mean Squared Error – 0.009%
Mean Abs Error – 0.976%
Min Abs Error – 0.037%
Max Abs Error – 2.989%
R - 0.997




C) Test set
Mean Squared Error – 5.190%
Normalised Mean Squared Error – 0.052%
Mean Abs Error – 1.904%
Min Abs Error – 0.233%
Max Abs Error – 4.182%
R - 0.979

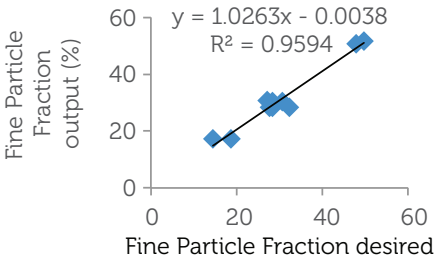



**Figure 1: Errors and the $R^2$ value produced for the multilayer perceptron ANN for the training set, where the ANN is trained to minimise errors between the desired output and expected output from: (A) known data, (B) cross validation set, and (C) test set. "FPF desired" is the actual FPF value generated from the NGI studies. This is compared with "FPF output"; the FPF predicted by the artificial neural network.**

The studies so far have been promising and have shown ANNs as a viable technique for predicting the output of NGI. In the future ANNs, with ongoing innovations and progress in this area such as those occurring at MedPharm, could be used instead of NGIs to predict the drug deposition of new inhalers, with NGIs employed only for quality control and confirmation purposes. In the nearer term, ANNs could certainly provide a method for formulation screening, prior to the commencement of costly NGI studies.

## MEDPHARM CSO PROFESSOR MARC BROWN ELABORATES:

*In silico* modelling is a growing area of research in pharmaceutics. Many different *in silico* methods have been used to help speed up production of inhaled products, including techniques such as Box Behnken and the Taguchi method. ANNs are another prediction tool that can be used to select the best API formulation candidates to take forward into testing and optimisation, reducing costs in the already expensive process of new product development. Overall, there is a vast range of *in silico* models that can be used to speed up the process of developing a formulation and cut the risk of attrition at a later stage by eliminating poorly performing formulations before they are taken forward into more expensive and time consuming studies.

## TISSUE MODELS

In addition to ANN, MedPharm is currently developing tissue models to allow PD activity of inhaled products to be examined. These models are particularly useful in the process of showing PD bioequivalence when developing a generic product. Currently, there are few bioequivalence tests that are accepted by the regulatory authorities. One of these is the NGI assay, which maps where the formulation is deposited.[8] However

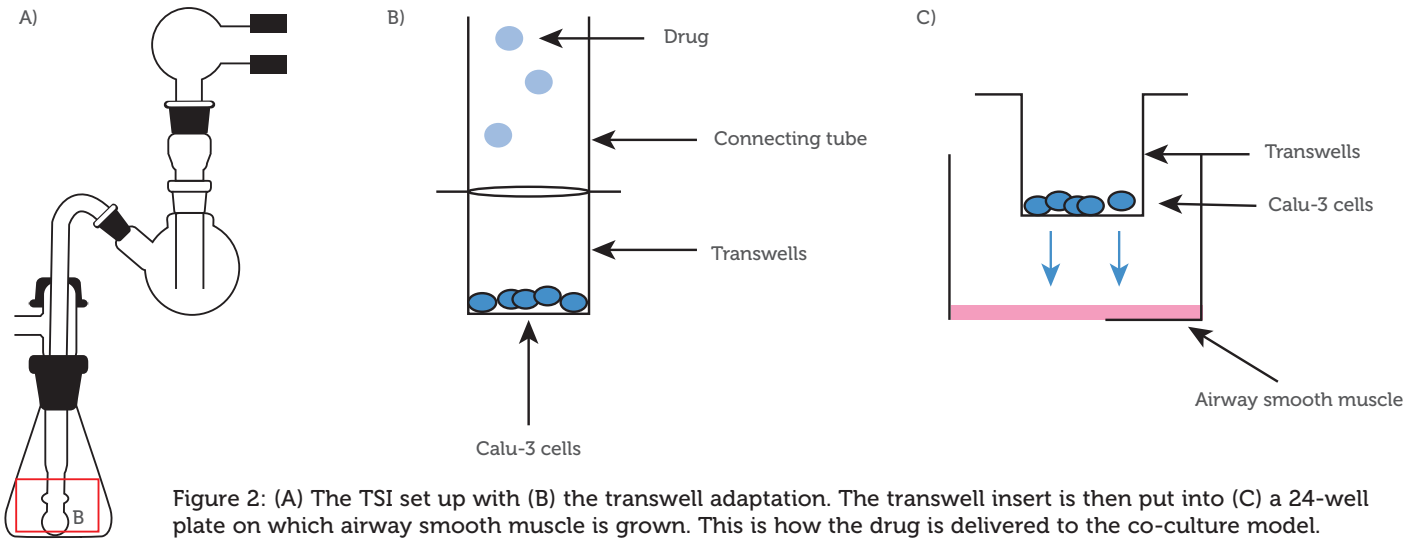



Figure 2: (A) The TSI set up with (B) the transwell adaptation. The transwell insert is then put into (C) a 24-well plate on which airway smooth muscle is grown. This is how the drug is delivered to the co-culture model.

NGIs do not examine whether the delivered formulation is biologically active at the site of deposition. At present, studies examining the PD and PK abilities of a drug are *in vivo* studies, which are often very costly and time consuming. MedPharm is providing a solution to this gap in the market that will enable its clients to generate vital data without the need for theses *in vivo* studies.

The basic model itself is a co-culture model which can be used to test bioequivalence between inhaled products. To date, work has involved using Twin stage impingers (TSIs), used to deliver potentially respirable powders with an aerodynamic diameter of less than 6.4 µm, onto Calu-3 epithelial cells grown on an air liquid interface.[9] Drug flux across the epithelial layer can then be analysed. This study has highlighted the feasibility of using this kind of method to assess formulation performance *in vitro*. Indeed, some of the FITC-dextran weights measured *in vitro* successfully correlated to *in vivo* canine pulmonary clearance. MedPharm is taking its model one step further by developing the co-culture model to allow measurement of the drugs' biological activity once absorbed. The novel model allows the delivery of the formulation, via TSI or NGI, to the Callu-3 cell epithelial layer, beneath which is a cultured layer of airway smooth muscle, allowing assessment of the PD activity of any drug that has been delivered (see Figure 2). This allows absorption, deposition and PD activity to be assessed at the same time.

In combination, all of MedPharm's models can be used to look at the efficacy and the *in vitro* performance of the inhaled formulation. This will help in candidate and formulation selection and provide a better model for bioequivalence testing. In addition, these techniques may also help to give a clearer picture of what happens in the lung without having to undertake *in vivo* studies.

Advances in R&D tools such as these, whilst perhaps not revolutionising the development process, will certainly help reduce costs and the time taken to bring a product to market. Risks can be minimised in a process early on.

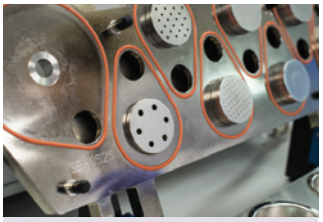
Described here are just two such advances in technology; and as part of MedPharm's contract services, the company offers the full range of services needed to take inhaled, as well as API formulations for transdermal and topical (skin, nasal, ophthalmic, buccal and mucosal) delivery, through formulation development, testing and clinical trial material manufacture.

MedPharm prides itself on developing novel research tools such as *in vitro* efficacy models and *ex vivo* toxicity assays to aid its clients' programmes. With hundreds of worldwide clients, and experience of helping to bring numerous products to market, including DPIs, pMDIs and nebulisers, as well as a host of other topical and transdermal products, the company comprises a highly experienced team, leading the field. As development companies increasingly look to take advantage of strategies to reduce risk and cost, innovative contract research and manufacturing companies such as MedPharm, who can offer turn-key solutions, are in a strong position to assist.

## REFERENCES:


1. *Restrepo et al, "Medication adherence issues in patients treated for COPD". Int J Chron Obstruct Pulmon Dis, 2008, Vol 3(3), pp 371–384.*
2. *Nazir et al, "Artificial neural network prediction of aerosol deposition in human lungs". Pharm Res, 2002, Vol 19(8), pp 1130-1136.*
3. *Nazir et al, "Artificial neural network prediction of the patterns of deposition of polydisperse aerosols within human lungs". J Pharm Sci, 2005, Vol 94(9), pp 1986-1997.*
4. *De Matas et al, "Predicting the clinical effect of a short acting bronchodilator in individual patients using artificial neural networks". Eur J Pharm Sci, 2010, Vol 41(5), pp 707-715.*
5. *De Matas et al , "Evaluation of an in vitro-in vivo correlation for nebulizer delivery using artificial neural networks". J Pharm Sci, 2007, Vol 96(12), pp 3293-3303.*
6. *De Matas et al, "Evaluation of in vitro-in vivo correlations for dry-powder inhaler delivery using artificial neural networks". Eur J Pharm Sci, 2008, Vol33(1), pp 80-90.*
7. *Muddle et al, "Modelling of In Vitro Deposition of Respirable Powder Formulations Using Artificial Neural Networks". Drug Delivery to the Lungs 24 Conference, Edinburgh, Scotland, UK, 2013.*
8. *European Medicine Agency, "Guideline on the requirements for clinical documents for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatments of asthma and chronic obstructive pulmonary disease (COPD) in adults and for the use in the treatment of asthma in children and adolescents". 2009.*
9. *Grainger et al, "The permeability of large molecular weight solutes following particle delivery to air-interfaced cells that model the respiratory mucosa". Eur J Pharmaceutics Biopharmaceutics, 2009, Vol 71(2), pp 318-324.*

# MEDPHARM – AIRWAY FORMULATION DEVELOPMENT EXPERTS



- Inhaled formulations
- Dermatologicals and Cosmetics
- Transdermal Delivery
- Topical/Mucosal delivery
- Medical Device Testing

**The Specialist CDMO** for your formulation design, *in vitro* performance testing & clinical supplies manufactured in our own UK based cGMP facility.

**Chancellor Court**
**50 Occam Road**
**Guildford Surrey**
**GU2 7AB UK**
Phone:
**+44 (0)1483 457580**
Email:
**busdev@medpharm.co.uk**

**MedPharm is a highly experienced team of pharmaceutics, formulation development and drug delivery experts.** We have helped the very largest down to the youngest companies to formulate their actives in to effective, safe, and stable inhaled, topical & transdermal formulations. We offer a fully integrated service for development with projects ranging from feasibility studies, formulation development & design optimisation through to preparation of cGMP clinical supplies.

---

MedPharm develop formulations and test devices and formulations for:
■ pMDI/MDI ■ DPI ■ Nebulisers ■ Nasal Delivery

---

- Established 1999
- More than 150 clients worldwide
- 19 formulations now marketed products
- GLP and GMP compliant
- *In Vitro* performance testing laboratories
- Excised tissue, cell culture, RHE and synthetic membrane models
- Proprietary tools designed to reduce development costs

**www.MedPharm.co.uk**

MedPharm

Powered by

**partneringONE®**

**PartneringONE®**, the most successful and highly regarded partnering tool in the market will be at Drug Delivery Partnerships Europe

# DRUG DELIVERY PARTNERSHIPS™ EUROPE

**17 – 18 September 2014**
**Radisson Blu Hotel Hamburg | Hamburg | Germany**

## *Collaborating to drive innovation in drug delivery*

- ✓ **Creating sustainable innovation and value in drug delivery**
- ✓ **Overcoming small molecule delivery challenges**
- ✓ **Advancing the delivery of biologics**
- ✓ **One-to-one networking powered by partneringONE®, the leading conference networking solution for the life sciences**

**partneringONE®**

### FEATURING REPRESENTATIVES FROM:

- **Pfizer**
- **Novartis**
- **Bayer**
- **F. Hoffmann La Roche AG**
- **Medimmune**
- **Lundbeck**
- **Fresenius Kabi**
- **Ipsen**
- **Merck**
- **GlaxoSmithKline**
- **Boehringer Ingelheim Pharma GmbH & Co. KG**

### KEY SPEAKERS:

**Anand Subramony,** Vice President Drug Delivery & Device Development, **Medimmune,** USA

**Keith Horspool, PhD** Vice President, Pharmaceutical Development, **Boehringer Ingelheim,** USA

**Mark McAllister,** Research Fellow, **Pfizer** Deputy Project Co-ordinator, **OrBiTo,** UK

**Andy Lewis,** Director Novel Delivery Technologies, **Ipsen,** France

**Prof. Dr. Claus-Michael Lehr,** Head, Dept. of Drug Delivery (DDEL), **Helmholtz-Institute for Pharmaceutical Research Saarland (HIPS),** Germany

Sponsored by Aptar pharma | HOVIONE

In Association with CRS Leading Delivery Science and Technology

Partnered by ON drugDELIVERY

**www.informa-ls.com/DDP**

**Please quote VIP Code CQ5233ODD when registering**

ONdrugDELIVERY

# ONdrugDelivery 2014/15 EDITORIAL CALENDAR

| Publication Month | Issue Topic | Materials Deadline |
|---|---|---|
| September | Prefilled Syringes | August 4th |
| October | Drug Formulation & Delivery, Services & Solutions | September 15th |
| November | Pulmonary & Nasal Drug Delivery (OINDP) | October 13th |
| December | Delivering Biotherapeutics | November 10th |
| January 2015 | Ophthalmic Drug Delivery | December 8th |
| February 2015 | Prefilled Syringes | January 12th |
| March 2015 | Transdermal Patches, Microneedles & Needle-Free Injection | February 3rd |
| April 2015 | Pulmonary & Nasal Drug Delivery | March 2nd |
| May 2015 | Injectable Drug Delivery: Devices Focus | April 13th |
| June 2015 | Novel Oral Delivery Systems | May 4th |
| July 2015 | Wearable / Bolus Injectors | June 1st |

# RESPIRATORY DRUG DELIVERY (RDD) 2014

## Fajardo, Puerto Rico, May 4-8, 2014

**Respiratory Drug Delivery® celebrated its 25th Anniversary** at the El Conquistador Resort in Fajardo, Puerto Rico, from May 4 to May 8, 2014.

RDD 2014 addressed contemporary science associated with inhaled drug products and other pharmaceuticals utilising non-aqueous and aqueous liquids, dispersions and solids which are of interest to many in our international audience. This year's conference attracted approximately 500 participants, representing 29 countries. Just over half (54%) came from the US and Canada, 36% from Europe and the remaining 10% from the various other territories including India, Australia and South America. Approximately 80% of attendees reported working for pharmaceutical companies or their suppliers while the remaining 20% were from academia and regulatory authorities.

### CHARLES G THIEL AWARD

The organisers of the meeting and Virginia Commonwealth University were honoured to award the 2014 Charles G Thiel Award, endowed at VCU by 3M Drug Delivery Systems, to Dr Dieter Hochrainer. The award recognises outstanding research and discovery in respiratory drug delivery. Dr Hochrainer played significant roles in the development at Boehringer Ingelheim of both the Handihaler® (the first DPI to replace gelatin with polymeric capsules thereby improving performance) and Respimat® (with its unique spray duration, patient interface and nozzle design). Dr Hochrainer's leadership of development teams working on both platforms led directly to clinical improvements in many patients suffering from COPD. He has also served the scientific community, both as Editor-in-Chief for the *Journal of Aerosol Science* and as an editorial board member for Journal of Aerosol Medicine, while representing Boehringer Ingelheim on international consortia and working groups to benefit aerosol science and respiratory drug delivery. Dr Hochrainer's peers said of him, "He combines the ingenious developer and the benevolent scientist in one person; he is the German Charlie Thiel!"


### CONFERENCE SPEAKERS

Dr Yvonne Huang, Associate Director, UCSF Adult Cystic Fibrosis Program (University of California, CA, US) delivered the plenary lecture, entitled: "The Microbiome and Airway Disease: Role in Pathogenesis, Presentation and Response to Treatment". Other renowned speakers offered their insight in the areas of airway pathogens, aerosols and immunologic homeostasis; inhaled product safety; optimising nasal and pulmonary formulations; accessing emerging global markets; PK and PD evidence for inhaled corticosteroids; device design; advances in testing and manufacturing science and *in vitro* testing.

At the request of delegates attending previous meetings the "*Posters on the Podium*" session was expanded allowing more of the latest research in pulmonary and nasal delivery to be shared with the entire audience.

Andy Clark led a discussion on realistic *in vitro* testing which debated the selection of mouth throat models and breathing profiles directed towards improved IVIVCs. The session was audio-recorded and will be made available by the organisers later in the year.

### POSTER & TECHNOLOGY EXHIBIT

The Scientific Poster Session and Technology Exhibition received excellent reviews for providing two days of effective scientific and commercial networking facilitated by serving lunch and refreshment breaks in the exhibition space. In addition, a Silver Anniversary Wine and Cheese Reception on Monday evening provided time for viewing more than 100 posters and 80 exhibitor tables.

### CONFERENCE PROCEEDINGS

Peer-reviewed speaker papers and poster abstracts were made available in print or electronically, according to delegate preference, and during the conference via a dedicated conference website. Hard copies of the RDD 2014 proceedings can be purchased at www.rddonline.com, which also houses the searchable database of papers from RDD 2014, and past meetings. Also available are links to aerosol testing equipment for sale, educational presentations, job postings and a calendar of events relevant to the aerosol scientist or manager.

### ACKNOWLEDGMENTS

The organisers thank the presenters, exhibitors, sponsors and all those in attendance who make the annual Respiratory Drug Delivery series a success. We encourage you to attend future conferences and consider sponsoring individual events or the conference in general so we can continue to showcase cutting-edge science from international opinion leaders.

*Our next meeting is RDD Asia 2014, to be held in Goa, India, November 12-14, 2014. RDD Europe 2015 will be held in Nice, France, May 5-8, 2015. Both meetings offer invited speaker, poster, exhibition, workshop and sponsorship opportunities.*

Please visit www.rddonline.com for deadlines and details, or contact info@rddonline.com with programming or speaker suggestions.

PLEASE MARK YOUR CALENDARS AND PLAN TO ATTEND!

# RDD ASIA 2014

## Respiratory Drug Delivery

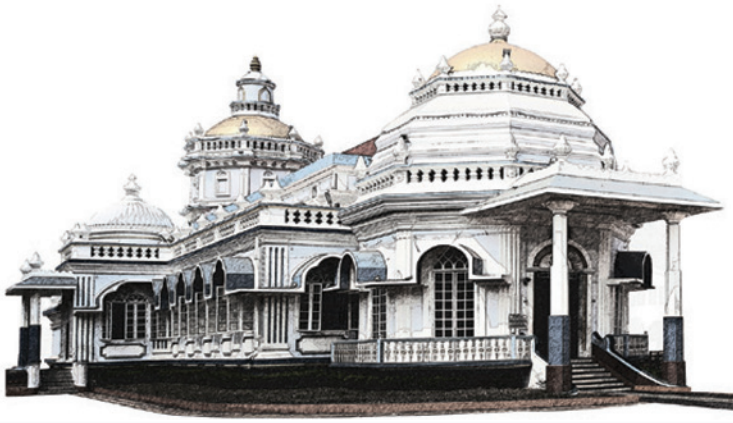
**NOVEMBER 12-14, 2014**

Goa Marriott Resort & Spa

Goa, **INDIA**

**Poster Abstract Submission**
**Deadline: June 30, 2014**

**For more information visit**
**www.rddonline.com/rddasia2014**



**RDD Asia is a conference jointly organized by**

RDD Online
Respiratory Drug Delivery

Aptar pharma

HOSOKAWA MICRON GROUP

# FORMULATION METHODS & SIZE REDUCTION FOR INHALERS

In this summary article, Bert Dekens, Team Manager, Pharma, Hosokawa Micron, highlights the importance of achieving the correct particle sizes, both for the API and the carrier (which are each required at different sizes) in formulations for inhalation, and describes some of the available equipment most suited to specific tasks.

Dry-powder inhaler formulations typically comprise a combination of a carrier substance with the active pharmaceutical ingredient (API). Sometimes additives are required to enhance the product properties, such as flowability, or to support the mechanical bonding of carrier with API.

The carrier material, often lactose, represents a high proportion of the final product and is often required to be of coarser particle size in the range of 40-200 µm. The API is only a small percentage of the inhalable formulation and needs to be of finer particle size, mostly in the single micron range.

APIs are very often cohesive, poorly flowing powders and sometimes a really tight particle size distribution is required. Special attention has to be paid to the amorphous content of the API.

> "API is blended with carrier particles which are prepared to have a defined surface area and surface energy"

Like in any another drug production, the actual manufacturing process, including crystallisation and drying cannot be sufficiently controlled and influenced to achieve the required particle size. Additional steps – in some cases only de-agglomeration after the dryer or real grinding – needs to be done to get the right particle size for inhalation.

Particle size is cited as being the single most important design variable of a DPI formulation.[1]

When choosing suitable milling equipment, it is necessary to characterise the different powders that are to be processed. Product properties such as hygroscopicity, flow properties and bulk density, among others, influence which types of mill are suitable.

## API

### Spiral Jet Mills

The most common jet mill used in pharmaceutical industry for micronisation of fine particles is the spiral jet mill or pancake mill. The particles fed to the grinding chamber are accelerated by the high gas flow (typically in the range of 4-8 bar g) and particles are crushed by collision with each other as well as partly at the walls of the grinding chamber. Due to the fact that there are no movable parts, no drives etc, they are relatively easy to inspect and clean. In general, jet mills do not create heat during grinding which is advantageous since many pharmaceutical powders are heat sensitive. Due to the above points, maintenance of these mills, and operation under contained conditions, are simple.

Spiral jet mills come in many sizes, depending on required capacities or batch sizes.

### Opposed-Jet Mills

Alternatively the opposed-jet mill (see Figure 1) can be used, whereby product is fed to the mill gravimetrically and falls into the grinding chamber. There the particles get accelerated by the fast gas stream and grinding takes place by particle to particle collision.

The ground particles are offered to the integrated air classifier. The air/gas flow has to go through the shown lamellas. The particles are subject to two forces. The

**Mr Bert Dekens**
Team Manager, Pharma
T: +31 (0) 314 37 33 33
F: +31 (0) 314 37 34 56
E: b.dekens@hmbv.hosokawa.com

**Hosokawa Micron BV**
Gildenstraat 26
7005 BL Doetinchem
The Netherlands

**www.hosokawamicron.nl**


Figure 1: The 280 AFG Fluidized Opposite-Jet Mill.

drag force of the air – and the centrifugal force of the classifier wheel. Fine particles rise with the air whereas coarse particles are rejected by the classifier and drop back into the mill. High classifier speed means fine end product, low speed means coarser product. These classifiers are typically most suitable for particle sizes in the range 5-150 µm (Figure 2).

## CARRIER

The carrier material is often lactose. To achieve the required properties such as the optimum flowability, the particle size distribution – for the carrier as well as for the API – is crucial. Depending on the type of applicator, the optimum fineness might be in the range of 40 µm or can be up to 200 µm. A high

Figure 2: The 200 ZPS Classifier Mill.

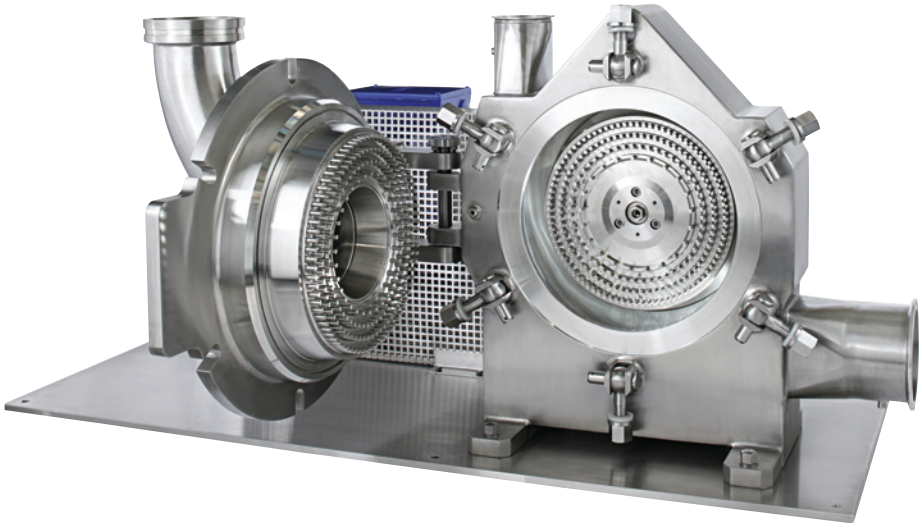


Figure 3: 315 UPZ Fine Impact Mill, Pharma Execution.

content of fine dust is normally not allowed and therefore the production of the carrier is often a combination of milling, classifying and sometimes blending steps. The fact that the carrier material is mostly coarser than the API requires typically a different mill type.

The difference between the different fluid energy impact mills used for the API compared with those used for the carrier is that the speed to which the carrier particles are accelerated is much lower, therefore the achieved particle size is coarser.

Those mills are suitable for medium-range finenesses and the advantage is that they can be equipped with a number of different grinding tools suitable for different products and requirements.

As an example, pin mills are used for fine grinding of lactose. Typical finenesses are around 300 µm and the typical maximum fineness with lactose is around 90% <75 µm.

When steeper particle size distribution or higher-end fineness is required, an impact mill with an integrated air classifier might have advantages (Figure 3).

The fact that no significant amount of fine dust is allowed very often leads to a second classifying step to remove the very fine end of the particle size distribution. The principle is more or less the same. The material is gravimetrically fed to the classifier from the side or from the top. There is an airflow created by a blower. The feed material will be dispersed in air/gas and then offered to the classifier. Coarse material will be rejected and will drop to the bottom where the coarse fraction (in this case the final product) is collected. The fine fraction will leave the classifier and is separated at a filter.

> "The flowability of the formulated material, as well as the fluidisation properties together with the entrainment and separation characteristics determine the physical behaviour of the formulation in the inhaler"

As we have seen with the jet mills, a typical mechanical impact mill can also be combined with an air classifier. The operating principle is similar.

## FORMULATION

The finely ground API is blended with carrier particles (excipients) which are prepared to have a defined surface area and surface energy. To achieve an even layering of API particles, an appropriate blender with the correct operational parameters needs to be selected (Figures 4 & 5). This allows for the proper handling (transportation, storage and dosing) of the API's,

Figure 4: High-Shear Blender, Five Litre Cyclomix, Pharma execution.

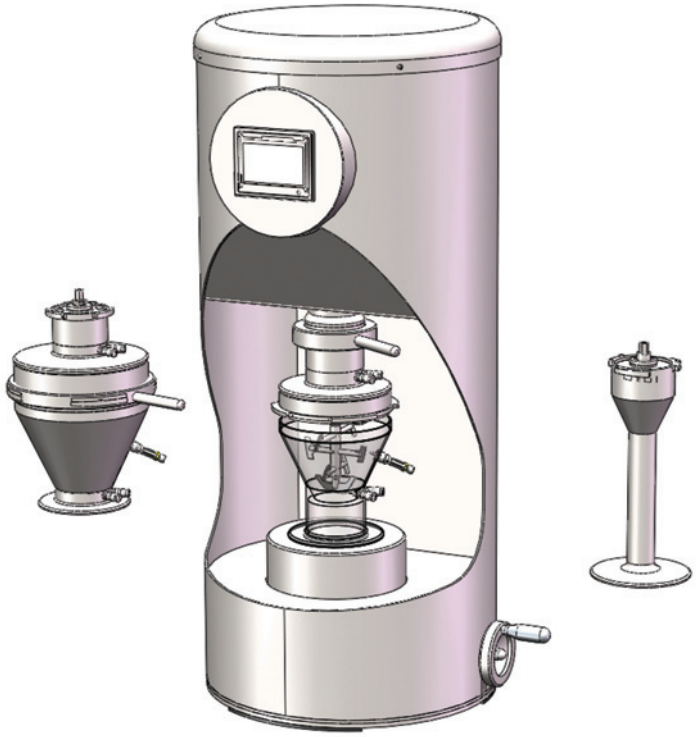


Figure 5: Lab-Scale High-Shear Blender with Exchangeable Product Bowls.

which is typically a cohesive powder and normally fairly difficult to work with, especially in the smaller quantities needed.

Phenomena related to the interaction between the carrier particles and the API play an important role in the final quality of the product. The blending properties and surface characteristics of the carrier particles will affect the bonding between API and the carrier. The flowability of the formulated material, as well as the fluidisation properties together with the entrainment and separation characteristics determine the physical behaviour of the formulation in the inhaler device.

In order to obtain the right formulation a balance has to be found between the sufficient mixing energy required to disperse the API, as single particles within the bulk carrier particles. On the other hand the mixing energy cannot be too high since this could lead to possible damage of the carrier particles resulting in undesirable variations in the product characteristics.

Similarly the bonding of the API particles onto the surface of the carrier particles has to be sufficiently strong to form a stable formulation. Just as above with the mixing, the bonding strength has to be such that while providing the proper handling characteristics it also needs to be capable of releasing the API while being inhaled in order for the API to be delivered as required.

Hence this will necessitate a dedicated mixing process as well as a proper selection and manipulation of the powder properties associated with the DPI formulation. The overall mixing mechanism takes care of the distribution of one component within the other. Key here is to be able to transport particles throughout the mixture. Optimal mixing is achieved when the different components can randomly be distributed.

To summarise, the advantages of a high intensity impact and shear mixer include:

- Perfect dispersion of fines due to the combination of impact and shear mixing
- Accurate temperature control with jacketed vessels
- Rounding-off or densification of particles possible
- Single layer coating achievable
- Create homogeneous mixture without lumps
- Reproducible processes
- With the conical design vessel, filling rates between 30-100%
- Full discharge through the central bottom discharge valve
- CIP and SIP able designs

## CONCLUSION

In conclusion we have reviewed the different technologies available for the size reduction of API and carrier particles as well as mixing technologies available for proper formulation of the final DPI product.

## REFERENCE

*1. Telko MJ, Hickey AJ, "Dry-Powder Inhaler Formulation". Resp Care, 2005, Vol 50(9), pp 1209-1227.*

# GENERIC PMDI PRODUCT DEVELOPMENT FOR THE US: KEY CONSIDERATIONS

In this technical paper, Badre Hammond, Associate Director, Business Development, Next Breath, highlights key considerations and addresses strategies that are believed to reduce risk and ultimately speed up the process for getting a generic pMDI product to the US market. The paper will focus on the key considerations and a stepwise approach that we believe are critical in managing the complexities and unknowns around the development of generic pMDIs.

## RATIONALE AND INTRODUCTION

Currently there are no generic asthma/COPD inhalers available in the US. This includes both categories of standard asthma treatment: rescue medication for quick relief and controller medications for long-term prevention. The average cost of these inhaler medicines ranges from US$35-$300 (£21-£180), rendering the treatment expensive for both insured and uninsured consumers.

In April 2013, the US FDA issued a draft guidance for albuterol sulphate.[1] Prior to this, generic companies were reluctant to invest in product development that ultimately may not be acceptable to the FDA. Nonetheless, many pressurised metered dose inhalers (pMDIs) are now approaching patent expiration, and the opportunity is ripe for generics companies wishing to be the first to market and to grab a slice of the US$5 billion pie.

## API SELECTION AND EXCIPIENTS

Selecting the proper API and excipients is a key consideration that must be made very early in the ANDA process. Ensuring that the selected API and excipients are comparable to the marketed Reference Listed Drug Product (RLD) is fundamental to achieving *in vitro* bioequivalence (IVBE). A generic formulation must be qualitatively and quantitatively similar to the RLD, which means that the API dose is identical to the label claim of the RLD and the excipient levels in the generic formulation are ±5% of the RLD concentrations. During API/excipients selection, ANDA applicants should source the API from multiple suppliers that have a proven track record of supplying APIs to products in regulated markets. Determination of the correct particle size of the API is critical for suspension pMDIs and will affect IVBE outcomes. The applicant should also request the manufacturer of the drug substance to provide pertinent chemistry, manufacturing, and controls information. Insuring that there is a DMF available (DMF; 21CFR 414.20) for the formulation components is an important step in the selection process.

In addition, a Certificate of Analysis should be requested to substantiate that the batch meets all tests and specifications. Where applicable, the API and excipients must adhere to USP monograph/National Formulary guidelines. Following evaluation of the documentation from the API manufacturer, ANDA applicants should perform a comprehensive screening study of the selected API at their own facility. The goal of this screening study is to confirm that the results generated on-site match the vendor's Certificates of Analysis. This confirmation step may appear trivial or redundant on the surface, but it can and has been a source of many delays, surprises, and wasted resources when the vendor's API specification cannot be reproduced when tested independently.

**Mr Badre Hammond**
Associate Director,
Business Development
T: +1 443 543 5809
E: badre.hammond@nextbreath.net

**Next Breath, LLC**
1450 South Rolling Rd
Baltimore
MD 21227
United States

**www.nextbreath.net**

Figure 1. pMDI using Landmark® Dose Indicator. (Image courtesy of Aptar Pharma, reproduced with kind permission.)

## CONTAINER AND CLOSURE SYSTEM

Unlike most dosage forms that contain formulations in simple packaging systems, pMDIs have unique features; a pMDI, for example that shown in Figure 1, consists of a container, a valve, an actuator (mouthpiece), and the formulation with a highly volatile propellant packaged under pressure. Some pMDIs also incorporate dose counters. The manufacturing process, packaging, and dispensing components play as much of a critical role in the overall success of the product as the formulation itself. These components collectively constitute the drug product that delivers the drug substance in the desired physical form to the biological target.[2] Therefore, all components of the pMDI design warrant a thorough consideration regarding chemistry, manufacturing, and controls and *in vitro* performance. These complex and subtle interactions between the drug substance, excipients, container closure system, and simulated patient use conditions can all have a significant impact on the *in vitro* BE of the Test product to the RLD of the marketed pMDI.

Following a thorough patent examination of the RLD of interest (these are generally available in the FDA's list of Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as The Orange Book), ANDA applicants should engage device vendors early in the development process. This is particularly critical for selecting the metering valve and actuator components given their impact on the aerosolisation and particle size distribution of the drug product. ANDA applicants should ensure that all necessary information for the Container Closure System is provided, including schematic drawings, full descriptions, chemical compositions, regulatory status, and in-house tests and specifications for acceptance or rejection of the aerosol can, actuator, actuator dust cap, and metering valve [21 CFR 211(Subpart E)].[3] This information is typically contained in the Drug Master File (DMF) from the packaging supplier or device supplier and should be referenced appropriately in the regulatory submission.

The FDA CDER's Division of Bioequivalence recommends that the ingredients used in the formulation should be qualitatively identical and quantitatively as close as possible to those of the reference product.[3] In addition, if the RLD pMDI contains a dose counter, the generic equivalent must also have a dose counter.[1] The valve and actuator of the RLD product may be proprietary to the innovator and, as a result, unavailable to ANDA applicants. The Division therefore recommends that the generics companies assure functional equivalence of test and RLD products through both *in vitro* and *in vivo* testing.[2]

In the early engagement process with device vendors, ANDA applicants should request vendors (some of which also supply the innovator) to provide alternative pMDI components that are comparable to the RLD device. They should also request data that supports the selection of the alternative test components. Device vendors that understand this paradigm have begun to generate preliminary data using their proposed generic alternatives to the RLD and may be able to provide them to ANDA applicants upon request.

## IN VITRO BE TESTING REQUIREMENTS

ANDA applications are required to demonstrate that the proposed generic product is pharmaceutically equivalent [21 CFR 320.1 (c)] as well as bioequivalent [21 CFR 320.1 (e)] to the RLD.[3] One of the key aspects to approval of generic drug products in the US, including locally acting orally inhaled drug

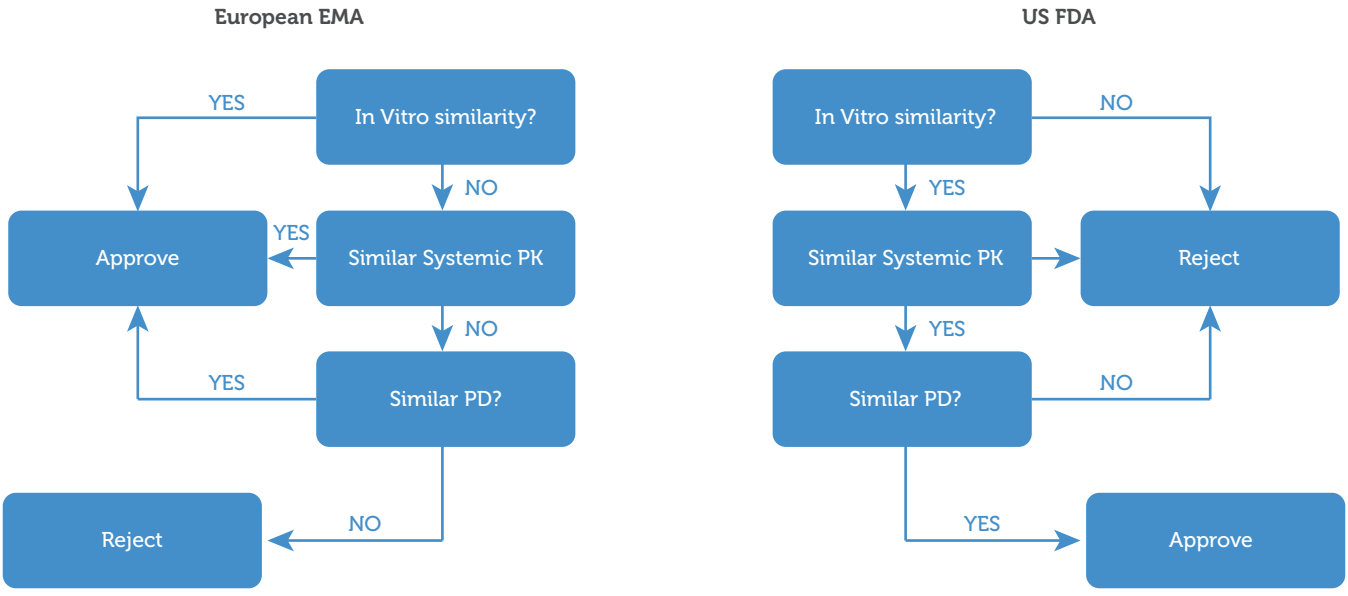



Figure 2: Flow charts comparing EMA and FDA decision processes for assessing IVBE of OIDPs. (Image adapted from Adams et al.[2])

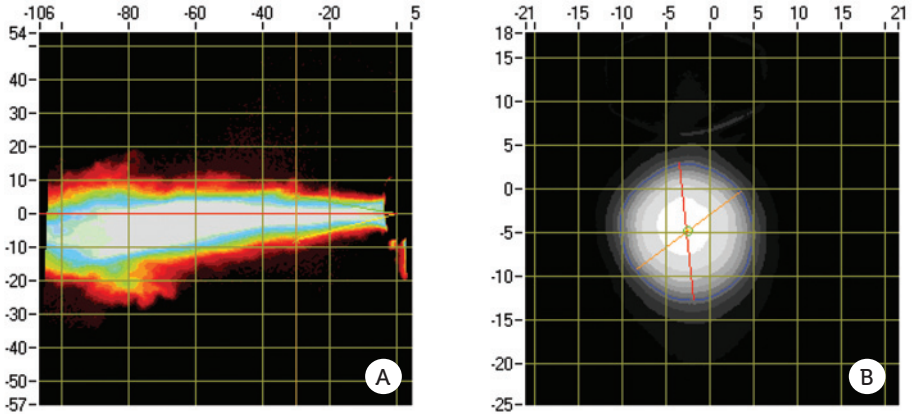



Figure 3: pMDI plume Geometry (A) and Spray Pattern (B) as visualised using Proveris' SprayView® (Image courtesy of Proveris Scientific, reproduced with kind permission.)

products (OIDPs), is the demonstration of *in vitro* and *in vivo* BE. The current US FDA approach for establishing BE of OIDPs is based on an aggregate weight of evidence.[5] It utilises *in vitro* studies to demonstrate equivalent *in vitro* product performance, PK studies to establish equivalent systemic drug exposure, and PD studies or clinical endpoint studies to support equivalence in local drug delivery.[3] It is important for ANDA applicants to ensure that the submission is aligned with the expectations of international regulatory agencies outside of the US. Different regulatory agencies have different recommendations for achieving BE. Figure 2 illustrates the different approaches between the European Medicines Agency (EMA) and the FDA to an ANDA application for OIDPs.[3]

The FDA approves pMDIs as specific combinations of formulation and device. Each of the major components, including specific formulation (propellant and concentrate), and container and closure system (valve, actuator, and container) contributes to the biopharmaceutical performance of the product. In the 2013 draft albuterol guidance, the key metrics for *in vitro* comparison are single actuation content uniformity (SAC), aerodynamic particle size distribution (APSD) by impaction methods, spray pattern, plume geometry and prime/reprime. Images of spray pattern and plume of geometry of a typical pMDI are presented in Figure 3.

One could infer that the types are applicable to all pMDI platforms such as inhaled corticosteroids. Additional studies to quantify the size of API in suspension by microscope or Raman imaging may also be a consideration for suspension-based drug products. The statistical requirements are defined in this guidance and the procedure for calculation of population bioequivalence is defined in a 2012 draft guidance on budesonide.[6,7]

These *in vitro* performance attributes estimate the total and regional deposition of drug substance in the lung and demonstrate quality attributes between test product and RLD, and are therefore central to demonstrating IVBE. In addition, ANDA applicants are required to perform long-term stability (test products only) and comprehensive *in vitro* testing as presented in the CMC guidance for pMDIs and DPIs.[8] For example, applicants should provide data on test products for profiling of actuations near cannister exhaustion for MDIs, the effect of resting time, the effect of storage on the distribution (in case of suspension MDIs), cleaning instructions, and others. (A complete list is available in the CMC guidance).

## CONCLUSION

The development and commercialisation of inhaled pressurised products presents a number of unique challenges for ANDA applicants. The complexities in the formulation, device design, performance, and absence of FDA guidance for pMDIs have created a high barrier to entry for new generic inhalers. In addition, innovator companies are making it increasingly difficult for generics by introducing modifications to devices and/or formulations to extend the lives of patents and to secure market exclusivity. For example, Teva introduced a dose counter to its already approved ProAir® (albuterol sulphate) following the FDA Draft Guidance requiring all new pMDIs to include a dose counter/indicator As a result of the guidance, ANDA applicants must now include dose counters on their test products to remain compliant with the sameness paradigm with the RLD.

This article attempts to shed some light on the complexities and the very demanding process of a generic pMDI. It is our judgment that if ANDA applicants follow a stepwise approach focusing on the key considerations discussed above and move to the next phase only if a "Go, No Go" decision is achieved at each stage, the development process will become more manageable.

## ABOUT NEXT BREATH

Next Breath, a member of AptarGroup, is a cGMP contract services organisation for pharmaceutical, biotech and medical device companies that bring pulmonary, nasal, and ophthalmic drug products to market. Next Breath provides comprehensive solutions to the development processes from proof-of-concept to commercialisation. Next Breath has led successful submissions for pulmonary and nasal drug products and devices in the US and international markets.

## REFERENCES


1. *US FDA Draft Guidance on Albuterol Sulfate, April 2013*
2. *Adams WP, et al, Office of Generic Drugs, US FDA, "Regulatory Aspects of Modifications to Innovator Bronchodilator Metered Dose Inhalers and Development of Generic Substitutes," J Aerosol Med, 1994, Vol 7(2).*
3. *Horhota ST, "Running Against the Wind. Can the Classic Paradigm for BE Really be Extended to Locally Acting OINDP? An Analysis of the Current Scientific and Regulatory Dilemmas of Inhaler Evaluation" Respiratory Drug Delivery 2012.*
4. *Adams, WP, "Bioequivalence Issues in Aerosol Drug Development." Regulatory Issues in Aerosol Drug Development, University of Kentucky College of Pharmacy Symposium, Arlington, VA., June 1991.*
5. *Adams, WP, et al., "Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products (OIDPs): Workshop Summary Report," J Aerosol Med Pulm Drug Del, 2010, Vol 23, pp 1-29.*
6. *US FDA Draft Guidance on Budesonide, September 2012*
7. *Bing VL, et al, OGD/CDER/FDA, GPhA/FDA, "A Step-Wise Procedure for Population Bioequivalence Analysis of OINDP Bioequivalence Studies," Oct 4th, 2011, Fall Technical Conference.*
8. *Draft FDA Guidance for Industry, "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation". 1998.*

Malvern

# SCOPING THE DESIGN SPACE FOR GENERIC NASAL SPRAYS

In this article, Deborah Huck-Jones, PhD, Product Manager, Analytical Imaging; and Paul Kippax, PhD, Micrometrics Product Group Manager & Pharmaceutical Portfolio Manager, both of Malvern Instruments, discuss analytical methods that can be helpful for demonstrating bioequivalence in the development of generic nasal sprays, highlighting the importance of understanding how spray formulations and devices interact to impact drug delivery performance.

As a result of the regulatory focus on using a Quality by Design (QbD) approach for ANDAs, generics manufacturers are placing increasing emphasis on the analytical tools that support its application. Most especially, there is a requirement for analytical technologies that help to scope the product design space efficiently. This is the multi-parametric space in which the properties that define clinical performance must lie to ensure consistent, controlled efficacy.

When developing nasal sprays, identifying the design space is complicated by the fact that critical features of the delivered dose, such as droplet size, are influenced by interactions between the formulation and the delivery device used. A detailed understanding of the impact of both of these elements is essential to achieving the QbD, knowledge-led approach now associated with successful development and commercialisation of a generic.

Here, we examine the complementary use of laser diffraction particle sizing, automated imaging and rheological characterisation to gather the information needed both for generic nasal spray development and the demonstration of bioequivalence. In combination these techniques help to elucidate the factors defining product performance. This enables efficient manipulation of the formulation properties and the features of the device in order to meet development targets.

## THE REGULATORY FRAMEWORK

In recent years, the US FDA's Office of Generic Drugs (OGD) has strongly encouraged the adoption of QbD in the development of generic drugs and, as of January 2013, all ANDAs are expected to follow this risk-based, scientifically rigorous approach. QbD includes the setting of a quality target product profile (QTPP) for the drug product, a specification that defines clinical performance, and identification of the critical quality attributes (CQAs) that deliver it.

The focus of generic product development is to replicate the exact pharmacological behaviour and bioavailability (BA) of an innovator drug, to demonstrate bioequivalence (BE) between the two products. Setting of a QTPP is therefore relatively straightforward. Identifying CQAs for the product, and learning how to manipulate them to meet performance targets, forms the bulk of the de-formulation process in the application of QbD for generic development.

Because of a global increase in respiratory disorders - particularly within recently industrialised regions[1] - OINDPs are an important target for generic development and manufacture. However, duplicating OINDP performance presents unique challenges since both the device and formulation require knowledgeable management to ensure complete emulation of the innovator.

Focusing on nasal sprays, the FDA guidance for characterising the BE of locally-acting drugs delivered by nasal sprays forms a useful basis for QbD studies.[2] This guidance includes a number of *in vitro* tests, placing the emphasis on attaining a comprehensive understanding of API particle and spray droplet size, and the way in which these change throughout the drug delivery process. Laser diffraction is the recommended technique for determining droplet size distribution while microscopy is highlighted for studies of the active ingredient within a suspension formulation.

**Dr Deborah Huck-Jones**
Product Manager,
Analytical Imaging.

**Dr Paul Kippax**
Micrometrics Product Group Manager & Pharmaceutical Portfolio Manager
T: +44 1684 892456
F: +44 1684 892789
E: paul.kippax@malvern.com

**Malvern Instruments Ltd**
Enigma Business Park
Grovewood Road
Malvern
Worcestershire
WR14 1XZ
United Kingdom

**www.malvern.com**

## MECHANISMS OF NASAL SPRAYS

Nasal spray formulations usually consist of an API that is dissolved or suspended in an aqueous solution. Controlling the size of the delivered droplets is crucial to successful *in vivo* drug deposition. Typically, nasal sprays destined for deposition in the naso-pharyngeal region – such as common cold and influenza remedies – will be designed to deliver a droplet size of 20-120 µm. Particles below the lower limit are susceptible to inhalation into the lungs while those that are too large tend to remain in the front of the nose or are lost through dripping. Droplet size is therefore a CQA – a performance-defining parameter – for nasal sprays.

The droplet size delivered by a nasal spray is a function of the physical properties of a formulation, most notably its viscosity, and also the mechanism and geometry of the nasal spray pump. Key characteristics of the pump include the applied actuation profile, the pump pre-compression ratio and the length, geometry and orifice size of the actuator. Together, these determine the shear-force applied to the formulation during actuation and, as a result, the size of the droplets delivered.

By manipulating device and formulation variables, product developers tune nasal spray systems to deliver the required droplet size. Therefore, both the parameters of the pump and the physical properties of the formulation, such as viscosity, are critical material attributes (CMAs), variables that have a direct impact on the CQA droplet size, which must be controlled to ensure the BE of a generic nasal spray.

Suspension nasal sprays bring a further level of complexity, as both the size of the droplets produced by the nasal spray and the size of the suspended API must be considered. The API particles are potentially vulnerable to changes in morphology during the actuation process. Such changes may, in turn, affect bioavailability. The API particle size is therefore another CMA which must be considered as part of the demonstration of BE, with the FDA's guidance suggesting measurements pre- and post-actuation.

In summary, the de-formulation of both solution- and suspension-based nasal spray products relies on understanding the dynamics of atomisation and how to control CMAs to meet droplet-size targets. For suspension-based products there is an additional requirement to assess the impact of actuation on the delivered API particle size. In combination these requirements for particle/droplet size analysis constitute the majority, and the most demanding, element of BE testing.

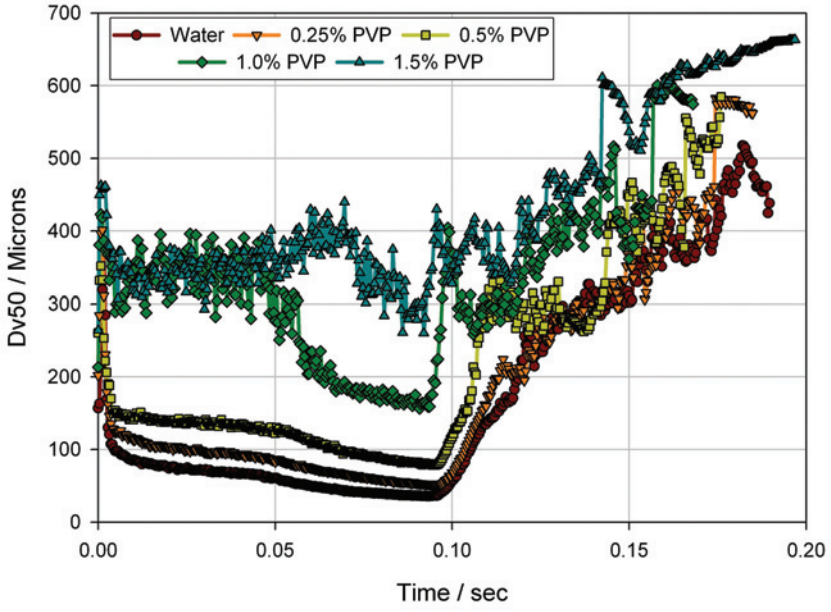



Figure 1: The evolution of droplet size (Dv50) during delivery via a nasal spray for solutions of PVP in water.

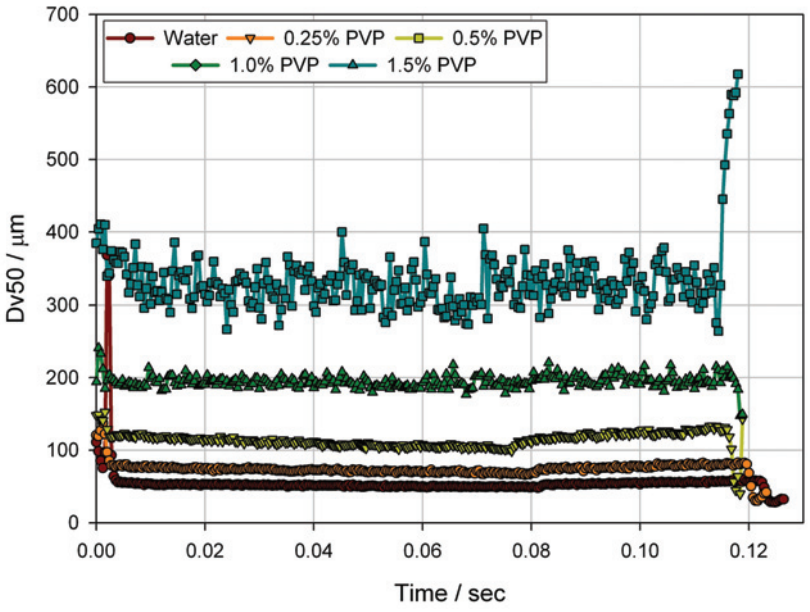



Figure 2: The evolution of droplet size (Dv50) during delivery using an alternative nasal spray pump for solutions of PVP in water.

## THE NASAL SPRAY DE-FORMULATION TOOLKIT

FDA guidance recommending the use of laser diffraction for droplet size measurement makes this technique central to the nasal spray de-formulation toolkit. The following case studies show how laser diffraction and automated image analysis work in tandem to elucidate the performance of nasal spray products and support de-formulation studies.

**Case study 1: Laser Diffraction to Investigate Impact of Formulation Viscosity**

Laser diffraction systems determine droplet size and size distributions by measuring the angular variation in the intensity of light scattered by droplets as a laser passes through a spray. Rapid data acquisition, coupled with the ability to measure size distributions over a wide range (0.1-2000 µm), makes laser diffraction an ideal tool for studying atomisation dynamics. Measuring droplet size distributions in real time during nasal spray actuation can help formulators quantify how variations in CMAs, such as formulation viscosity or nozzle geometry, impact droplet size.

Figure 1 illustrates how laser diffraction measurements can be used to investigate the impact of changes in formulation viscosity on atomisation behaviour and delivered

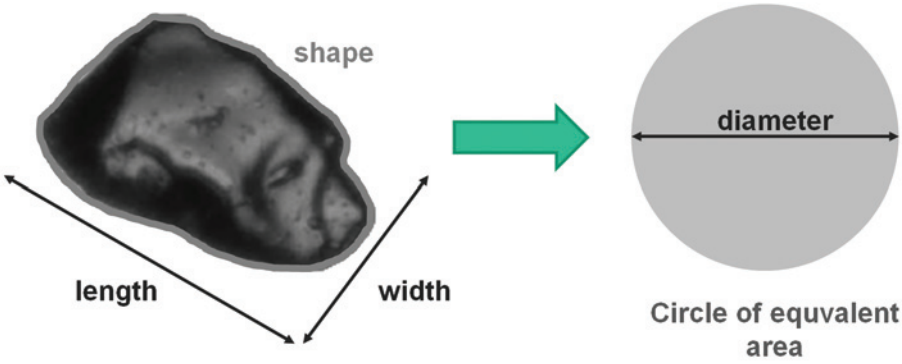



Figure 3: Automated morphological imaging captures individual 2D particle images and uses them to determine size/shape distributions. Conversion to a circle of equivalent area enables a spherical equivalent diameter to be calculated.

droplet size for a nasal spray. In these tests four polyvinylpyrrolidone (PVP) solutions of different concentrations and one water sample were atomised using a commercially-available nasal pump. Actuation was carried out using a fixed actuation velocity and the evolution of droplet size was tracked, from actuation through to completion of the spray event, using a Spraytec laser diffraction particle size analyser (Malvern Instruments, UK). The entire spray event lasts only 160 ms, emphasising the need for rapid data capture.

For the three lower-viscosity solutions, three discrete phases – formation, fully formed/stable dispersion and dissipation – are observed, as defined in the FDA's BA/BE guidance.[2] During the formation phase the droplet size decreases sharply as the pump becomes primed and the flow rate of the liquid formulation through the device increases. During the stable phase a steady flow rate is established through the pump nozzle and the bulk of the dose is delivered at a consistent droplet size. However, as the device begins to empty, flow through the nozzle decreases once again leading to a larger droplet size in the dissipation phase.

At higher viscosities, for the 1.0 and 1.5 % w/w PVP solutions, the actuation process is clearly less successful. Droplet size is not only much larger, but it is also unstable and the fully developed phase is less well defined. The inference from this experiment is that the formulation must have a viscosity that is equal to or below that of the 0.5 % w/w PVP solution if successful delivery with this device is to be ensured.

In this example, viscosity measurements in combination with laser diffraction particle sizing enable the determination of a desirable range of viscosity. This is an important step in scoping the design space for the product.

**Case study 2: Laser Diffraction to Investigate Impact of Pump Mechanism**

When the same PVP solutions are atomised using a nasal spray pump with an alternative operating mechanism, the results obtained can be quite different. Figure 2 shows how a second pump design produces a long and stable phase for every solution, even those that have a high formulation viscosity, suggesting more consistent, reproducible delivery. This clearly illustrates how the pump design can have a marked impact on the success, or otherwise, of drug delivery.

The nasal pump that generated the results shown in Figure 2 employs an energy storage unit which releases only when the pump reaches a pre-determined hydraulic pressure. However, even with this more sophisticated device, delivered droplet size remains a function of viscosity. At high viscosities the shear applied by the pump is still insufficient to fully atomise the formulation in order to yield the fine droplets produced at lower viscosities. These droplet sizing results, as with those in the preceding case study, allow the definition of a desirable range for viscosity, one that delivers consistent dispersion to the target droplet size, with the specific device.

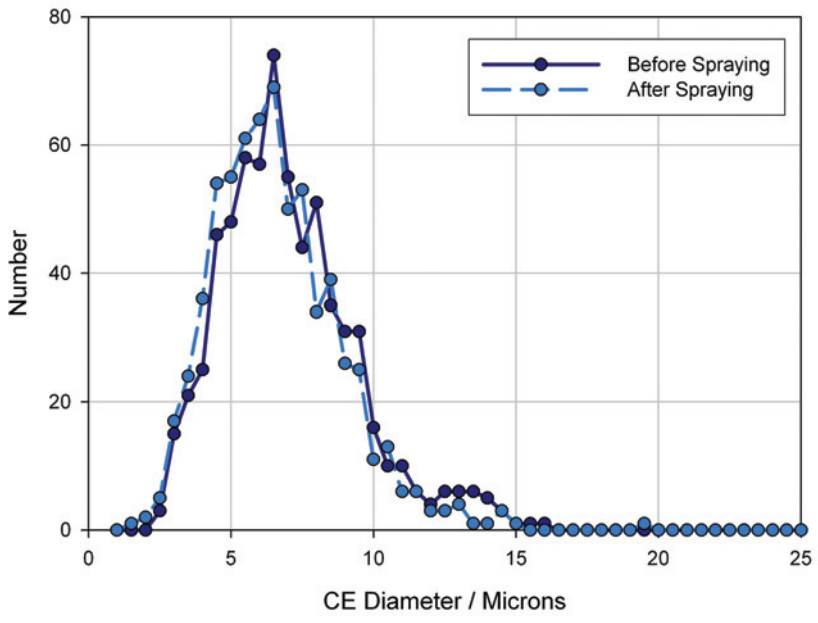



Figure 4: The API within a nasal spray suspension shifts slightly to the left following actuation, suggesting particle dispersion.

**Case study 3: Automated Morphological Imaging for API Particle Sizing**

Both of the first two case studies described demonstrate the utility of laser diffraction in de-formulation research. They highlight the technique's ability explore the physical aspects of the formulation and the device, producing information that helps formulators to achieve the target droplet size for nasal spray solutions. However, laser diffraction makes measurements on the formulation as a whole. It does not provide component-specific measurements of the API suspended within a droplet. For suspension nasal sprays, supplementary analysis is required to differentiate the API from other suspended solids and to quantify the impact of the spray process on API morphology.

The requirement set out in the FDA BE guidance, to measure the particle size of the API pre- and post-actuation, can be met using manual microscopy. Automated imaging is an alternative approach that offers substantial benefits, not least because automation removes subjectivity from the analysis and significantly reduces operator input. Automated imaging involves capturing individual two-dimensional images of dispersed particles and building size and shape distributions from the dimensions of each image (Figure 3).

Figure 4 shows particle size distribution data for an API dispersion within a nasal spray suspension, before and after actuation,

gathered using an automated morphological imaging system (Morphologi G3, Malvern Instruments). In this formulation the excipients and API had distinctly different morphology, so classification based on size and shape alone was sufficient to identify the API population, and produce component-specific particle size distribution data. The particle size distribution profiles shown in Figure 4 indicate that actuation produces a slight shift in API particle size towards finer sizes, suggesting particle dispersion during the atomisation process. Such an effect may impact the bioavailability of the API and its uptake *in vivo*, potentially influencing clinical efficacy.

In the preceding example, API and excipient were differentiated on the basis of shape alone. In many suspensions this is not possible, and this is where the additional capability of Raman spectroscopy – chemical identification – becomes valuable in enabling successful de-formulation. Morphologically directed Raman spectroscopy (MDRS), as applied in the Morphologi G3-ID (Malvern Instruments), involves gathering spectra from targeted particles, identified on the basis of size and shape. These spectra are then compared with a set of reference spectra to determine the chemical nature of the individual particles. Particles with a high correlation with a specific reference spectrum, as assessed using a least-squares fit correlation factor, can be positively identified. If features from multiple reference spectra are identified then this may indicate that a particle is an agglomerate.

Figure 5 shows Raman spectral correlation scores for particles in a nasal spray formulation containing morphologically similar components. The scatter plots show two distinct particle populations, one cluster with a high correlation score relative to an API reference spectrum and another with a high correlation compared with an excipient reference spectrum.

Images of particles identified as API show that they are relatively spherical compared with the more elongated excipient particles. Figure 6 shows shape distribution data for the two-component populations. These data suggest that particles with an elongation ratio of 0.5 or higher can be allocated to the excipient population. However, there are an appreciable number of particles that, on the basis of the shape, could be either API or excipient. Targeting Raman spectroscopy on particles with these properties ensures accurate particle size determination while at the same time minimising the longer measurement times associated with the application of standard Raman mapping.

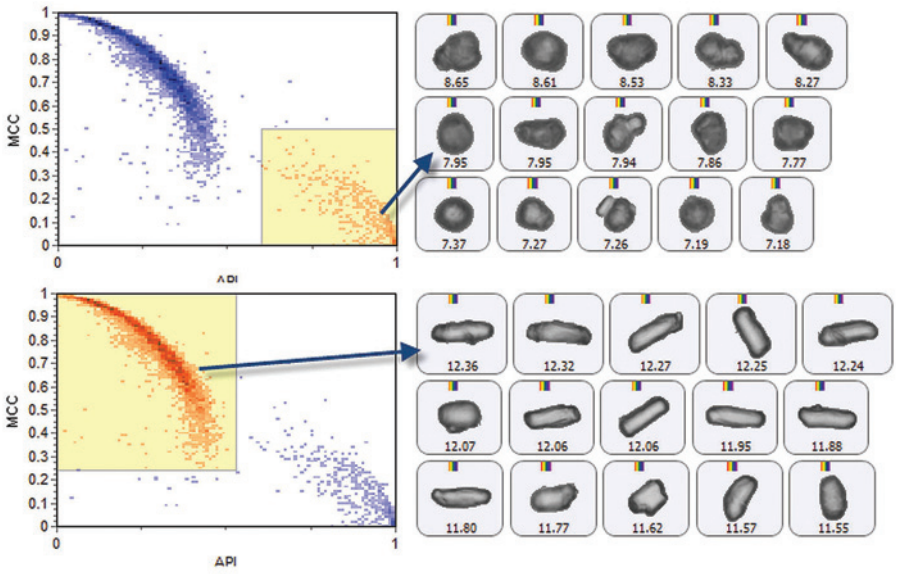



Figure 5: Scatter plots for Raman correlation scores of API and excipient particles quantify the relative amounts of each constituent, overcoming morphological similarity.

## LOOKING FORWARD

OINDPs present a unique challenge to developers of generic pharmaceuticals because achieving bioequivalence relies on knowledgeable manipulation of the physical properties of the formulation as well as the characteristics of the device. Techniques such as laser diffraction and MDRS have an important place in the de-formulation toolkit. In combination with rheological characterisation, most especially viscosity measurement, these tools help with fast and efficient QbD ANDA submissions.

*The authors would like to acknowledge the kind support of Next Breath in helping to define and carrying out the measurements described.*

## REFERENCES

1. *Khaled N et al, "Chronic respiratory diseases in developing countries: the burden and strategies for prevention and management". WHO Bulletin, 2001, 79.*
2. *"Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action", US FDA CDER Biopharmaceutics, April 2003.*

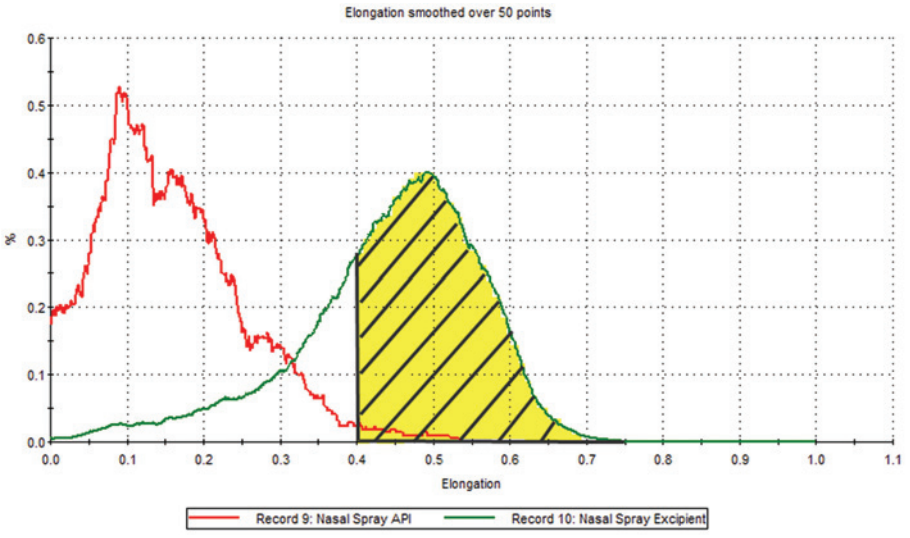



Figure 6: Shape distribution data for excipient and active ingredients within a formulation successfully identified using morphologically-directed Raman spectroscopy. The region shaded within the excipient distribution was not target for Raman analysis as particles in this region could be identified by size and shape alone.

3M DRUG DELIVERY SYSTEMS | INHALATION SYSTEMS

# Just because we make it look easy doesn't mean it is

## A contract manufacturer that can navigate complexity to commercialize your innovation

- Gain a competitive edge by selecting a partner with experience and expertise
- 3M developed the first Metered Dose Inhaler (MDI)
- FDA approval of six new MDI products in six years, in conjunction with our partners
- Pressure-fill and cold-fill systems technology and the people with the skills to use it properly
- Expertise at commercializing innovation that will get your product ready for market faster

**Watch the contract manufacturing video: go.3M.com/Inhalation**

US: (1) 800 643 8086
UK: (44) 1509 613626
ASIA: (65) 6450 8888



EXPERTS AT COMMERCIALIZING INNOVATION

3M