P04 PHARMA-DIGITAL TECH PARTNERSHIPS: IT'S JUST AN APP, ISN'T IT?

P14 ADVANCES IS PULMONARY DELIVERY OF INHALED ANTI-INFECTIVES

P34 ENHANCING DPI PEFORMANCE USING BREATH-ACTUATED MECHANISMS

PULMONARY & NASAL DELIVERY

ON drugDELIVERY

APRIL 18TH 2016 • ISSUE N° 66

Aptar pharma

Cambridge Consultants

CAPSUGEL

Chiesi
People and ideas for innovation in healthcare

Chimera Consulting Combination Product Training Institute

Nemera

noble

NOVI AUTOMATION SYSTEMS

Phillips Medisize
Partnerships Built on Innovation

PRESSPART

pulmatrix

Qualicaps Engineered to perform

ONdrugDelivery Issue N° 66, April 18th, 2016

PULMONARY & NASAL 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.

12 MONTH EDITORIAL CALENDAR

May	Injectable Drug Delivery: Devices Focus
Jun	Connected Delivery Devices
Jul	Novel Oral Delivery Systems
Sep	Wearable Injectors
Oct	Prefilled Syringes
Nov	Pulmonary & Nasal Delivery
Dec	Delivering Biotherapeutics
2017 Jan	Ophthalmic Delivery
Feb	Prefilled Syringes
Mar	Skin Drug Delivery: Dermal, Transdermal & Microneedles
Apr	Pulmonary & Nasal Drug Delivery

SUBSCRIPTIONS:

9-10 issues of ONdrugDelivery Magazine published per year, in PRINT & PDF.
PDF subscription is always completely **free**.
PRINT subscription costs **£189/year**.
Print subscription includes delivery of a printed copy of each issue to one address anywhere in the world.
E: subscriptions@ondrugdelivery.com.

EDITORIAL AND ADVERTISING:

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

MAILING ADDRESS:

Frederick Furness Publishing Ltd
The Candlemakers, West Street, Lewes,
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 "Inhalia™ Valves", courtesy Nemera. Reproduced with kind permission.

CONTENTS

4 - 7	It's Just An App, Isn't It? Vaishali Kamat, Head of Digital Health and Jaquie Finn, Senior Consultant, Digital Services Cambridge Consultants
8 - 11	Systems Engineering For Complex Portable Drug Delivery Device Development Bill Welch, Chief Technical Officer Phillips-Medisize
14 - 19	Advances in Pulmonary Delivery of Inhaled Anti-Infectives David L. Hava, Chief Scientific Officer Pulmatrix
20 - 24	Capsule-Based Dry Powder Inhalers, an Optimal Solution for Different Inspirational Rates Gabriela Dujovny, Scientific Business Development Manager Qualicaps
26 - 27	Company Profile: Novi Systems Adam Smith, Director Novi Systems
29	Product Profile: DF30 with COCe Aptar Pharma
30 - 32	Bioequivalence For Nasal Sprays: Importance of Device Performance Pascale Farjas Nemera
34 - 38	Enhancing The Performance of Dry Powder Inhalers: Breath Actuated Mechanisms Alan Tweedie, Senior Scientist and David Lewis, Head of Laboratory Chiesi
40 - 42	Company Profile: Noble
44 - 46	Modifying MDI Canister Surfaces to Improve Drug Stability & Drug Delivery Richard Turner, Business Development Director Pharmaceutical Presspart
48 - 51	FDA Issues Final Guidance on Medical Device Human Factors Studies Michael Gross, Principal Consultant Chimera Consulting Adam Shames, Chief Executive Officer (Core Human Factors) Core Human Factors

Cambridge Consultants

A connected life

We have a world-class reputation in the design and development of market-leading drug delivery devices and wireless products.

Find out how we can help you become connected.

Product Developers & Technology Consultants

www.CambridgeConsultants.com

Cambridge Consultants is part of the Altran group, a global leader in innovation. www.Altran.com

Cambridge Consultants

IT'S JUST AN APP ISN'T IT?

Although the interest in connected devices and solutions is growing rapidly, there is limited understanding of what a successful digital health solution should encompass or how partnerships should work. Vaishali Kamat, Head of Digital Health, and Jaquie Finn, Senior Consultant, Digital Services, at Cambridge Consultants, outline some key questions that pharma companies should ask before embarking on the development of a connected health solution, and provide insights that could help companies make the most from their investment.

The global digital health market reached a record-breaking value of $55 billion (£39 billion) in 2014 and is forecast to grow at a compound annual growth rate (CAGR) of 21.4% to 2020.[1]

BI Intelligence estimates that there will be more than 646 million connected devices used for healthcare within the same period.

This interest in connected devices and solutions is, to a large degree, driven by change in the healthcare industry landscape. While the availability of suitable technology at an acceptable cost point has made implementation simpler, the rush to develop connected medical devices in the last year or so can be primarily attributed to the focus on reducing cost of care and the pressure to demonstrate improved outcomes.

As healthcare payment structures move away from traditional pay-for-service methods, the burden on the pharmaceutical and medical device industry of proving the benefits increases. This in turn underscores the importance of harnessing the power of connected health for companies to stay relevant and competitive in this changing market landscape.

THE RACE FOR THE SMART INHALER

As big pharma considers the likely changes in payment structures and looks to differentiate in the face of the threat from generics, the interest in connected drug delivery devices has increased rapidly. The respiratory disease sector has been one of the first to get attention, with significant moves towards smart inhalers from several major players in asthma and COPD. 2015 saw partnership announcements from both Boehringer Ingelheim and GSK with Propeller Health[2] and AstraZeneca with Adherium[3] for development of sensors for their existing inhalers. Novartis announced its collaboration with Qualcomm Life[4] for clinical trials, while generics maker Teva bought smart inhaler company Gecko Health Innovations[5] and announced its partnership with IBM to build global e-Health solutions on Watson Health Cloud.[6]

> "As healthcare payment structures move away from traditional pay-for-service methods, the burden on the pharmaceutical and medical device industry of proving the benefits increases."

While it is still early days for these partnerships, and the current focus seems to be on clinical trials with "smart" versions of existing inhalers, it wouldn't be surprising to see future inhalers launched with integrated electronics and embedded software.

Vaishali Kamat
Head of Digital Health
T: +44 1223 420 024
E: vaishali.kamat@cambridgeconsultants.com

Jaquie Finn
Senior Consultant, Digital Services
T: +44 1223 420 024
E: jaquie.finn@cambridgeconsultants.com

Cambridge Consultants
Science Park
Cambridge
CB4 0DW
United Kingdom

www.CambridgeConsultants.com

However, the big question is how many of these players – or others, who look to follow in their footsteps to tackle other diseases – have figured out what is really involved in deploying a successful digital health solution? Despite the plethora of partnership announcements for smart inhalers, these companies have said little with regard to a coherent digital health roadmap and how smart inhalers will fit in it. It remains unclear what type of connectivity they are aiming to achieve and why, what type of data will be captured, and who will access it and how.

This is perhaps because it is too soon. Yet it is uncharacteristic for pharma companies, which are typically generous in providing information about their products, e.g. molecular mechanisms, enzymatic activity, pharmacokinetics, clinical results, etc. Can the lack of clear messaging around digital health be attributed to the fact that, in the race to have the first smart inhaler in the market, people have not stopped to figure out what having a connected device in their portfolio will mean? Is it because they have not fully grasped the wave of change that connected devices will bring to their business? For example, have they planned how they will scale the solution and provide the services that will be needed to maintain it? Have people taken the time to think about how the smart inhalers will help them achieve their strategic long-term business ambitions? Is the path to achieving suitable return on investment (ROI) within a reasonable time frame identified?

Connected health can bring a huge upside – but only if solutions are well developed and efficiently deployed. Simply making a wireless inhaler will not achieve the goals that these solutions are meant to achieve. It is critical for anyone entering this smart device race to recognise and acknowledge that there is more to it than just adding a Bluetooth chip or developing an app.

UNCHARTED TERRITORY

Development of connected devices and supporting digital services involves a substantial investment – and the risk of failure should not be underestimated. Electronics, software and IT are not core capabilities of pharma companies, many of which only have a limited engineering capability in-house, thus restricting their ability to understand what is involved and evaluate options. Furthermore, their existing device supply chain has historically focused on mechanical rather than electromechanical or electronic systems, so they face an expertise gap.

To address this, some companies are bringing on staff from the technology industry to help them navigate this new landscape. However, often these new hires have limited understanding of the pharma industry – making joining the dots difficult.

But, technology aside, the bigger struggle many companies seem to face is to answer some fairly basic yet important questions that should ideally help inform the technology choices and solution definition. For example:

- What do we want to achieve with a connected solution?
- Do we need to be first or does it make more sense to follow?
- Which stakeholders do we want to target? What will they gain from our product and service?
- How can we differentiate? What will be needed to truly protect market share?
- Do we want to influence parts of the ecosystem? How can we do so?
- Should we develop an open or closed system? What is the impact of each?

The following sections provide some suggestions and best practice to help inform the creation and deployment of connected health solutions. While we use smart inhalers as an example, most of these insights apply to other types of medical devices as well.

DEFINE STRATEGIC INTENT

There are many reasons to develop connected devices – and why pharma companies seem to be locked in a race for the first smart inhaler on the market. But prior to entering this race, it is important to think and articulate the strategic intent of a connected device solution.

Each company has a different ambition and a different appetite for risk based

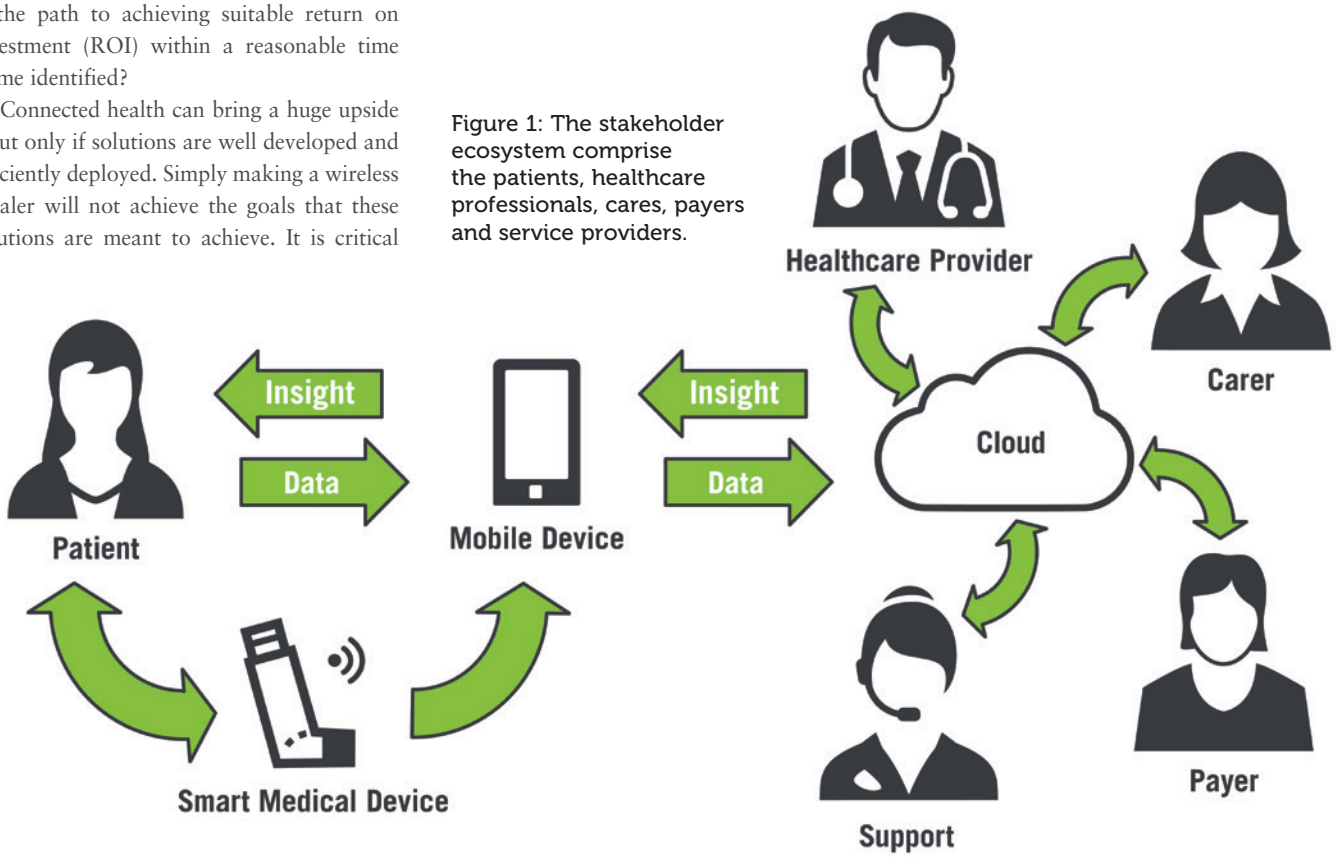


Figure 1: The stakeholder ecosystem comprise the patients, healthcare professionals, cares, payers and service providers.

on their current competitive market position. Thus, the nature of solutions and services that each company develops will – or should – be different. Moreover, the drivers pushing particular players into the connected device space vary slightly per organisation which in turn will define the goals to be achieved via connected health, e.g. some want to streamline clinical trials and run them in a more cost-effective manner, while others have a wider ambition and see themselves transforming from a pharma or device company into a healthcare services company.

Unless these goals are identified, understood, and disseminated within the organisation, it is difficult – if not impossible – to make appropriate technical decisions and select suitable implementation partners. It is equally important to define metrics for success, both short- and long-term, as well as work out the commercial value proposition – the business model – for the new offerings. Defining these will help the implementation team pick direction and stay on course.

UNDERSTAND STAKEHOLDER NEEDS

Let's assume that smart inhalers are being developed because of the belief that by tracking device usage and reminding patients to take their doses, one can improve adherence to therapy. However, improved adherence may not result if the new system does not deliver a better user experience or if the reason for poor adherence is not forgetfulness. It is critical to understand the real unmet needs that a connected solution can help meet – and ensure it does not present an additional burden.

Connected devices and their data-driven solutions can and should be targeted not just at the patients but also other stakeholders in the ecosystem (Figure 1). Caregivers, clinicians and payers, as well as the industry players themselves, are all important stakeholders who can benefit from a connected health solution. Whether it is to reduce a concerned parent's worries or manage the cost of care for a population of chronic disease patients, identifying how the same data can help various stakeholders will enable you to maximise your return and realise the full potential of connected health.

Different disease conditions, different types of patients, different socio-economic groups and different geographies all have an impact on the requirements of a connected health solution. Everything from the choice of wireless technology to the features in an app depends on the needs you are trying to meet or the problems you are trying to solve.

Gaining insights from patients and other stakeholders is critical in tackling these issues, and specifying the optimal solutions. Similarly, testing prototype solutions with real users can help refine the offering. But user studies and trials can only go so far. Digital solutions need to be rolled out to a sufficiently large population in order to uncover issues that come with scale, obtain a wide enough perspective on user preferences and ultimately to gain actionable insights from the data.

You will never know what is going to work and what will fail unless you get feedback from real users in an uncontrolled setting. Thus the pilot-launch-iterate-launch cycle must be undertaken. This is counterintuitive to traditional medical device development, but a necessity for digital solutions.

SELECT A SUITABLE TECHNOLOGY PLATFORM

The technology stack required to realise an end-to-end connected health solution consists of much more than just a Bluetooth chip and a smart phone app. Unfortunately, much of this stack is invisible and its impact ill-understood. For example, some interpret the "cloud" as this enigmatic and tangled web that they want to stay away from for fear of the regulatory implications, whereas others simply equate it to a data storage system like AWS, Microsoft Azure or an in-house server farm. The back end of a connected health solution needs to do so much more – it is, in fact the backbone that enables the solution to be deployed, maintained, upgraded and, more importantly, monetised.

DEFINING THE SYSTEM

Of the various components required to enable a connected health solution, only a few will constitute the "medical device" or "system" from a regulatory perspective. Where the boundaries of your regulated product/solution will be drawn will depend on the features you put into the device, the app and the backend, as well as the fundamental nature of the device itself. For example, an app that goes along with a smart inhaler will very likely be considered part of the combination product and thus require the same amount of rigour during development and sufficient documentation for regulatory submission.

On the other hand, an app that works with several devices, or is drug independent may qualify for an independent 510(k) submission or – in some instances – fall under the discretionary category and thus not require clearance. It is important to define "the system" related to your smart inhaler or other connected device early in the development cycle so that feature partitioning and other design decisions can be made appropriately (Figure 2).

DEVICE HARDWARE

The primary additions required to turn a traditional mechanical inhaler into a smart inhaler are:

- A means to sense and record device usage
- Actuation
- Storage and communication protocols to transmit that data/event to a collection device usually a smart phone or home hub.

The sensing technology – and its placement within a device – is critical as it will define how accurately you can capture device usage as well as what aspects of the usage can be recorded, e.g. airflow, aerosol formation, other physical parameters, etc. This in turn will dictate the claims you can make about your smart inhaler, e.g. can you claim that a successful dose has been delivered or do you need to simply state that the device has been actuated? The difference between the two seems minor but can have a big impact on the system and its end user benefit.

The choice of wireless technology has been made simple by the widespread adoption of Bluetooth Smart (also called Bluetooth Low Energy) in mobile phones. Most connected devices are thus incorporating Bluetooth Smart. However, thought should be given to the associated complexity and hence user experience of such a system.

Moreover, since you are making decisions today for a device that won't get to market for two or more years, attention must be paid to longevity of the selected technology / hardware and to alternatives that may become available / suitable in that time frame.

SOFTWARE

When dealing with a connected device, you need to consider three software elements. The first is firmware in the device itself, next is the

smart phone app and finally the technology stack that constitutes the backend.

The firmware will be dictated by the choice of wireless technology, sensors and other functions of the device. The app will need to be developed suitably, based on its regulatory classification and key stakeholders that must interact with it, bearing in mind the impact of phone hardware changes and the even more frequent OS updates that are beyond your control.

Finally, the backend technology stack needs to consist of the basic data storage and handling with appropriate user access control and privacy protection, along with other functionality to enable data analysis, and reporting, as well as maintenance. The ability to fix bugs, add features and roll out updates on a regular basis is critical when dealing with consumer electronics platforms – a concept that is alien to the medical device and pharma industry.

It is safe to assume that it will not be necessary for the medical device or pharma company to develop all this software from scratch. Several big technology vendors have compelling offerings that can give you a leg up. However, selecting the appropriate solution for each of the software elements can be confusing and complex. Moreover, we recommend that you only enter partnerships where you have control over the user experience as well as unfettered access to the data gathered – the two elements which are of utmost value. To make your job easier, you may want to solicit assistance from technology savvy yet independent partners who can help you make an informed decision rather than pushing one particular option.

PREPARE FOR ORGANISATIONAL CHANGE

Last but not least, you must acknowledge, prepare and be ready for the changes that owning a connected device solution will bring to your organisation. Everything from your marketing strategy to customer service and technical support services will need to be revised and updated to meet the needs of this new offering. The business operations, as well as the development operations function that you will need to put in place for ongoing maintenance of the connected solution are a non-trivial undertaking. Once again, we recommend choosing an experienced partner to hold your hand and guide you on this path – which is very much worth taking but does need some significant effort and investment.

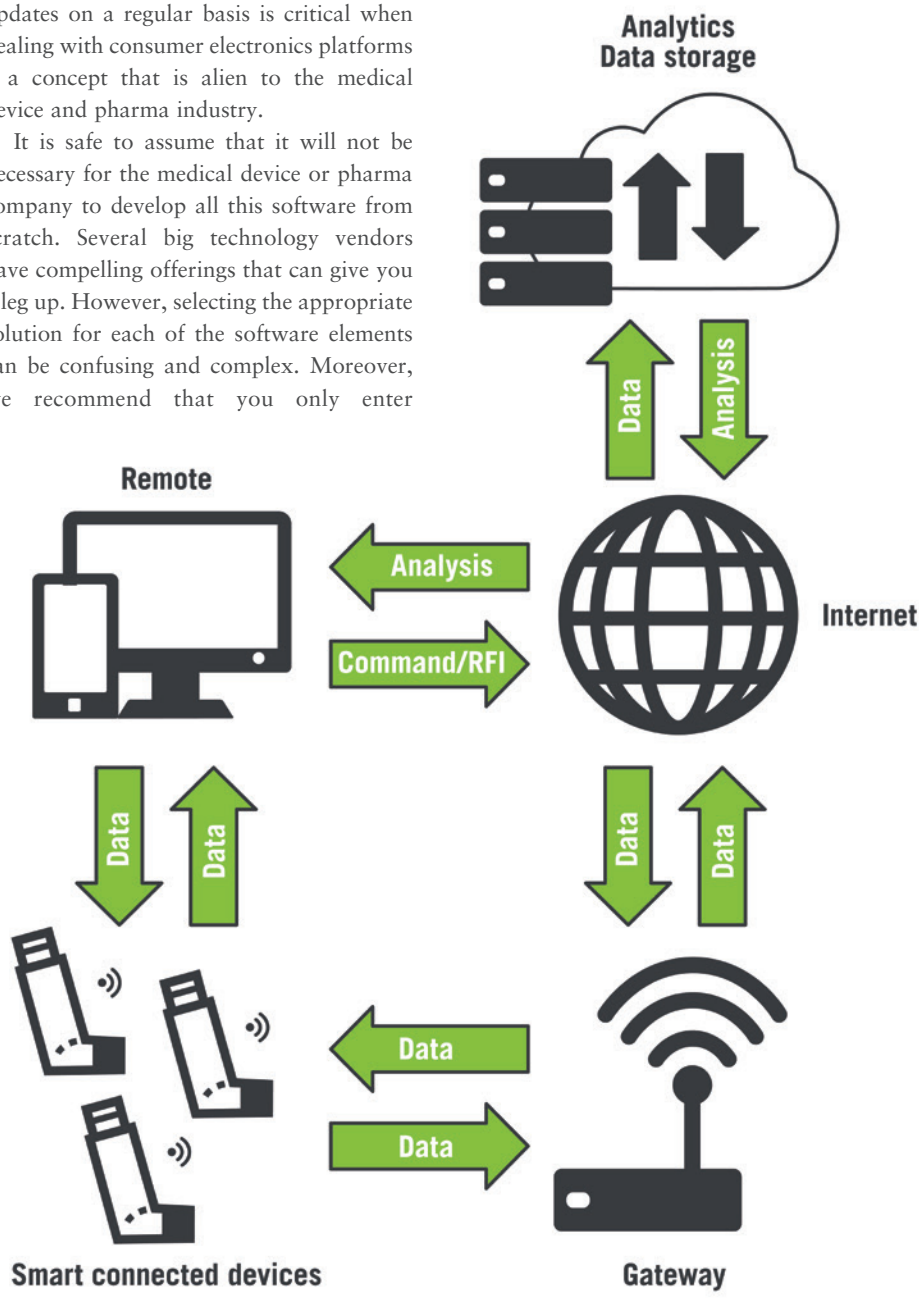


Figure 2: The digital system goes beyond a smart connected device.

CONCLUSION

Digital health solutions have the power to offer an improved user experience by enabling people to use – for healthcare purposes – technologies that they are already familiar with. Increased patient engagement and motivation to manage disease can result in improved outcomes and reduced cost of care.

The medical device and pharmaceutical industry along with significant technology players have a huge role to play in realising this dream. COPD, asthma, diabetes, cardiovascular disease, neuro-degenerative disease and other chronic disorders will be among the first targets.

While it may seem simple to trial a connected device and show results in a controlled setting, it is imperative to recognise that the dream of shifting the outcome and cost needle will not happen unless these solutions can be launched at scale. And that is a complex task which should not be underestimated.

REFERENCES

1. *https://www.psmarketresearch.com/market-analysis/digital-health-market.*
2. *http://mobihealthnews.com/36942/boehringer-ingelheim-propeller-health-team-up-for-sensor-enabled-inhaler-pilot.*
3. *http://mobihealthnews.com/45620/astrazeneca-adherium-to-create-smart-inhaler-adherence-program-for-patients.*
4. *https://www.novartis.com/news/media-releases/novartis-pharmaceuticals-collaborates-qualcomm-digital-innovation-breezhalertm.*
5. *http://mobihealthnews.com/47039/teva-pharmaceuticals-buys-smart-inhaler-company-gecko-health-innovations.*
6. *http://www-03.ibm.com/press/us/en/pressrelease/47632.wss.*

Phillips Medisize

Partnerships Built on Innovation

SYSTEMS ENGINEERING FOR COMPLEX PORTABLE DRUG DELIVERY DEVICE DEVELOPMENT

Bill Welch, Chief Technology Officer, Phillips-Medisize Corporation explains how a systems-engineering approach provides an efficient method of developing smaller, smarter and more complex inhaler devices. With the ever-growing requirements for these devices, systems engineering can address the whole device system and reduce the risk of technical or schedule risk.

As the demand for complex, portable drug delivery devices continues to grow, reducing risk and increasing efficiency during the development of these products should be paramount.

Taking a systems-engineering (SE) approach to development provides a holistic, organised and deliberate method for identifying as well as reducing both patient and business risks early in the process.

> "While adopting an SE approach to product development does not totally eliminate development risk, it does reduce risk significantly."

The latest inhalers on the market reflect the relentless industry-wide drive towards smarter, smaller and more portable drug delivery devices. To ensure reliability and repeatability, however, such complex devices demand a greater number of requirements, as well as more testing and validation during their development, than do the larger, simpler devices of previous decades. In turn, they also carry with them greater technical and schedule risk. Applying systems engineering to the development of these devices addresses the whole device system and determines the following features:

- All subsystems (a discrete selection of components that work together to per form a function) that make up the full system
- Each subsystem-to-subsystem dependency
- All of the rules that will need to be drawn up in order for the subsystems to work together, or integrate
- The order in which those rules will be drawn up so that subsystem integration occurs correctly.

This approach differs from the traditional linear product development approach, typically in that it breaks the whole product idea into subsystems and – beyond simply establishing requirements for those subsystems – devises an order in which each subsystem must be defined. It also determines which dependencies between subsystems are needed for proper operation. Systems engineering requires both subsystem-specific engineers and the overall systems engineer, who focuses on establishing the requirements for the interactions and integration of the subsystems – that is, what makes the whole system work together.

Bill Welch
Chief Technical Officer
T: +1 715 386 43203
E: info@phillipsmedisize.com

Phillips-Medisize Corporation
1201 Hanley Road
Hudson
WI 54555-5401
United States

Phillips-Medisize (Europe)
Edisonstraat 1
2181 AB Hillegom
The Netherlands
T: +31 252 576 888
E: eu_sales@phillipsmedisize.com

www.phillipsmedisize.com

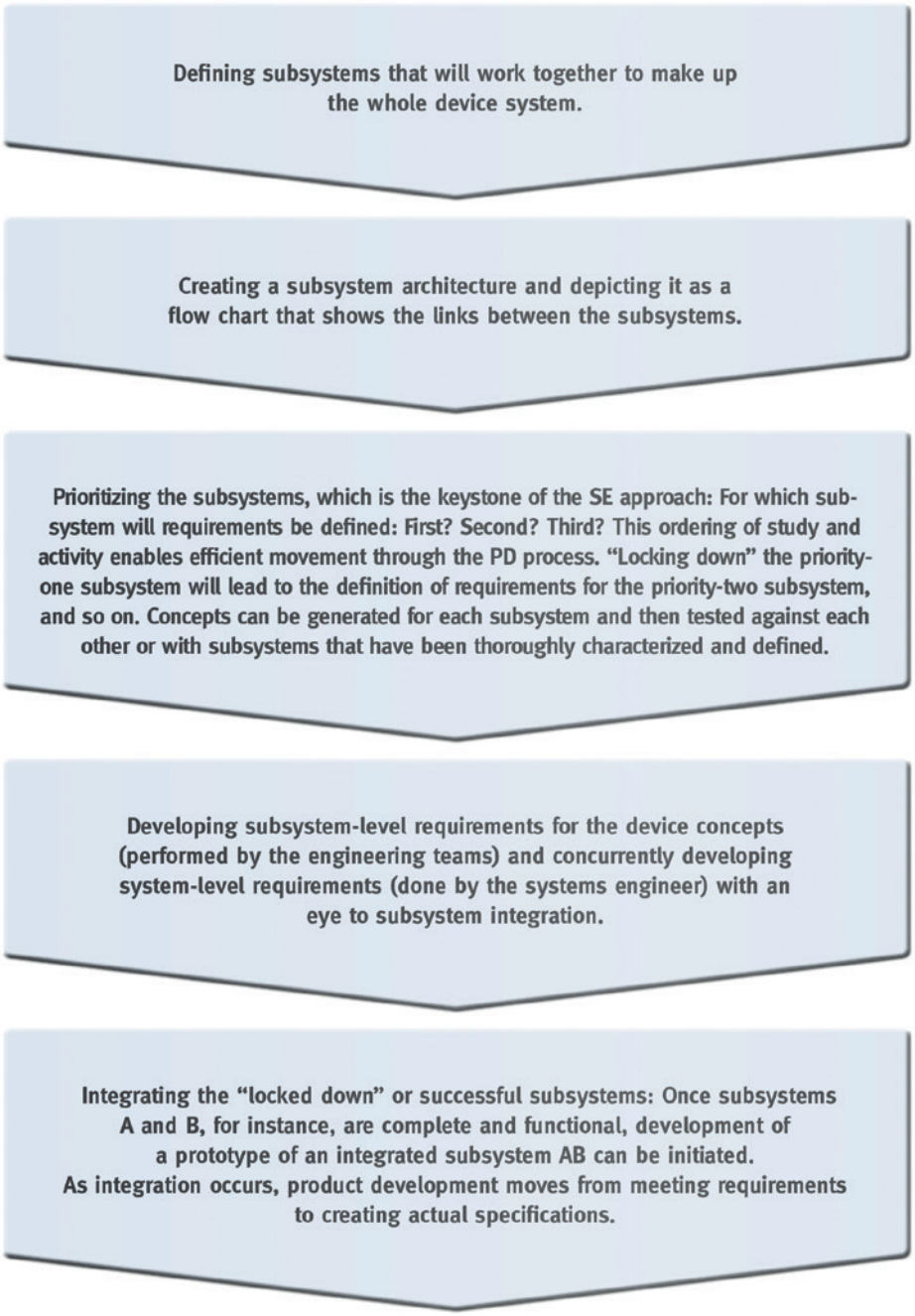


Figure 1: Key steps in the process for using a systems-engineering approach.

SYSTEMS ENGINEERING STEP BY STEP

To kick off the SE process for a complex, portable inhaler, the user and stakeholder needs must first be determined by the client (the device company), then communicated to the product development (PD) team. Once the PD team has a firm grasp of what the client wants, the team members will typically brainstorm ways in which those wishes can be fulfilled. Next up after brainstorming are the crucial steps shown in Figure 1.

ILLUSTRATION OF SYSTEMS ENGINEERING WITH AN AUTOMATIC-DOSING INHALER

The SE approach can be illustrated using a hypothetical complex portable drug delivery device: an automatic-dosing albuterol inhaler, which represents an upgrade of the traditional manually dosed albuterol inhaler. This mechanical upgrade features automatic dosing triggered by the user's inhalation as well as a dose counter that tracks the number of doses that have been administered.

In early brainstorming, the team decided the order of operation would occur as shown in Figure 2.

Several subsystems are present in the entire device, including canister design and drug formulation, user interface, drive-mechanism cocking, drive mechanism (spring), stem and opening, canister activation, dose-counter mechanism and an inhalation-activated trigger. Rather than jumping right to the creation of a total-product concept that incorporates all of these subsystems at once – thereby making it difficult to define what is critical about

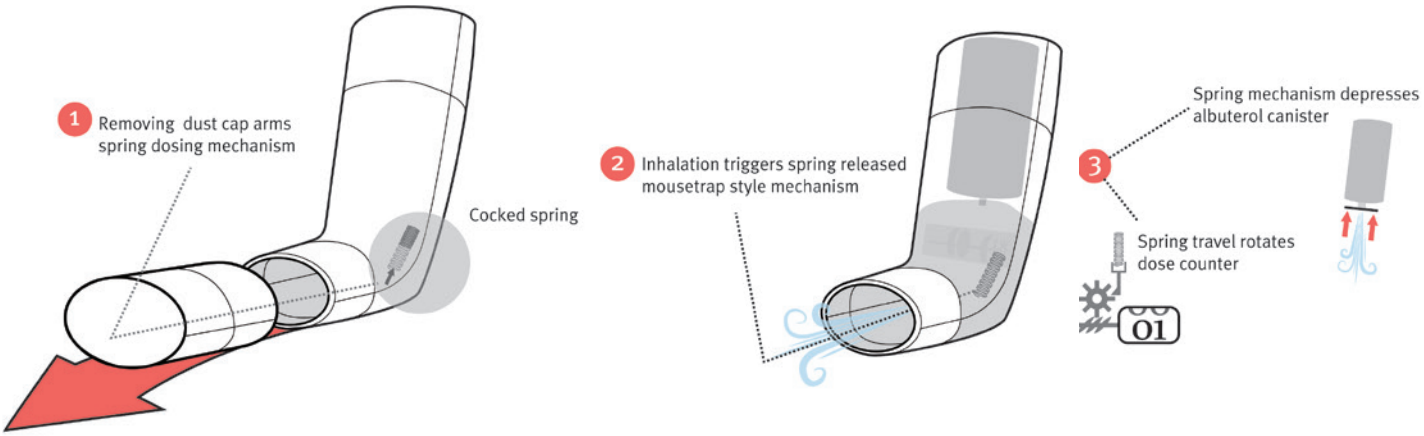


Figure 2: Order of operation for upgrading an automatic-dosing inhaler device.

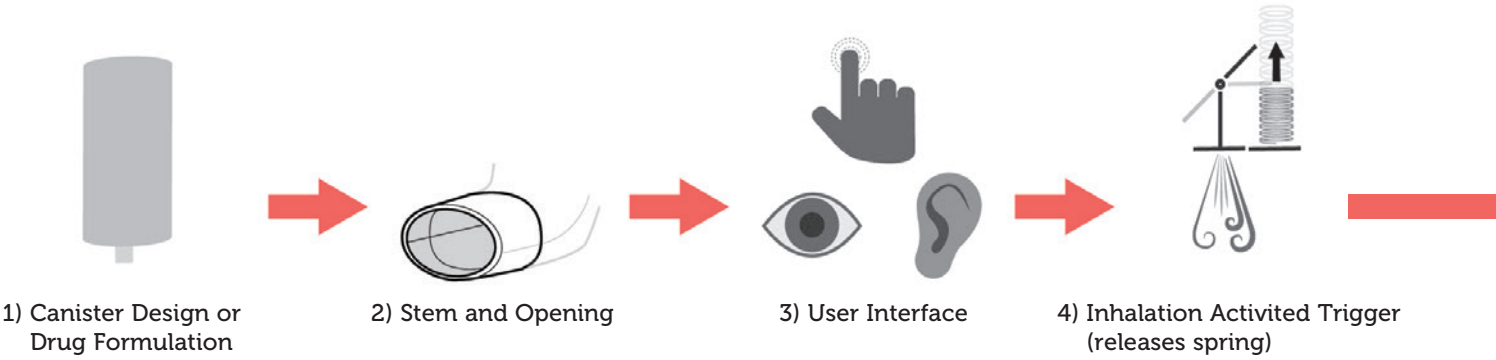


Figure 3: The links between the subsystems in order of priority.

> "Healthcare products continue to shrink, feature greater connectivity and grow more complex. These trends are not going away, and the SE approach to product development is the best choice for firms creating these devices ... reducing user, patient, product, financial and schedule risk and improving PD lifecycle efficiency."

each subsystem and its components – the SE approach first establishes the individual subsystems, determines the links between them, prioritises those links, defines and tests in a logical order, and then finally, integrates the subsystems.

Figure 3 depicts the links that have been established between the subsystems of the hypothetical automatic-dosing inhaler, along with how the links have been prioritised.

As is illustrated, the PD team has determined that defining the requirements for the canister design and drug formulation are the most important, followed by the stem and opening from which the drug will exit the canister.

These two subsystems and their interaction can then be studied on their own, independent of other variables, such as the drive mechanism. Subsystems 1 and 2 are used to define the requirements for Subsystems 3, 4, and 5.

Finally, Figure 4 illustrates the structured, deliberate manner in which integration of the inhaler's subsystems occurs.

ADVANTAGES OF SE

While adopting an SE approach to product development does not totally eliminate development risk, it does reduce risk significantly. By defining each subsystem and specifying the order in which those subsystems must be characterised, troubleshooting during subsystem integration becomes more efficient and straightforward. Engineering teams can work backwards through the system, if needed, to determine where gaps may have occurred.

Patients, ultimately will benefit from a product that does not cause harm and that functions as intended while the manufacturer will benefit from a timely product launch.

"Learn early and inexpensively" is a useful mantra here: by focussing on subsystem- and system-level requirements during the proof-of-concept phase, the team will set up a solid foundation for the more-expensive development work that follows.

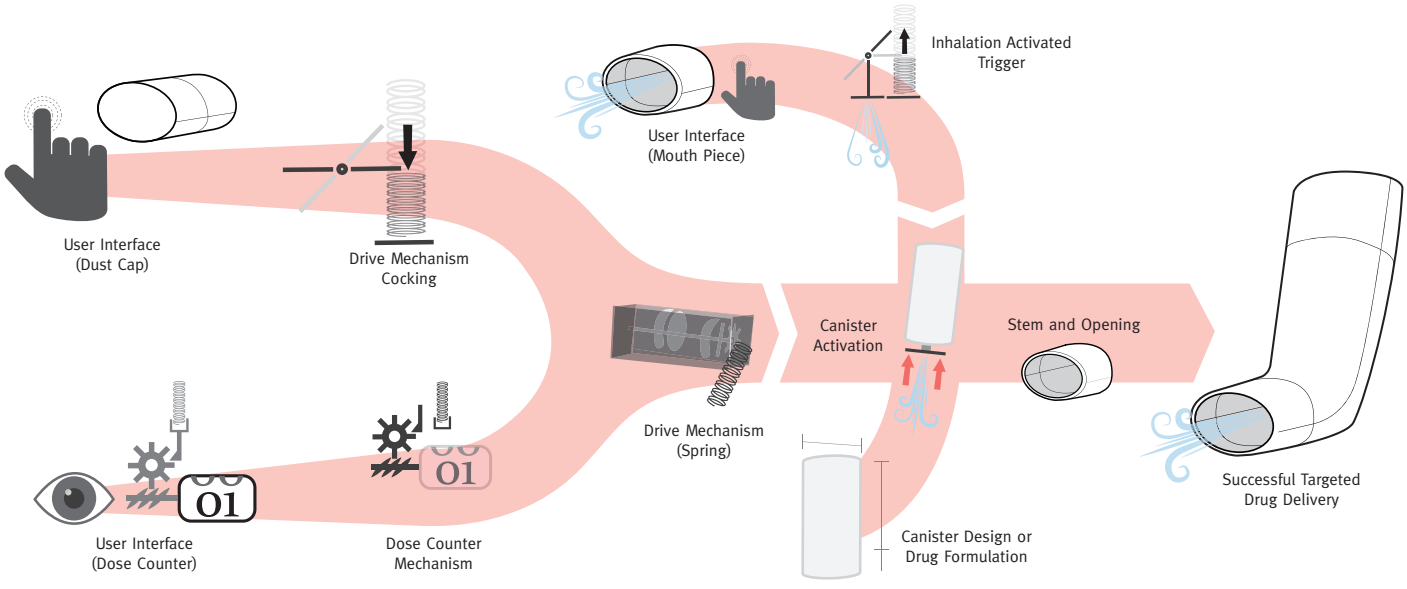
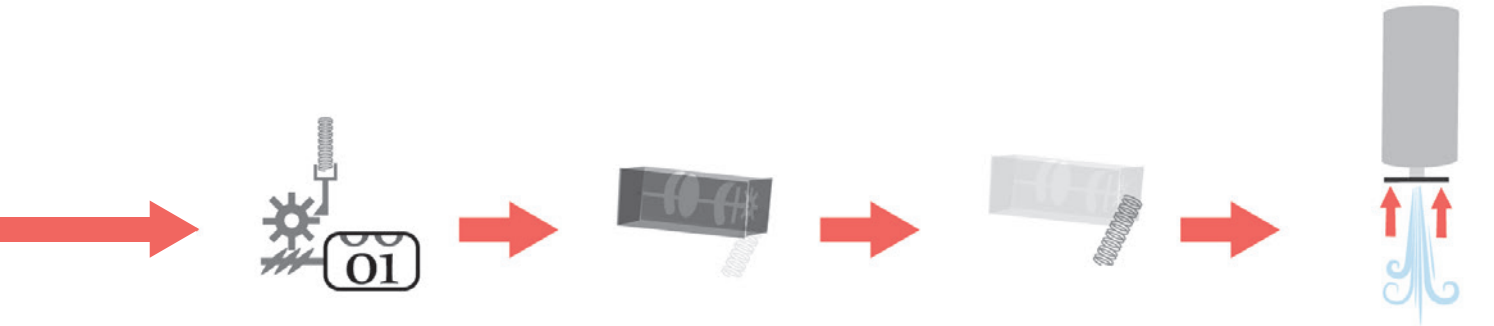


Figure 4: Integration of the inhaler's subsystems.



5) Dose Counter Mechanism

6) Drive Mechanism (Cocking)

7) Drive Mechanism (Spring)

8) Canister Activation

UNDERSTANDING AND TRUSTING SYSTEMS ENGINEERING'S VALUE

Although SE for complex portable drug delivery devices demands a greater expense up front, it is well worth it in the long run. A less-seasoned drug delivery device manufacturer that has no experience with problematic late-stage PD issues, for example, may not immediately understand the value of the SE approach. However, medical device makers should have faith that the extra up-front costs required by SE will pay off in reduced risk, more timely development schedules and greater efficiency.

Medical device makers that understand SEs' high value should listen carefully to the language potential vendors use. Such SE terms as subsystem, integration, subsystem interactions, and system-level requirements and specifications indicate that the vendor's SE approach is sound and credible.

Additionally, when asked about how it approaches proof of concept, the vendor should be able to explain that its engineers work out the functional aspects of the device in question "on the bench" first, rather than jumping straight to a fully integrated product concept.

SE FOR FUTURE DELIVERY DEVICES

Healthcare products continue to shrink, feature greater connectivity and grow more complex. These trends are not going away, and the SE approach to development is the best choice for firms creating these devices. Delivery device manufacturers can stay current and competitive by taking the SE approach to product development for reduced user, patient, product, financial and schedule risk *and* improved PD lifecycle efficiency. Those who don't, may find themselves falling behind.

PLEASE MARK YOUR CALENDAR AND PLAN TO ATTEND!

RDD ASIA 2016

Respiratory Drug Delivery

NOVEMBER 8-11, 2016

Grand Hyatt Hotel • Goa, INDIA

Poster Abstract Submission
June 24, 2016
Email: info@rddonline.com

For more information visit
rddonline.com/rddasia2016

RDD Asia is a conference jointly organized by

RDD Online
Respiratory Drug Delivery

Aptar
pharma

Offering the Shortest Path to Market with our Unique Inhalation Technology Platform

Providing a uniform dose in a portable, easy-to-use system, capsule-based DPI is a simple and cost-effective way to deliver medication via the pulmonary route.* Capsugel's capsules are custom engineered to provide optimal performance between the capsule/device and capsule/formulation to achieve the highest safety and efficacy of the drug product. Complementing Capsugel's 20 years expertise in specialized inhalation capsules, Bend Research provides a full range of services and know-how in particle engineering for small and large molecules, as well as fast track programs for new chemical entities and generics.

Contact us today to learn more about our unique technology platform for inhalation drug delivery.

* Twister® - courtesy of Aptar Pharma.

dpicapsule.com 888-783-6361

CAPSUGEL®

ADVANCES IN PULMONARY DELIVERY OF INHALED ANTI-INFECTIVES

With the growing problems caused by antimicrobial resistance, there is increasing interest in the use of improved strategies for drug delivery. David L. Hava, PhD, Chief Scientific Officer, Pulmatrix, explores the benefits of nebulised inhaled antibiotics delivered via high throughput nebulisers for aqueous formulations or dry powder inhalations for cystic fibrosis patients.

Pulmonary infectious diseases afflict millions of people annually, with significant morbidity and mortality associated with bacterial, viral and fungal infections. Patients with respiratory disease are particularly susceptible to infection, where respiratory infections are associated with exacerbations of disease and worsening lung function. The impact of infectious diseases and the growing threat of antimicrobial resistance have heightened the need for novel anti-infectives and led to incentives aimed at the pharmaceutical industry to discover and develop drugs to meet this need.

INHALED DRUG DELIVERY OF ANTI-INFECTIVES

A complementary approach to improving anti-infective therapies is to develop improved strategies for drug delivery that enable higher therapeutic indices and higher drug concentrations at the sites of infection. This strategy has been especially effective in the development of inhaled antibiotics for cystic fibrosis (CF) patients with *Pseudomonas aeruginosa* infection (Table 1). Due to impaired mucociliary clearance and mucus accumulation in the airways, patients with CF become colonised with a number of different bacteria early in life and eventually become chronically colonised with pathogens such as *P aeruginosa*.

> "In the specific case of inhaled anti-infectives, given the high drug loads required for efficacy in the lung, lactose-based technologies are inadequate to deliver these drug in sufficient quantities. Therefore, novel DPI technologies are required to enable anti-infective products for inhalation."

In a landmark study, Ramsey *et al* studied the effect of inhaled tobramycin on pulmonary function and *P aeruginosa* infection in CF patients over a 24-week period.[1] They found that patients treated with inhaled tobramycin had an increase in FEV1 of 10% and decreased *P aeruginosa* density in sputum at week 20 compared with placebo. Importantly, inhaled tobramycin was not associated with accumulation of drug in plasma or the ototoxicity and nephrotoxicity that can be associated with systemically delivered aminoglycosides.[2,3]

This study led to the approval of

David L. Hava
Chief Scientific Officer
T: +1 781-357-2333
F: +781-357-2399

Pulmatrix, Inc
99 Hayden Ave
Suite 390
Lexington, MA
United States

www.pulmatrix.com

Drug product	Drug substance	Target	Format	Company	Status
TOBI®	tobramycin	*P aeruginosa*	Nebulized	Novartis	Approved
TOBI® Podhaler™	tobramycin	*P aeruginosa*	DPI	Novartis	Approved
Cayston®	aztreonam	*P aeruginosa*	Nebulized	Gilead	Approved
Colobreathe®	colistin	*P aeruginosa*	DPI	Forest	Approved (EU)
Arikace™	amikacin	NTM	Nebulized	Insmed	Phase 3
Ciprofloxacin DPI	ciprofloxacin	*P aeruginosa*	DPI	Bayer	Phase 3
AeroVanc™	vancomycin	MRSA	DPI	Savara	Phase 3
Pulmaquin™	ciprofloxacin	*P aeruginosa*	Nebulized	Aradigm	Phase 3
FTI	fosfomycin - tobramycin	*P aeruginosa*	Nebulized	CURx	Phase 3
FAI	fosfomycin - Amikacin	Gram negative bacteria / VAP	Nebulized	Cardeas	Phase 2
PUR1900	itraconazole	*Aspergillus spp*	DPI	Pulmatrix	Preclinical

Table 1: Current inhaled anti-infective therapies approved or in development

Tobramycin Inhalation Solution (TOBI®; Novartis AG, Basel, Switzerland) in 1999, for the management of CF patients with *P aeruginosa*. TOBI is supplied as a liquid solution to be used with a reusable jet nebulizer (Pari LC Plus, PARI, Midlothian, VA, US) and an air compressor. TOBI is administered twice daily, with each administration taking approximately 15 minutes to complete.[4]

Subsequently, a second antibiotic, aztreonam, has been developed as a nebulised liquid formulation by Gilead (Cayston®; Gilead, Foster City, CA) for similar use, with other nebulised products in development (Table 1).

The development of nebulised inhaled antibiotics provided a major advance to address significant unmet need in CF. While nebulised products are suitable for patients in a hospital setting, such as those with ventilator-associated pneumonia (VAP), the formulation of inhaled antibiotics into a portable, user-friendly format is desired to reduce treatment burden and improve compliance.

High throughput nebulisers for aqueous formulations or dry powder inhalers (DPI) have been two approaches to solve this challenge. For decades, lactose blends have been the cornerstone of inhaled dry powder therapies for asthma and chronic obstructive pulmonary disease (COPD), where small doses of drug, typically less than 500 µg are required for efficacy. Lactose-based DPI, formulations are created with small, respirable (<5 µm) crystalline drug particles blended with large particles of micronised lactose (~150 µm), whereby the drug particles detach from the lactose carrier during inhalation and the drug is then available for delivery to the lung (Figure 1a, next page).

> "The majority of inhaled anti-infective approaches have focused on the treatment of P aeruginosa infection, with more recent programs focused on MRSA and non-tuberculoid mycobacterium."

This technology has been successfully applied to potent small molecules and small molecule combinations for COPD and asthma. In the specific case of inhaled anti-infectives, given the high drug loads required for efficacy in the lung, lactose-based technologies are inadequate to deliver these drug in sufficient quantities. Therefore, novel DPI technologies are required to enable anti-infective products for inhalation.

Particle engineering using spray drying allows for the manufacture of dry, respirable particles that can be loaded with high weight percentages of drug. Early technologies that utilised this approach, Pulmospheres™ (Novartis AG, Basel, Switzerland) and the ARCUS™ technology (Acorda Therapeutics, Ardsley, NY, US), were developed as low-density, porous particle technologies in which geometrically large particles (>5 µm) could be manufactured such that the particle morphology resulted in particles with small aerodynamic size.[5,6]

The resulting particles overcome several major limitations of lactose blend DPIs: obviated the need for lactose blending by avoiding the use of highly cohesive small drug particles,[7] improved delivery efficiency to the lungs and allowed for delivery of high drug loads. Pulmospheres are the underlying technology used to develop TOBI Podhaler™, a dry powder version of tobramycin.

In clinical trials, TOBI Podhaler™ efficacy was comparable with the inhalation solution,[8,9] yet results in lower total drug exposure (112 mg dry powder to 300 mg nebulised) in a drug product configuration that allows the dose to be administered in only a few minutes using a portable system. A number of other dry powder formulations are advancing through clinical development (Table 1), including ciprofloxacin DPI (Bayer HealthCare Pharmaceuticals, Whippany, NJ, US) for treating *P aeruginosa* and AeroVanc™ (Savara Inc, Austin, TX, US) for methicillin-resistant *Staphylococcus aureus* (MRSA).

A more recently developed particle engineering technology, iSPERSE™ (Pulmatrix Inc, Lexington, MA, US) leverages advantages of both the first generation spray drying technologies and small, dense drug particles to enable unique inhalation products for treating respiratory disease. In contrast to Pulmospheres and ARCUS particles, iSPERSE particles are both geometrically and aerodynamically small with higher density particles (typical tapped densities >0.4 g/cc).

In contrast to small and dense neat drug particles that require lactose blending for drug dispersibility (Figure 1a), iSPERSE particles (Figure 1b) are dispersible in the absence of carrier and result in consistent drug delivery to the lungs independent of inspiratory flow rate and patient effort. Due to the high density of the particles, iSPERSE-based products can be developed across a range of DPI technologies, including capsule, blister and reservoir-based devices.

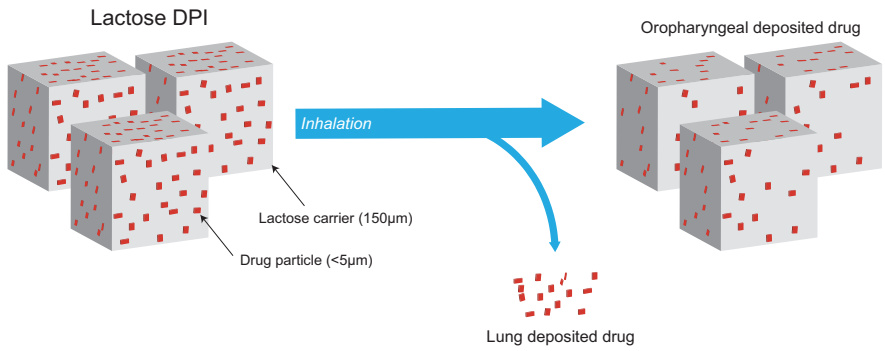


Figure 1a: Lactose DPI are formulated with crystalline, micronized drug particles (red) blended with large lactose particles. During inhalation, drug particles detach from the lactose carrier allowing a fraction of the drug to be inhaled into the lungs. Due to their large size, the lactose particles, with remaining attached drug, deposit in the oropharyngeal cavity and are swallowed.[7]

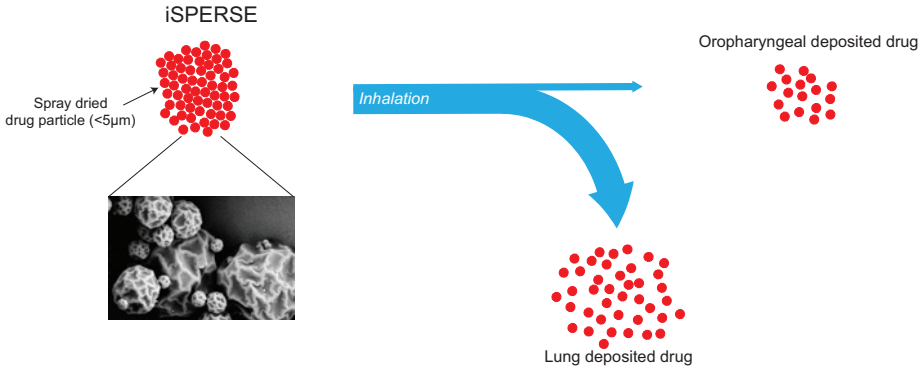


Figure 1b: Spray dried iSPERSE particles are formulated with drug & excipients in the same particle with no need for blending. Upon inhalation, the small drug particles readily disperse and a high fraction (>50%) of the particles are delivered to the lung, with a smaller fraction depositing in the oropharynx. The resulting efficiency results in 3-4 times the amount of drug delivered to the lungs compared with lactose DPI.

MORBIDITY AND MORTALITY OF PULMONARY FUNGAL INFECTIONS

The majority of inhaled anti-infective approaches have focused on the treatment of *P aeruginosa* infection, with more recent programs focused on MRSA and non-tuberculoid mycobacterium (NTM). In addition to bacterial infections, pulmonary fungal infections, particularly those caused by the spore-forming mould *Aspergillus fumigatus* cause significant morbidity and mortality in a number of patient populations.

A fumigatus is the predominant species causing disease, however, other species such as *A niger*, *A terrus*, *A flavus* infect humans as well. Pulmonary *A fumigatus* infections manifest as a range of diseases depending on the host immune state and underlying lung disease.[10] In immunocompromised hosts, invasive pulmonary aspergillosis (IPA) is a life-threatening disease occurring in patients with impaired immunity as a result of treatment for haematological cancers, solid organ transplantation or other immunosuppressive conditions.

The mortality rate of IPA in neutropenic and hematopoietic stem-cell transplant recipients is >50% and 90%, respectively.[11,12] Because of the significant mortality associated with IPA, antifungal prophylaxis is used to reduce the risk of infection.

A fumigatus also causes chronic infection in patients with chronic lung disease such as asthma, COPD and CF. *Aspergillus spp* are the most common fungi present in the lungs of patients with CF, with *A fumigatus* being predominant.[13,14] CF patients with chronic *A fumigatus* infection have lower percent predicted FEV1 than uninfected controls and persistently infected patients have a higher rate of hospitalisations for pulmonary exacerbations.[15]

Pulmonary infection with *A fumigatus* can cause allergic bronchopulmonary aspergillosis (ABPA), an allergic response resulting from hypersensitivity to fungal antigens. ABPA is characterised by a local and systemic eosinophilic and IgE inflammatory response, and acute exacerbations that lead to worsening lung function.[10] Chronic *Aspergillus* infection and ABPA are not commonly associated with invasive aspergillosis.

The annual burden of chronic aspergillosis and ABPA is significantly higher than that of IPA, with more than 3 million cases of chronic disease and 4.8 million cases of ABPA annually (www.gaffi.org).[16] The majority of ABPA represents disease in asthmatics, which equates to 1-2.5% of all asthmatics worldwide. In CF, reports of ABPA prevalence vary from 1 to 15%,[17] with reports of colonisation rates in respiratory samples ranging from 6 to 58%.[15,16,18]

New methods to detect *Aspergillus spp* in sputum using quantitative PCR and galactomannan ELISA have the potential to increase significantly the sensitivity of detection and ultimately, diagnosis. These techniques have been used recently to classify patients into four subgroups; those without aspergillosis, those sensitised to *Aspergillus spp*, those with ABPA and those with aspergillus bronchitis.[16]

Using this methodology, Baxter *et al* classified 130 CF patients and found that 30% had aspergillus bronchitis and 17.7% had ABPA. Armstead *et al* extended these findings by comparing these rates with the reported rates of ABPA in CF registries and literature reports for adult CF patients from 30 different countries.[19] They found that the number of ABPA cases diagnosed and reported is likely a significant under-

representation of the estimated cases when more sensitive diagnostic assays are utilised. Of particular interest, in the US the number of documented adult CF cases of ABPA (869 cases) was 34.6% of the estimated cases (2510 cases) defined by Armstead *et al*. Using the more recent data, almost 50% of US adult CF patients are predicted to have either ABPA or aspergillus bronchitis.[19]

Anti-fungal treatment regimens for ABPA and aspergillus bronchitis commonly rely on oral triazoles, such as itraconazole and voriconazole, that inhibit fungal cytochrome P450 synthesis of ergosterol, a critical component of the fungal cell wall.[20] ABPA is a more severe disease than aspergillus bronchitis where oral corticosteroid therapy is recommended, with the addition of oral itraconazole to treatment regimens in certain situations.[17] Long-term oral steroid use, while effective at reducing inflammation, is associated with severe side effects that must be managed and monitored.[21] Oral corticosteroid side effects have led to intense efforts to develop steroid sparing agents for a number of diseases including ABPA.

Oral itraconazole therapy has a demonstrated benefit in the treatment of aspergillus bronchitis[22] and ABPA,[23-25] and a number of case reports and case studies have demonstrated a benefit of antifungal therapy in treating ABPA in both CF and non-CF patients.[26] Two randomised, placebo-controlled studies have explored the anti-inflammatory effect and clinical response to oral itraconazole in asthmatics with ABPA.[23,24]

These studies both describe a benefit of oral itraconazole therapy *versus* placebo. Stevens *et al*[24] performed a 16-week double blind, placebo-controlled randomised study in 55 asthmatics with ABPA, with a 16-week open label extension in which all patients received oral itraconazole. The primary endpoint was the clinical response to therapy, defined as a combination of decreasing corticosteroid use and decrease in systemic IgE, with either an improvement in lung function or exercise tolerance.

The study found a significant improvement in clinical response in the itraconazole group compared with placebo (13/28 *versus* 5/27; p=0.04), with more than 70% of patients reducing oral corticosteroid dose by 50% or more. Notably, 12 of 33 patients who did not respond in the double blind portion of the study had a clinical response in the open label extension.[24] In a complementary study, Wark *et al* studied the impact of oral itraconazole on pulmonary inflammation by assessing sputum eosinophilia and sputum levels of eosinophil cationic protein (ECP) in 29 stable patients with ABPA.[23] Itraconazole therapy was associated with a significant drop in sputum eosinophils over the first month of therapy (35% reduction *versus* placebo; p<0.01) that was maintained over 16 weeks. Similar effects were seen with ECP in sputum and in serum levels of IgE and *Aspergillus*-specific IgG.

The results from the studies by Wark *et al* and Stevens *et al* are supportive of broader and more consistent use of antifungal therapy to treat ABPA. Two smaller studies have examined the role of oral itraconazole in treating ABPA in CF patients. Denning *et al* evaluated itraconazole therapy in six ABPA patients, three of which had CF.[25] All three CF patients successfully reduced corticosteroid use, and two of the three showed substantial clinical improvement, including improved lung function and reduced serum IgE.

> "Clinical development of PUR1900 is planned to initiate in 2016 and comes at a time when there is an urgent need for novel anti-fungal drugs and a relatively sparse development pipeline."[36]

A larger case series studied 16 CF patients with ABPA.[27] Itraconazole use was associated with reductions in corticosteroid use (47% reduction) and acute exacerbations (55% reduction). Due to the increased risk of long-term steroid use on the development of diabetes, osteoporosis and growth, the opportunity to reduce steroid use through the treatment with oral itraconazole is highly desired.[28,29]

LIMITS OF CURRENT ANTI-FUNGAL TREATMENTS

Despite the promise of oral itraconazole and triazoles in the treatment of aspergillus bronchitis and ABPA, these therapies have significant limitations that limit their long-term utility (Table 2). Limitations include side effects such as hepatoxicity and phototoxicity with voriconazole, variability in the bioavailability of itraconazole following oral dosing and extensive drug-drug interactions (DDI) due to the metabolism of azoles in the liver.

Variability in the achieved plasma levels of itraconazole have been reported in a number of studies and suggested as a variable that may account for inconsistent clinical responses.[25,27] Oral bioavailability of itraconazole in healthy volunteers is 55%, which may be further reduced in patients with poor digestive function.[30]

Itraconazole pharmacokinetics (PK) following oral dosing have been evaluated in CF patients. An exploratory PK study in 12 CF patients ≥16 years old and five CF patients <16 years old examined plasma concentrations of itraconazole and its active metabolite, hydroxy (OH)-itraconazole, over 14 days.[31] After eight days, steady-state concentrations were achieved with high inter-subject variability. None of the young patients and only 50% of the older patients achieved steady-state itraconazole trough concentrations >250 ng/mL. Plasma concentrations of >250 ng/mL have been defined as the target trough concentration required to get sufficient itraconazole lung levels to treat infection.[32]

These results were similar to a second study that examined serum and sputum concentrations in 11 CF patients with ABPA aged 5-15 years.[33] Five patients failed to reach itraconazole plasma trough concentrations >250 ng/mL at steady state. Additionally, sputum concentrations of itraconazole were variable across patients, with five of 11 failing to achieve sputum concentrations above the reported 90% minimum inhibitory concentration (MIC90) for *A fumigatus* both at trough and 4h after oral dosing. Inconsistency in itraconazole exposure systemically and consequently in the lung may account for some of the variability in clinical responses.

A larger trial aimed at studying the therapeutic benefit of oral itraconazole in CF patients failed to show a clinical benefit of itraconazole, with the majority of patients failing to achieve therapeutic blood levels of itraconazole.[34] Thus, despite the potential benefit of treating ABPA and aspergillus bronchitis with itraconazole, it is challenging to achieve consistently high exposure in plasma and lungs, with oral dosing. An inhaled version of itraconazole via DPI could seemingly overcome these limitations and provide a better option for patients.

Attribute	Oral delivery	Inhaled delivery
Total dose	> 400 mg daily	< 40 mg daily
Lung to plasma exposure ratio	Low	High
Bioavailability	55% - itraconazole > 95% - voriconazole	> 60% directly to site of infection
Lung exposure	Variable; affected by diet	Consistently high
Side effects	Systemically and orally driven • Gastrointestinal • Phototoxicity (Voriconazole) • Drug-drug interactions	Locally driven

Table 2: Oral versus inhaled itraconazole.

BENEFITS OF INHALED ANTI-FUNGALS OVER CONVENTIONAL THERAPIES

PUR1900 or Itraconazole Inhalation Powder, is a dry powder formulation of itraconazole formulated in the iSPERSE platform technology. PUR1900 is engineered to have a small aerosol particle size for efficient pulmonary delivery and is intended to be delivered using a capsule-based DPI. PUR1900 formulations in development have mass median aerosol diameters (MMAD) of ~3 µm and high fine particle doses (FPD; % of the nominal dose < 5 µm), resulting in more than 50% of the nominal dose reaching the lungs. Notably, the aerosol target range of PUR1900 is similar to that of *Aspergillus* conidia, allowing for itraconazole delivery to lung sites where fungal spores also deposit upon inhalation.

Pulmonary delivery of itraconazole is expected to overcome many limitations of oral anti-fungal therapies (Table 2). PUR1900 enables the delivery of high doses of itraconazole (>10 mg) to the lungs that exceed both the minimum inhibitory concentration of itraconazole against *A fumigatus* and the levels achieved with oral dosing, while limiting systemic exposure. The profile of achieving high lung concentrations and low plasma concentrations reverses the profile achieved with oral dosing where high plasma concentrations are needed for achieving therapeutic lung levels. In Figure 2, plasma concentration is depicted for an orally dosed drug (aqua) and an inhalation drug (purple). Oral dosing (A) results in high plasma concentrations that may lead to toxicity or drug-drug interactions. High plasma exposure is necessary to achieve therapeutic exposure in the lungs. In contrast, inhaled dosing requires less exposure overall and results in significantly less systemic exposure. Inhaled dosing (B) achieves higher local concentrations in the lung that significantly exceed the minimum inhibitory concentration (MIC) of the drug over a long period of time. Due to the direct delivery of high concentrations of drug directly to the lung, the achieved pulmonary concentrations following inhalation may greatly exceed those achieved by oral dosing.

High lung concentrations achieved through inhalation may increase the time that lung drug levels remain above the minimum inhibitory concentration of itraconazole, a critical parameter of triazole efficacy,[35] and may further lead to concentrations that achieve fungicidal activity. Low plasma exposure following inhalation will reduce the risk of drug-drug interactions, which is especially important since azoles affect the PK of recently approved CFTR modulators that will be widely used by CF patients. The lower systemic exposure is also expected to ease the side-effect burden in the CF patients.

Clinical development of PUR1900 is planned to initiate in 2016 and comes at a time when there is an urgent need for novel anti-fungal drugs and a relatively sparse development pipeline.[36] The mainstays of current anti-fungal therapy centre on azoles, echinocandins and amphotericin B, each with limitations in both activity, convenience of dosing (IV *versus* oral) and toxicity. While drugs with novel mechanisms of action are in development, these come with the added risk of both uncertain activity and unknown toxicities in man. Similarly, new drugs in existing drug classes must be studied comparatively with standard of care to demonstrate safety or efficacy benefits to support their adoption.

As a reformulation of a drug with years of clinical data, known activity and addressable limitations via inhalation, PUR1900 has the potential to provide a valuable addition to current treatment options for pulmonary fungal diseases.

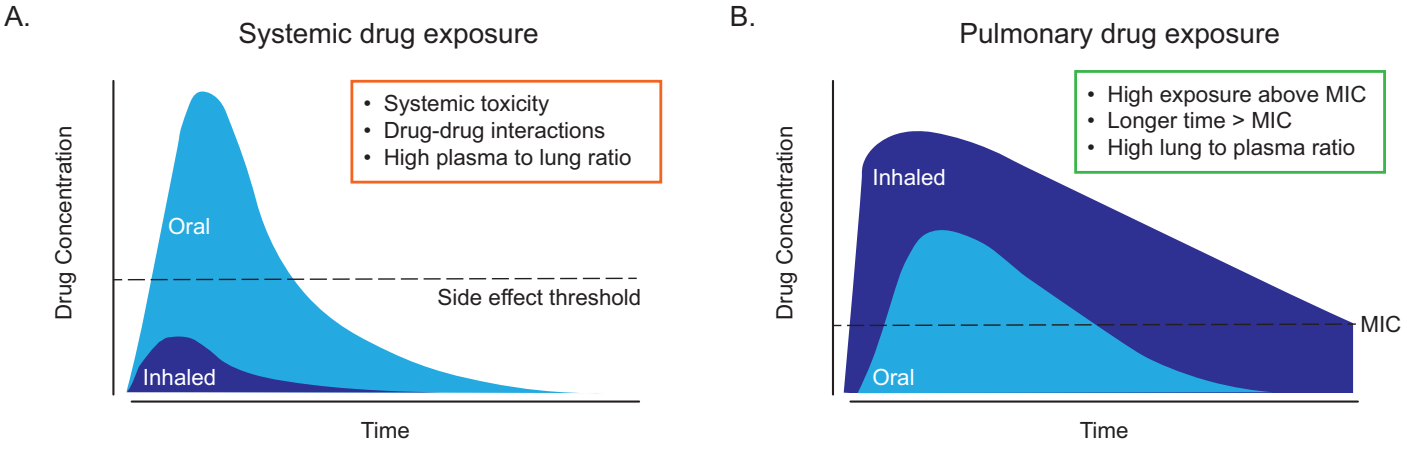


Figure 2: Inhaled delivery of anti-fungal increases lung exposure while reducing systemic exposure that leads to side effects.

REFERENCES

1. *Ramsey BW et al, "Intermittent administration of inhaled tobramycin in patients with cystic fibrosis". Cystic Fibrosis Inhaled Tobramycin Study Group. N Engl J Med, 1999, Vol 340(1), pp 23-30.*
2. *Leis JA, Rutka JA and Gold WL, "Aminoglycoside-induced ototoxicity". CMAJ, 2015, Vol 187(1), pp E52.*
3. *Wargo KA and Edwards JD, "Aminoglycoside-induced nephrotoxicity". J Pharm Pract, 2014, Vol 27(6), pp 573-577.*
4. *Novartis, TOBI: Tobramycin Inhalation Solution Package Insert.*
5. *Weers J and Tarara T, "The PulmoSphere platform for pulmonary drug delivery". Ther Deliv, 2014, Vol 5(3), pp 277-295.*
6. *Edwards D A et al, "Large porous particles for pulmonary drug delivery". Science, 1997, Vol 276(5320), pp 1868-1871.*
7. *Telko MJ and Hickey AJ, "Dry powder inhaler formulation". Respir Care, 2005, Vol 50(9), pp 1209-1227.*
8. *Konstan MW et al, "Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial". J Cyst Fibros, 2011, Vol 10(1), pp 54-61.*
9. *Konstan MW et al, "Tobramycin inhalation powder for P aeruginosa infection in cystic fibrosis: the EVOLVE trial". Pediatr Pulmonol, 2011, Vol 46(3), pp 230-238.*
10. *Kousha M, Tadi R and Soubani AO, "Pulmonary aspergillosis: a clinical review". Eur Respir Rev, 2011, Vol 20(121), pp 156-174.*
11. *Yeghen T et al, "Management of invasive pulmonary aspergillosis in hematology patients: a review of 87 consecutive cases at a single institution". Clin Infect Dis, 2000, Vol 31(4), pp 859-868.*
12. *Fukuda T et al, "Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning". Blood, 2003, Vol 102(3), pp 827-833.*
13. *Pihet M et al, "Occurrence and relevance of filamentous fungi in respiratory secretions of patients with cystic fibrosis – a review". Med Mycol, 2009, Vol 47(4), pp 387-397.*
14. *Sabino R et al, "Molecular epidemiology of Aspergillus collected from cystic fibrosis patients". J Cyst Fibros, 2015, Vol 14(4), pp 474-481.*
15. *Amin R et al, "The effect of chronic infection with Aspergillus fumigatus on lung function and hospitalization in patients with cystic fibrosis". Chest, 2010, Vol 137(1), pp 171-176.*
16. *Baxter CG et al, "Novel immunologic classification of aspergillosis in adult cystic fibrosis". J Allergy Clin Immunol, 2013, Vol 132(3), pp 560-566 e10.*
17. *Stevens DA et al, "Allergic bronchopulmonary aspergillosis in cystic fibrosis--state of the art: Cystic Fibrosis Foundation Consensus Conference". Clin Infect Dis, 2003, 37 Suppl 3, pp S225-264.*
18. *de Vrankrijker AM et al, "Aspergillus fumigatus colonization in cystic fibrosis: implications for lung function?" Clin Microbiol Infect, 2011, Vol 17(9), pp 1381-1386.*
19. *Armstead J, Morris J and Denning DW, "Multi-country estimate of different manifestations of aspergillosis in cystic fibrosis". PLoS One, 2014, Vol 9(6), pp e98502.*
20. *Cowen LE and SteinbachWJ, "Stress, drugs, and evolution: the role of cellular signaling in fungal drug resistance". Eukaryot Cell, 2008, Vol 7(5), pp 747-764.*
21. *Liu D et al, "A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy". Allergy Asthma Clin Immunol, 2013, Vol 9(1), pp 30.*
22. *Chrdle A et al, "Aspergillus bronchitis without significant immunocompromise". Ann N Y Acad Sci, 2012, 1272, pp 73-85.*
23. *Wark PA et al, "Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: a randomized controlled trial". J Allergy Clin Immunol, 2003, Vol 111(5), pp 952-957.*
24. *Stevens DA et al, "A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis". N Engl J Med, 2000, Vol 342(11), pp 756-762.*
25. *Denning DW et al, "Adjunctive therapy of allergic bronchopulmonary aspergillosis with itraconazole". Chest, 1991, Vol 100(3), pp 813-819.*
26. *Moreira AS et al, "Antifungal treatment in allergic bronchopulmonary aspergillosis with and without cystic fibrosis: a systematic review". Clin Exp Allergy, 2014, Vol 44(10), pp 1210-1227.*
27. *Nepomuceno IB, Esrig S and Moss RB, "Allergic bronchopulmonary aspergillosis in cystic fibrosis: role of atopy and response to itraconazole". Chest, 1999, 115(2), pp 364-370.*
28. *Eigen H et al, "A multicenter study of alternate-day prednisone therapy in patients with cystic fibrosis". Cystic Fibrosis Foundation Prednisone Trial Group. J Pediatr, 1995, Vol 126(4), pp 515-523.*
29. *Bhudhikanok GS et al, "Correlates of osteopenia in patients with cystic fibrosis". Pediatrics, 1996, 97(1), pp 103-111.*
30. *Prentice AG and Glasmacher A, "Making sense of itraconazole pharmacokinetics". J Antimicrob Chemother, 2005, 56, Suppl 1, pp i17-i22.*
31. *Conway SP et al, "Pharmacokinetics and safety of itraconazole in patients with cystic fibrosis". J Antimicrob Chemother, 2004, Vol 53(5), pp 841-847.*
32. *Boogaerts MA et al, "Antifungal prophylaxis with itraconazole in prolonged neutropenia: correlation with plasma levels". Mycoses, 1989, 32 Suppl 1, pp 103-108.*
33. *Sermet-Gaudelus I et al, "Sputum itraconazole concentrations in cystic fibrosis patients". Antimicrob Agents Chemother, 2001, Vol 45(6), pp 1937-1938.*
34. *Aaron SD et al, "Treatment of Aspergillus fumigatus in patients with cystic fibrosis: a randomized, placebo-controlled pilot study". PLoS One, 2012, Vol 7(4), pp e36077.*
35. *Lepak AJ and Andes DR, "Antifungal pharmacokinetics and pharmacodynamics". Cold Spring Harb Perspect Med, 2015, Vol 5(5), pp a019653.*
36. *Denning DW and Bromley MJ, "Infectious Disease. How to bolster the antifungal pipeline". Science, 2015, Vol 347(6229), pp 1414-1416.*

Qualicaps Engineered to perform

CAPSULE-BASED DRY POWDER INHALERS, AN OPTIMAL SOLUTION FOR DIFFERENT INSPIRATIONAL RATES

There is a wide range of devices available to deliver inhalation therapies, but there is increasing interest in the use of dry powder inhalers (DPIs) due to improved engineering and powder formulations. In this article, Gabriela Dujovny, PhD, Scientific Business Development Manager, Qualicaps, looks at the advantages and disadvantages of the DPIs currently available and reports on a study of dry powder inhalation aerosolisation performance at different flow rates.

There are several routes available for drug administration, of which the most popular have been oral and injectable. Advances in drug delivery technology have led to the development of several non-invasive, self-administered forms that offer excellent alternatives to these more traditional routes. For example, inhalation technology of medicines offers significant and unique benefits as the delivery of the active compounds targets the lungs directly, minimising side effects from systemic distribution and allowing for a lower dose together with a rapid onset of action.

It is the preferred route for drug administration in chronic respiratory diseases, primarily asthma and chronic obstructive pulmonary disease (COPD); although besides the treatment of respiratory diseases, inhalation drug delivery is also being investigated for a wide range of potential systemic therapies, such as insulin, oxytocin, antibiotics, vaccines and drugs (including peptides and proteins) for neurological disorders.

Pulmonary drug delivery technologies are based on developing simple, easy-to-use, cost effective devices. These devices should provide consistent drug delivery, with high lung penetration and a multiple dosage capacity. Portable devices can be essentially grouped into two main categories: pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs). DPIs are gaining market share and are forecasted to become the dominant player by 2018[1] (Figure 1).This growth is due to new developments along with improved device engineering and more adequate powder formulations. In addition, DPIs are activated by the patient's inspiratory airflow and subsequently are breath-actuated, therefore eliminating the dependence on hand-mouth co-ordination required with pMDIs.

> "One of the most important characteristics of micro-dispersed particles generated after inspiration is their particle size."

DPIs currently available on the market include:

- Single-dose capsule DPIs, e.g. Aerolizer, Novartis, Basel, Switzerland; Handihaler, Boehringer-Ingelheim, Ingelheim am Rhein, Germany
- Multi-dose devices:
  - Those devices with a bulk drug reservoir which is metered by the patient during use, e.g. Turbuhaler, AstraZeneca, London, UK; Twisthaler, Schering, Kenilworth, NJ, US.

Dr Gabriela Dujovny
Scientific Business Development Manager
T: +34 916 630 869
E: gdujovny@qualicaps.es

Qualicaps S.A.U.
Avda. Monte Valdelatas 4
28108 Alcobendas
Madrid
Spain

www.qualicaps.com

- Those with pre-metered dispensed doses packaged inside blisters, Diskus (Accuhaler® in the UK), GSK, Brentford, UK.

Each inhaler type has advantages and disadvantages that must be considered with regard to drug delivery performance.

FACTORS THAT AFFECT DPI DRUG DELIVERY PERFORMANCE & EFFECTIVENESS

The effectiveness of powder drug delivery to the lungs depends on several factors:

- Powder formulation
- Inspiratory airflow rate generated by the patient
- Device intrinsic resistance to airflow defined as the turbulence produced inside the device to generate the respirable inhalation aerosol
- Humidity, that can affect the dose delivery from the DPI.

The inspiratory airflow generated by the patient represents the only active force able to produce the micro-dispersion of the powder formulation for inhalation. One of the most important characteristics of micro-dispersed particles generated after inspiration is their particle size.

Inhaled drug particles will deposit in different regions of the respiratory tract according to their particle size: particles of 1–5 µm will deposit at the end of the respiratory airways – the target area of therapeutic application – while particles >5 µm will predominately deposit in the oropharynx. This relates to particle dynamic behaviour and describes the main mechanisms of aerosol deposition:

- **Inertial impaction:** which mainly influences the deposition of larger particles where the ability to follow the respiratory flow is reduced proportionally to velocity of flow. This occurs mainly with large or high-velocity particles, i.e. those with high inertia, that are unable to follow the airstream when it changes direction, thus impacting on the airway wall, usually the upper part of the airways.
- **Sedimentation:** process proportional to the aerodynamic particle size and to the period during which the particles remain in the lungs.[2,3] Momentarily withholding one's breath after inhaling increases the likelihood of lung deposition.[4]
- **Diffusion:** particles smaller than 0.5 µm may not deposit at all, since they move by Brownian motion and settle very slowly.

In order to de-agglomerate powder particles from a bond on larger carrier molecules (such as lactose) into a respirable dose, a sufficient flow rate must be achieved in the DPI device.

On the other hand, stronger air flows cause a higher grade of impaction, resulting in higher rates of oropharyngeal deposition. Therefore, lung deposition in most DPIs depends considerably on the patients' inspiratory flow rate and the particular device's intrinsic resistance.

The intrinsic resistance to airflow through the device is an important determinant of the final flow rate resulting in the inhaler. It defines how much inspiratory flow should be created in the device to release the correct amount of the delivered drug. However, flow resistance differs from device to device, and the recommended evaluation to determine the correct flow rate for a particular DPI is *in vivo*/*in vitro* testing of the device.

To calculate the correct flow rate to be tested, it is necessary to establish the flow rate that produces a drop in pressure with the device of approximately 4 kPa, comparable with that found *in vivo* when using a particular inhaler under study with its specific resistance.[5] The efficacy of DPIs depends on the strength and duration of a single inhalation by the user. The duration of the test is set on the basis of the total air volume typically inhaled in one adult breath, adjusted to be four litres in the case of the EurPh and two litres in the case of the USP.

DPI devices have different intrinsic degrees of resistance to flow, i.e. some require more effort to inhale than others. A low-resistance device presents less resistance to airflow, meaning that it may be easier to use and therefore more effective for patients. Conversely, in high-resistance devices, patients need to apply greater effort to generate the necessary inspiratory flow to allow for an optimum drug delivery.[6]

However, the dependency of a DPI on inspiratory flow rates involves contradictory aspects that can generate a conceptual misunderstanding that comes into play when deciding which DPI is more convenient for the patient in real life. It has been shown that a higher intrinsic resistance of a DPI needs stronger inspiratory capacity, but reduces oropharyngeal deposition of the particles because the impaction of particles in larger airways is diminished.

Although low-resistance devices are associated with the concept of "the most effective DPIs", they require inspiratory abilities sufficient enough to de-agglomerate the medication formulation into particles suitable for lung deposition (micro-dispersion)[7] and frequently cannot be achieved by those affected with a disease-induced airflow limitation.[8] A patient capable of reaching a flow rate of more than 60 L/min is considered ideal for use of most DPI devices.[9]

The other factor that can affect DPI performance and effectiveness of drug delivery is humidity, which can cause clumping of the particles and reduce the de-agglomeration of the respirable aerosol. For example, reservoir-based DPIs have chambers

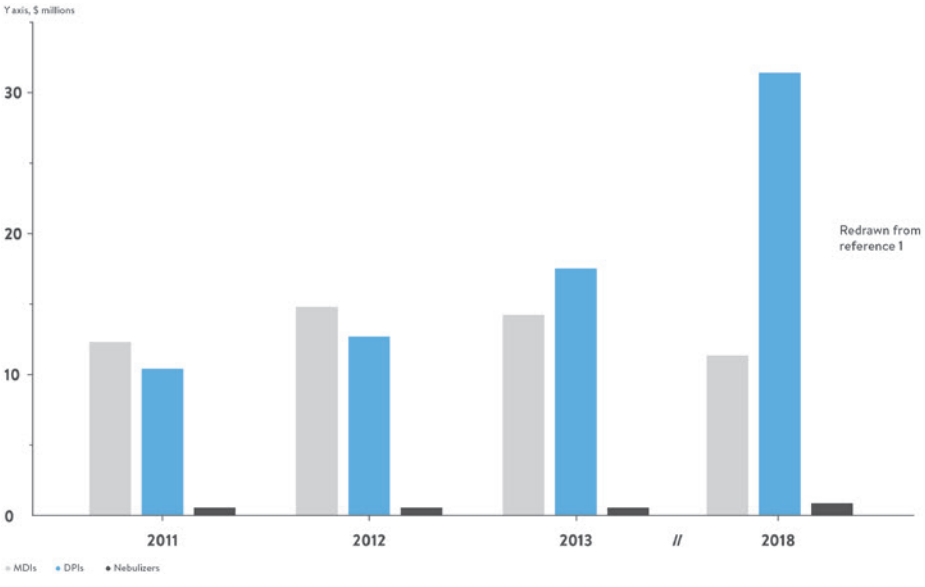
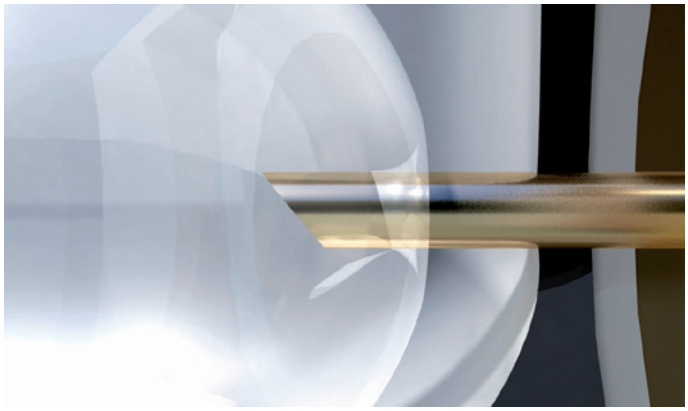


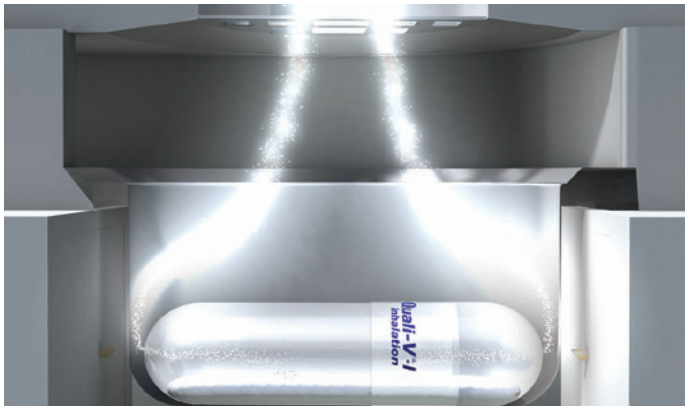
Figure 1: Global market for pulmonary drug delivery technologies, a comparison in the growth in the three main types.

1) Device opening

2) Puncturing



3) Aerosolization



4) Patient inspiration

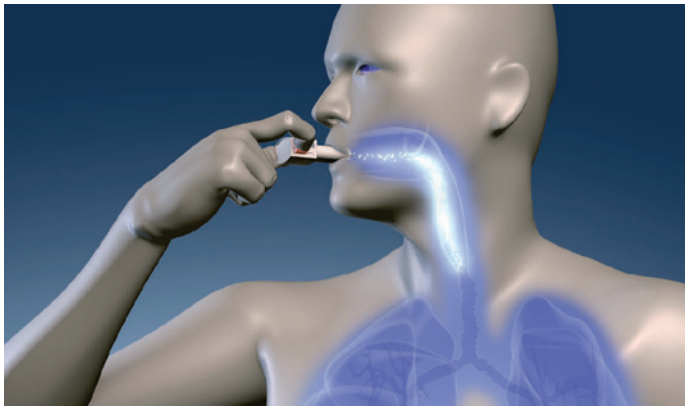


Figure 2: Steps followed by capsuled-base DPIs inhalation.

containing multiple doses for dispensing and offer less protection from humidity in the environment than capsules, so they must be stored in dry conditions.

In contrast, two-piece, hard-shell capsules are an established dosage form for DPI systems, in which they are used as a single-dose container for a powdered drug,[10] protected within blisters and thus unaffected by changes in ambient humidity. Capsule-based DPIs are loaded before each inhalation and punctured within the device, so that the powder is evacuated from the shell with minimum retention (Figure 2).

USING CAPSULES FOR DPI DEVICES

The first marketed product in a capsule-based DPI used gelatin capsules. However, they have a well-known drawback of becoming brittle as they lose moisture when exposed to low humidity, because water acts as a plasticiser for the shells. To minimise this issue drastically, capsules were developed from another polymer, hypromellose (HPMC), which is not dependent on moisture content to maintain its structure. This resulted in

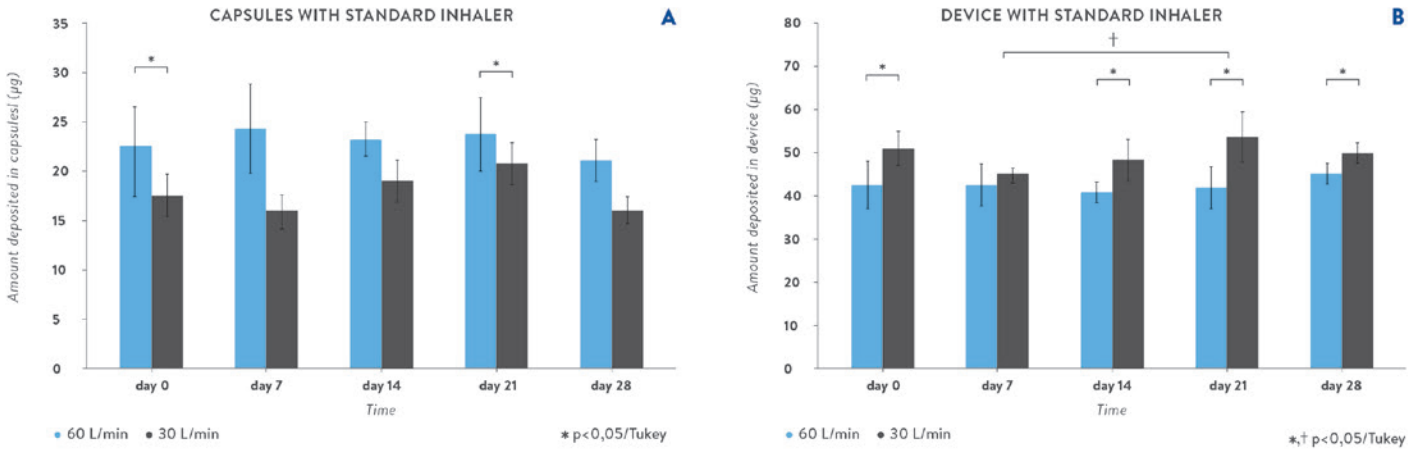


Figure 3: Deposition of salbutamol sulphate remaining in (A) capsules and (B) device, following aerosolisation at 60 L/min and 30 L/min from a 2-pin standard inhaler (Mean ± SD, n=6). * indicates significance between 30 and 60 L/min. # - indicates significance between different time points at 60 L/min. † indicates significance between different time points at 30 L/min.

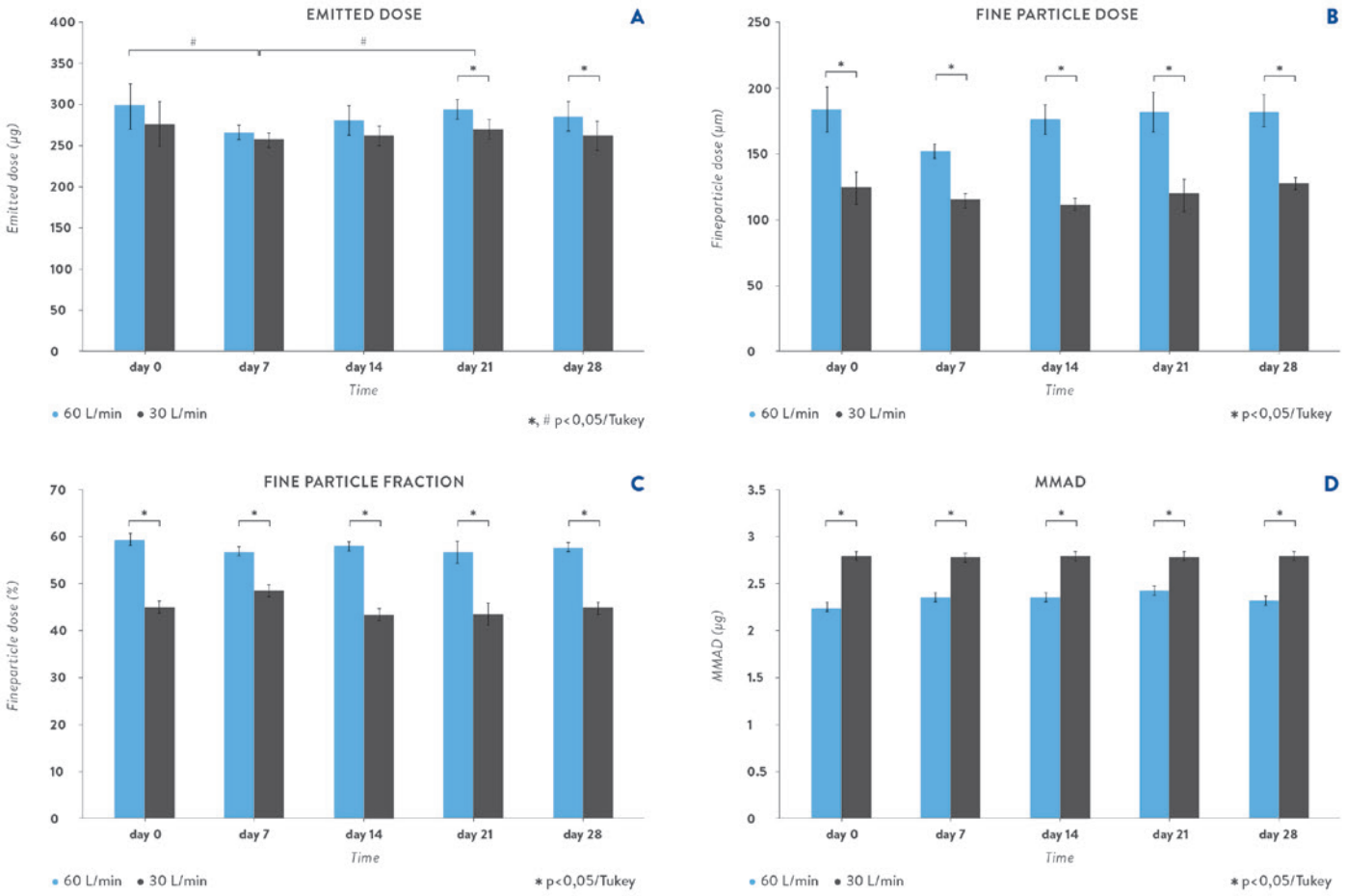


Figure 4: (A) Emitted dose (µg), (B) Fine particle dose (µg), (C) Fine particle fraction (%), (D) MMAD (µm) of salbutamol sulphate at 30 and 60 L/min from a 2-pin standard inhaler (Mean ± SD, n=6). * indicates significance between 30 and 60 L/min. # indicates significance between different time points at 60 L/min.

Quali-V® (HPMC) capsules launched by Qualicaps® in 2002,[11] that were later specifically tailored for the inhalation application and branded as Quali-V®-I.

The grade of HPMC chosen for these capsules had the correct hydroxypropyl/methyl ratio and the correct molecular weight distribution to ensure exceptional puncturing and cutting properties. Their moisture content of 4.5-6.5% is lower than that of gelatin capsules (13-16%), thus providing a capsule suitable for moisture-sensitive active ingredients. These capsules can be dried down to lower moisture contents if required without affecting their physical properties.

STUDY: DRY POWDER INHALATION AEROSOLISATION PERFORMANCE AT DIFFERENT FLOW RATES

The aim of the study* was the investigation of the aerosolisation properties of a dry powder formulation composed of inhalation-grade lactose and micronised salbutamol, in Quali-V®-I (size 3) capsules, using a standard low resistance 2-pin inhaler device RS01 (Plastiape Spa, Osnago, Italy) at different flow rates (30 and 60 L/min) in order to assess the ability of patients to effectively use the device with various degrees of airway obstruction.

Preparation of inhalation-grade lactose mixed with micronised salbutamol (50:1 w/w), *in vitro* drug deposition and analysis of Salbutamol were performed.[12] The capsules were dispersed through a 2-pin DPI RS01 low-resistance inhaler and punctured. *In vitro* impaction measurements were taken for the two formulations at 30 and 60 L/min to determine the influence of a sub-optimal air flow rate on the aerodynamic properties of the RS01 low-resistance inhaler.

The key aerosolisation parameters were evaluated. The emitted dose (ED) was calculated as the total mass of drug depositing in the mouthpiece, induction port, pre-separator and new generation impactor (NGI) stages. The fine particle dose (FPD) was determined as the mass of drug deposited in the NGI with aerodynamic diameters ≤ 3.99 µm for 30 L/min and 4.46 µm for 60 L/min.

The fine particle fraction percentage (% FPF) of each dose was the ratio of the drug mass depositing in the NGI over the emitted dose. Mass median aerodynamic diameter (MMAD) was calculated by subjecting the inertial impaction data to log-probability analysis. Mass of drug remaining in capsule and device were measured.

Comparing capsules and device:

- Less deposition of the drug was observed in capsules with 30 L/min compared with 60 L/min (Figure 3A). Neither a significant increase nor decrease can be observed at both the flow rates with time.
- A significant difference in the deposition of salbutamol in the standard inhaler was observed between the flow rates (Figure 3B).

Comparing ED, FPD, FPF & MMAD:

- There was no significant difference in the aerosolisation parameters of salbutamol across different weeks of analysis (Figure 4).
- There was a significant difference between the different flow rates used (30 and 60 L/min) for: ED, FPD, FPF and MMAD (Figures 4A–D).

- A higher flow rate (60 L/min) indicated more FPD and FPF with lower MMAD when compared with the lower flow rate (30 L/min) (Figures 4B–D).

CONCLUSIONS OF THE STUDY

- The results indicate significant differences in powder retention with higher deposition at 60 L/min within capsules and 30 L/min in the device.
- In addition, the ED, FPD, FPF was significantly greater at 60 L/min compared to 30 L/min at each time point.
- This demonstrates the important relationship between inhalation, therapeutic dose and lung deposition.
- However, despite these differences there was very little significant variability when comparing each flow rate over time. Hence, there is very good dose reproducibility, which is important for ensuring equivalent doses are administered during the treatment cycle.

Integration of all the above data highlights that there is a link between the emitted dose (especially particle size under 5 µm), total lung deposition and ultimately clinical response.

In its standard version, the RS01 is a low-resistance device reaching a pressure drop of 4 kPa at 100 L/min. The results obtained showed that this capsule-based device was useful even at lower flow rates than 60 L/min; it is therefore suitable for use on a wide range of patients. However, for acute asthma or COPD (low-respiratory capacity in patients), there are other capsule-based DPIs with a high-resistance to airflow, such as HandiHaler, that work properly for inspiratory flow rates of less than 50 L/min to produce a pressure drop of 4 kPa, recommended to obtain powder de-agglomeration.[11, 13]

On the other hand, previous studies using the multi-dose device inhalers Diskhaler and Easyhaler showed salbutamol FPF values of 30.5% and 32.1% for 60 L/min and 90 L/min in the case of Diskhaler and 36.0% for 60 L/min using Easyhaler.[14] In comparison, data obtained in the present study showed that for a flow rate of 30 L/min, FPF was approximately 40%, which is higher than those provided by studies referenced in the following bibliography. Overall, data demonstrated that HPMC capsules specifically designed for inhalation (marketed as Quali-V®-I) represent an ideal option for DPI devices.

** This research was conducted in its entirety by Imran Y. Saleem, PhD, School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK, and sponsored by Qualicaps®.*

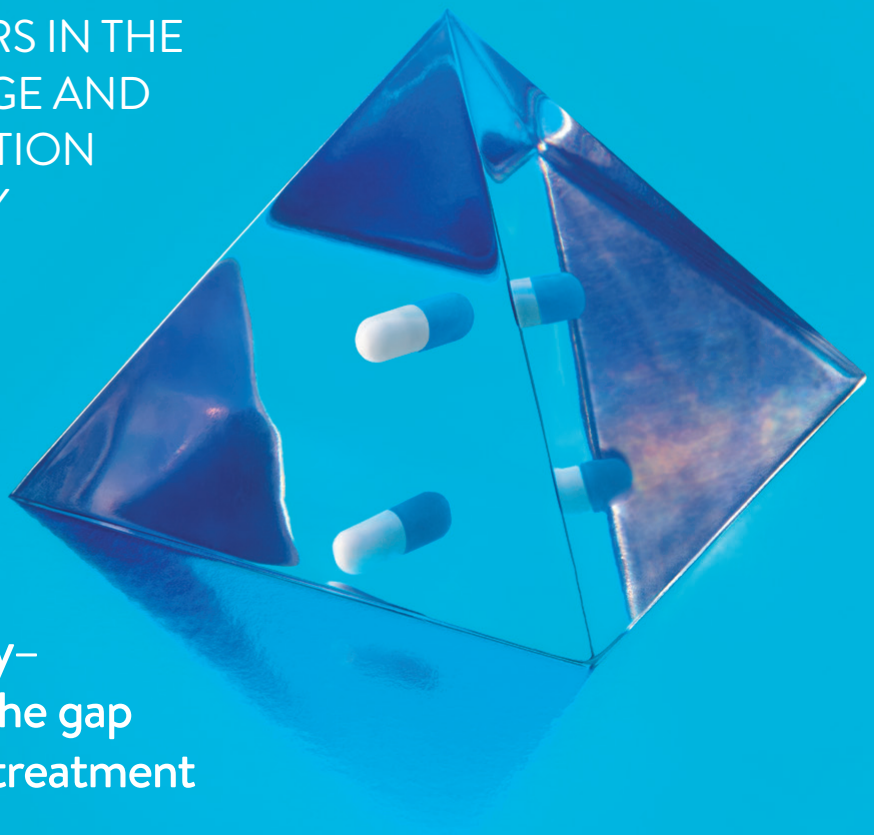
REFERENCES

1. *BCC Research. "Pulmonary drug delivery systems: technologies and global markets". May 2014.*
2. *Newman SP, "Aerosol deposition considerations in inhalation therapy". Chest, 1985, 88 (Suppl. 2), pp152S–160S.*
3. *Bell J, "Why optimize inhaler technique in asthma and COPD?" Br J Prim Care Nurs, 2008, Vol 2 (2), pp 37–39.*
4. *Voshaar T, "Therapie mit Aerosolen". 2005, Uni-Med: Bremen.*
5. *Colombo P et al, "Inhalation Drug Delivery: Techniques and Products". 2013, Chapter 6. Edited by Paolo Colombo, Daniela Traini, Francesca Buttini.*
6. *Capstick TGD, and Clifton IJ, "Inhaler Technique and Training in People With Chronic Obstructive Pulmonary Disease and Asthma: Effect of Resistance of Inhaler Device on Lung Deposition". 2012, CME Released: 01/27/2012; http://www. medscape.org/viewarticle/757312_5.*
7. *Rau JL, "The inhalation of drugs: advantages and problems." Respir Care, 2005, Vol 50, pp367–382.*
8. *Dal Negro RW, "Dry powder inhalers and the right things to remember: a concept review". Multidisciplinary Respiratory Medicine, 2015, 10:13 DOI 10.1186/s40248-015-0012-5.*
9. *Newman SP,"Drug delivery to the lungs from dry powder inhalers". Curr Opin Pulmon Med, 2003, Vol (supp 1), pp 517-520.*
10. *Islam N et al, "Dry powder inhalers (DPIs)—a review of device reliability and innovation." Int J Pharm, 2008, Vol 360, pp 1–11.*
11. *Jones B, "Quali-V®-I: A new key for dry powder inhalers". Drug Del Tech. 2003, Vol 3(6), pp 52-57.*
12. *Fink JB et al. "Problems with inhaler use: a call for improved clinician and patient education". Respir Care, 2005, Vol 50, pp1360–1374.*
13. *Saleem I et al, "Investigation of Dry Powder Inhalation Aerosolisation Performance at Different Flow Rates From a Conventional Capsule-Based Inhaler Device". 2015, Drug Delivery to the Lungs 26 Conference, Edinburgh, Scotland, UK.*
14. *Laube BL et al, "What the pulmonary specialist should know about the new inhalation therapies". Eur Resp J, 2011, Vol 37, pp 1308–1331.*

LOOKING FORWARD

ONE DAY WE IMAGINED HOW CAPSULES COULD BE USED FOR MORE PATIENT-FRIENDLY DRUG ADMINISTRATION VIA INHALATION.

TODAY WE ARE LEADERS IN THE SCIENTIFIC KNOWLEDGE AND SPECIALIZED PRODUCTION OF CAPSULES FOR DRY POWDER INHALERS.



Quali-V®-I capsules
for inhaled drug delivery–
contributing to bridge the gap
between medicine and treatment

Strict Microbiological Control

Better Aerosolization

Inner Surface Control

Reduced Powder Adhesion

Superior Puncturing Properties

Qualicaps *Engineered to perform*

COMPANY PROFILE: NOVI SYSTEMS

In December 2015 the inhaler automation specialists Novi Systems launched their latest product, a ten-way shake and fire system for pMDIs called DecaVertus. Novi continues to innovate, bringing efficiency, precision and repeatability to inhalation labs around the world.

INNOVATING FOR MORE THAN TWO DECADES

Novi's long association with the inhaler industry started more than twenty years ago when British multinational Fisons asked it to create a system for automatically shaking an inhaler. Since then, Novi has shaken and fired inhalers in every way you may think of, recovered drug from impactors and DUSAs, collected countless waste shots and detected countless plumes.

ICTUS

Novi's main technology platform is a fully automated Andersen Cascade Impactor (ACI) system called the Ictus. The user loads up to thirty inhalers onto the system and returns later to find rows of vials with drug recovered from ACI stages ready for HPLC analysis. Each Ictus is built according to the specification of the customer and over the years has incorporated all elements of inhaler preparation and drug recovery for aerodynamic particle size distribution and dose content uniformity test methods.

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

Using the tried-and-trusted Ictus technology base, Novi has created a family of bench-top devices that can be used in more flexible arrangements in smaller scale R&D and production environments.

Novi continues to innovate, both through custom projects and their ever-expanding portfolio of products.

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

VERTUS

The predecessor to Novi's new ten-inhaler tester DecaVertus is the single-inhaler tester, the Vertus (Figure 1). The Vertus has proven popular since its launch in 2010 and has been delivered across the world. It automates all aspects of dose delivery of pMDIs to ACIs, NGIs, DUSAs and waste. The analyst fits a collection device, fits an inhaler, selects the method to use and presses "Start".

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

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

DECAVERTUS

The DecaVertus, discussed in more detail in Novi's previous article ("*A New, Advanced Highthroughput System for Automated Inhaler Testing*", *ONdrugDelivery Magazine, Issue 62 (December 2015), pp 14-17*), was designed from the ground up to set a new standard in pMDI dosing to waste. It uses identical technology to the Vertus to shake and fire the inhalers, and to control airflow through waste filters – which are again the same on both systems. This means that methods can be readily transferred from one system to the other with no adjustment required.

The Vertus and DecaVertus can work alongside each other and waste shots conducted on either with the assurance that results will be the same. Issues can be diagnosed and firmware updated remotely.

The primary advantages of the DecaVertus are:

- The entire inhaler is tested as it would be used by a patient (although cans can also be tested on their own)
- A large range of programmable control over shaking, firing & airflow parameters
- Assurance that each inhaler is experiencing the correct shaking, firing and airflow parameters set

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

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

www.novi.co.uk

- Greatly reduced cleaning requirement and improved health and safety
- Flexible – any pMDI can be tested, in-actuator or can-only
- Independent airflow control at every channel
- Modern, slick and intuitive touch screen interface
- Fitting inhalers to the system is quick and intuitive.

FLUTUS

Flutus Air is an airflow controller for pMDI testing which takes up no more room on your lab bench than a small laptop.

The Flutus gives you airflow without a pump by generating precisely controlled airflow without use of noisy, high maintenance vacuum pumps – it plugs straight into your lab air supply.

Its intuitive touch screen display is simple and convenient to use. Simply plug in the power and lab air supply, connect your Impactor and you are ready to:

- Perform automatic leak tests on demand
- Precisely set the airflow
- Record how the airflow is affected as the pMDI is fired into the Impactor.

WaSC

WaSC is a bench-top waste shot collector for inhalers. It is considerably smaller and cheaper than a fume cupboard – but it can trap thousands of shots safely and conveniently.

There is no need for a vacuum pump as WaSC plugs straight into your lab air supply. WaSC switches on automatically when you approach it. (Alternatively, if you need precise control over timing, an external switch can be attached.) Bag and remove the filter with just a twist for safe and clean disposal in seconds.

VERY HIGH-THROUGHPUT PLUME DETECTION

Novi has developed a high-speed plume detection system for in-process testing of inhalers on production lines. It can detect a plume up to once a second per channel for over 25,000 shots with no break in operation. The system controls the airflow through the inhaler and can be used for breath-actuated inhalers. The system captures the entire waste drug in a cartridge that can be double-bagged and unclipped for quick and safe disposal.

CUSTOM PROJECTS

Over the years Novi has been involved in automating inhaler testing it has created many bespoke systems to meet test requirements that standard equipment cannot deliver. Examples of such bespoke systems are:

- pMDI shot weight systems
- pMDI arc-shaking systems
- DPI and other inhaler handling systems
- ACI plate-coating systems
- Dose preparation for plume detection systems

Novi has gathered a lot of experience of what works well and what doesn't, what is worth doing, and what is too expensive for the benefit gained. Get in touch with them for your next requirement and find out how they can help you.

DDL27

drug delivery to the lungs 27

EDINBURGH INTERNATIONAL CONFERENCE CENTRE
Wednesday 7th – Friday 9th December 2016

Drug Delivery to the Lungs is Europe's premier conference and exhibition dedicated to pulmonary and nasal drug delivery

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

About the Conference Programme

DDL27 will have 5 themed sessions each with a combination of invited and submitted lectures given by experts in the field of inhalation and students working to advance respiratory science.

Submissions for podium and poster presentations are invited and areas of particular interest for DDL27 include:

- INHALERS – WERE THEY REALLY MEANT FOR HUMANS?
- BEYOND ASTHMA AND COPD.
- 60 YEARS OF THE PMDI.
- INNOVATIONS IN AEROSOL DELIVERY.
- THE PAT BURNELL NEW INVESTIGATOR AWARD

For further information relating to sponsorship opportunities at DDL27 please visit our website.

To find out more about attending or exhibiting, please contact conference organiser Sheila Coates at Sheila@ddl-conference.com or visit our website www.ddl-conference.com

PRODUCT PROFILE: DF30 WITH COCe: ULTRA-CLEAN, ROBUST & VERSATILE

Aptar pharma

Aptar Pharma's new DF30 metering valve version incorporates a cyclic-olefin-copolymer (COC) neck gasket to enhance its performance further. It is the result of continuous improvement to today's world-leading DF30 technology platform.

Aptar Pharma's DF30 metering valve technology platform (Figure 1) has been the industry gold standard for more than 20 years and we are constantly striving to optimise our DF30 product offering.

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

COC is a well-known and characterised material used for injectable drug containers. COCe is a specific version of COC that has unique elastomeric properties while being ultraclean and inert.

The new version of DF30 – that incorporates a neck gasket which is manufactured with COCe – offers several key benefits:

- Step change improvement as a barrier to leakage
- Ultra low extractible level
- Compatibility across a wider range of drug formulations, including ethanol-containing formulations
- Suitable for all pMDI filling technologies
- Robust design for accurate and consistent performance.

Each year, Aptar Pharma manufactures and supplies several hundred million metering valves which are used by the world's leaders in the pharma industry.

For more information on DF30 Technology Platform, please visit: www.aptar.com/pharma.

ABOUT APTAR PHARMA

Aptar Pharma – part of the Aptargroup family of companies along with Aptar Beauty + Home and Aptar Food + Beverage – creates innovative drug delivery systems that meet the evolving needs of biotechnology, healthcare and pharmaceutical companies around the world.

The company provides its customers with a wide range of delivery technologies and analytical services backed by decades of proven expertise.

Aptar Pharma's primary technologies associated to Asthma and COPD inhalation applications are metering valves for pressurised metered-dose inhalers (MDIs), and dry-powder inhalers (DPIs).

"COC is a well-known and characterised material used for injectable drug containers. COCe is a specific version of COC that has unique elastomeric properties while being ultraclean and inert. The new version of DF30 that incorporates a neck gasket manufactured with COCe offers several key benefits."

For Allergic Rhinitis, CNS and other applications, Aptar Pharma offers a broad range of multidose spray pumps and single- and bi-dose disposable spraying and dispensing devices. The company also offers a full set of associated services to support customer speed-to-market and provide global support to branded and generic customers around the world.

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

Aptar Pharma
36, rue de la Princesse
78430 Louveciennes
France

T: +33 1 39 17 20 20
F: +33 1 39 58 12 98
E: info.pharma@aptar.com

www.aptar.com/pharma

Nemera

BIOEQUIVALENCE FOR NASAL SPRAYS: IMPORTANCE OF DEVICE PERFORMANCE

Here, Pascale Farjas, Global Category Manager ENT Products, Nemera, describes the company's Device Equivalence Program, which enables Nemera to preselect and propose an appropriate delivery system per identified drug to companies wishing to save time in their nasal spray development pipeline.

The most common use of multi-dose nasal sprays is for allergy related symptoms, such as allergic rhinitis. We will focus on nasal preparations for the administration of locally acting drugs (e.g. nasal steroids, nasal decongestants). Because the efficacy of the drug depends upon the spray device's ability to deliver a uniform dose as well as a reproducible droplet size and plume, the delivery system is a critical element for nasal spray performance.

> "Nemera has established a Device Equivalence Program in order to respond to market enquiries in terms of nasal spray equivalence and second-sourcing needs. Nemera's main objective is to preselect and propose an appropriate delivery system per identified drug to companies wishing to save time in their nasal spray development pipeline."

Nemera has established a Device Equivalence Program in order to respond to market enquiries in terms of nasal spray equivalence and second-sourcing needs. Nemera's main objective is to preselect and propose an appropriate delivery system per identified drug to companies wishing to save time in their nasal spray development pipeline. The program features:

- A preliminary bioequivalence study: de-risking approach to speed-up project development
- High-level protocol and robust statistical approach based on the EMA and US FDA guidelines
- Specific methodology to support "performance matching" activities in nasal sprays
- A cutting-edge laboratory for device performance *in vitro* testing support.

The Device Equivalence Program process is summarised in Figure 1.

Nemera's standard platform for nasal sprays comprises the SP270+ pumps range and various nasal actuators (Figure 2). The new optimised SP270+ pump is the result of continuous improvements to the SP270 pump platform and has been qualified to comply with FDA and EMA requirements and has a Drug Master File (DMF).

Predefined doses are available in the standard SP270+ range, from 50 µL up to 140 µL. The preliminary bioequivalence study is performed with the closest pump engine to demonstrate that the average dose is consistent through container life.

In order to propose a customised packaging system that is as close as possible to the reference product, our

Pascale Farjas
Global Category Manager
ENT Products
T: +33 4 74 94 92 94
F: +33 4 74 94 90 60
E: pascale.farjas@nemera.net

Nemera
20, Avenue de la Gare
38290 La Verpillière
France

www.nemera.net

Originator Product Qualification
Product description | Bill of materials | Dimensions

↓

Alternate Delivery System Identification
Dose | Spray | Raw materials | Look & feel

↓

Equivalence Verification: Preliminary Tests
Comparative study between Originator & Nemera delivery system

↓

Customised Device

↓

Nemera Delivery System Validation
Proven equivalence to the Originator

Figure 1: Device Equivalence Program process overview.

Figure 2: Nemera's standard platform for nasal sprays comprises the SP270+ pumps range and various nasal actuators.

> "We develop a customised dose via a dedicated pump engine to match a value within ±5% tolerance of nominal originator dose."

Device Equivalence Program relies upon the following four main parameters:

- **Dose**
- **Spray performance**
- **Raw materials**
- **Look and feel (design, priming, actuation force, etc).**

Then we develop a customised dose via a dedicated pump engine to match a value within ±5% tolerance of nominal originator dose. While dose adjustment is performed through pump engine fine-tuning, spray performance is accomplished through actuator re-design.

STRONG REGULATORY SUPPORT

Nemera has considered guidelines for the United States (FDA), Europe (EMA) and Brazil (ANVISA), regarding characterisation of nasal spray drug products and *in vitro* demonstration of pharmaceutical equivalence between two products:

✓ Draft Guidance for Industry-Bioavailability and Bioequivalence for Nasal Aerosols and Nasal Sprays for Local Action: FDA, April 2003

✓ Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products: EMEA/CHMP/QWP/49313/2005 Corr.

✓ Guidance for Pharmaceutical Equivalence and the Bioequivalence of Nasal Sprays and Aerosols: ANVISA, July 2008.

The FDA draft guidance is the most detailed and stringent regulation compared with the approved European and Brazilian regulations. The US regulation encompasses the requirements of the other regulations although some differences in test procedure may be noticed. For common tests, the Brazilian regulation refers widely to the US regulation while the European guidance offers only a few indications. Therefore, our Device Equivalence Program is based

mainly upon the FDA guidance testing requirements, such as:

- Single actuation content (SAC) through container life
- Droplet size distribution (DSD)
- Spray pattern
- Plume geometry
- Priming and re-priming.

ROBUST STATISTICAL METHODOLOGY

The statistical analysis methodology used for each *in vitro* test to compare the equivalence of Test (T) and Reference (R) data tests and ultimately to conclude on the *in vitro* equivalence of the devices, is essentially based on guideline: "US/FDA Statistical Information from June 1999 Draft Guidance and Statistical Information for *in vitro* Bioequivalence Data", posted on August 18, 1999," which indicates:

- For the following tests (SAC, DSD [D50 and SPAN] & Spray Pattern), a bioequivalence criterion (geometric mean ratio T/R) and a bioequivalence limit (95% Upper Confidence Bound) should be calculated. This 95% value estimation is based on the assumption of normal distributions of the log-transformed data. If the result of bioequivalence limit calculation is negative, Reference and Test products are considered equivalent.
- For the plume geometry test, the bioequivalence criterion geometric mean ratio T/R after log-transformation is compared to the bioequivalence limit defined as point estimate: 90%-111%.
- For priming and re-priming tests, no statistical analysis is required.

Figures 3, 4 and 5 show example data from: a DSD test; plume geometry test; and a spray pattern test, respectively.

A RELIABLE & ROBUST SOLUTION

Nemera's Device Equivalence Program provides a high confidence level on results of the final product registration thanks to this preliminary bioequivalence study. Its objective is to propose a delivery system with comparable performance to the branded device in terms of design, patient usage and performance. The *in vitro* bioequivalence study can be performed with third-party formulations in our laboratory.

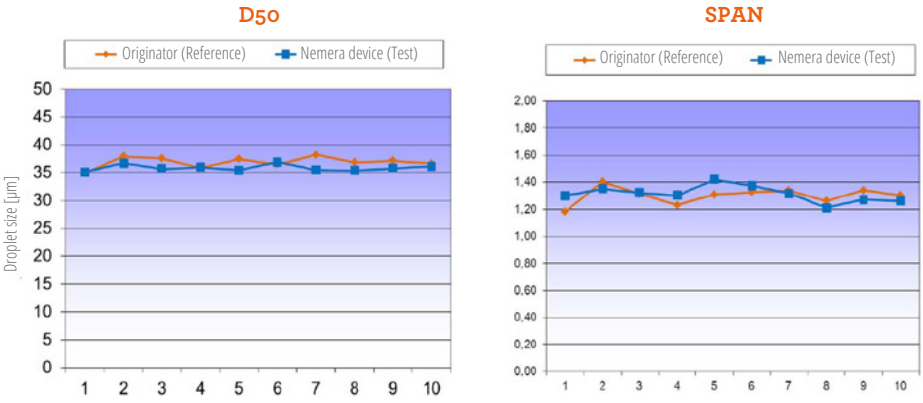


Figure 3: Examples of Droplet Size Distribution (DSD) test results data.

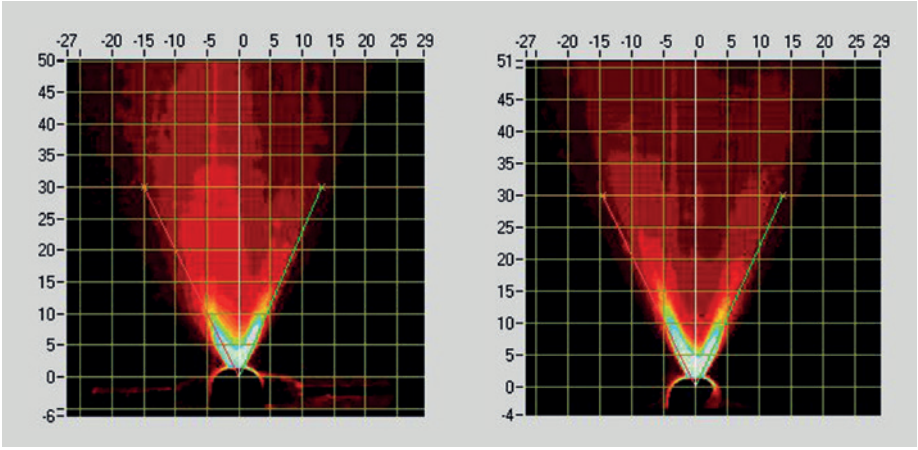


Figure 4: Example data from Plume Geometry (comparison of angle and shape of plume).

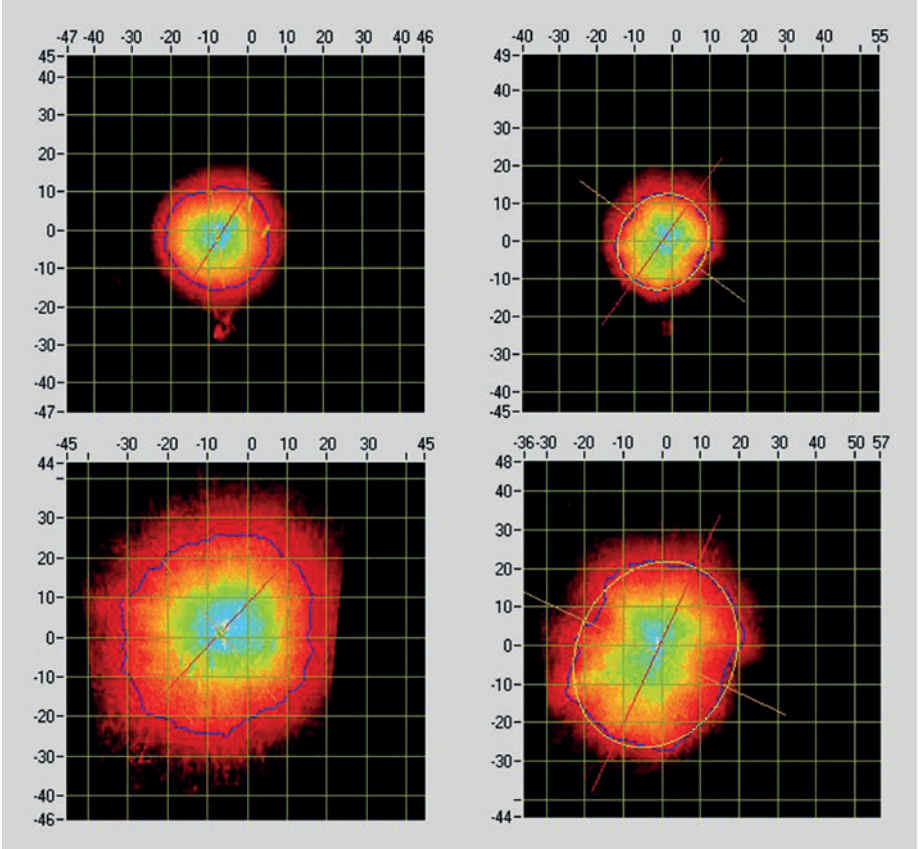


Figure 5: Data from Spray Pattern test at two distances from the actuator orifice.

Nemera

nasal/
buccal/
auricular

pulmonary

dermal/
transdermal

parenteral

ophthalmic

SP270+

Advancia®

SP270 PUMP PLATFORM
FOR **ENT SOLUTIONS AND SUSPENSIONS**
AND **ADVANCIA NEW USER INDEPENDENT NASAL SPRAY PLATFORM**

Nemera provides solutions for the pharmaceutical industry, including standard innovative products, development of custom devices and contract manufacturing.

we put patients first

www.nemera.net • information@nemera.net • Phone: +33 (0)4 74 94 06 54

Chiesi

People and ideas for innovation in healthcare

ENHANCING THE PERFORMANCE OF DRY POWDER INHALERS: BREATH ACTUATED MECHANISMS

The vast majority of dry powder inhalers (DPIs) rely solely on the energy provided by the inhalation action of the patient to achieve successful drug delivery. In many DPIs the only control that is imposed on this process is to increase or lower the internal resistance of the device, but some, more sophisticated systems deploy breath-actuated mechanisms (BAMs). In this article, David Lewis, PhD, Head of Laboratory, and Alan Tweedie, Senior Scientist, both of Chiesi, explain how BAMs work and present experimental data demonstrating their ability to control dose delivery.

Inhaled pharmaceutical therapies are the cornerstone of treatments for obstructive lung disease treatment. They allow for effective administration and high lung deposition of the active pharmaceutical ingredients (APIs), while at the same time minimising systemic bioavailability, and any associated adverse side effects. Along with metered-dose inhalers (MDIs), DPIs are among the most commonly used devices for drug delivery in the treatment of asthma and chronic obstructive pulmonary disease (COPD).

Commercially available since the 1970s, DPIs are often considered simpler to use than MDIs, as they are breath-activated; eliminating the need to co-ordinate inhalation and actuation. In addition, they avoid the use of propellants, add-on spacers and do not produce the "Cold Freon" sensation associated with some MDIs.[1]

DPIs currently on the market are mainly passive devices, which rely on a patient's inspiratory air flow to disperse the powder formulation into single particles or agglomerates small enough for deposition in the lung, typically less than 5 µm.

Ensuring adequate de-aggregation occurs from the inhalation technique of the patient is the primary challenge associated with DPI technology. Patients are typically encouraged to breathe forcefully and deeply when using a DPI though some patients have problems achieving a fast inhalation rate[2] and compliance/inadequate technique remains an issue.[3,4]

> "The use of BAMs has been proposed as a way of addressing the issue of inconsistent/poor dose dispersion with certain breathing profiles."

Additionally, the breathing pattern of a patient is influenced by physical size and strength, and health. Geriatric and paediatric patients, or those with severely compromised respiratory capacity, may be unable to produce the same breathing profile as a healthy adult and might, therefore, struggle to disperse an API dose effectively.[3] This can result in a lower dose of API to the lungs and, ultimately, poor disease control, which in the case of chronic conditions may be undetectable to the patient.

Alan Tweedie
Senior Scientist
T: +44 1249 466930
E: a.tweedie@Chiesi.com

Dr David Lewis
Head of Laboratory
T: +44 1249 466930
E: d.lewis@Cheisi.com

Chiesi Limited
Chippenham
Wiltshire
SN14 0AB
United Kingdom

www.chiesi.com

USING A BAM TO CONTROL DOSE DISPERSION

The use of BAMs has been proposed as a way of addressing the issue of inconsistent/poor dose dispersion with certain breathing profiles, and these are now incorporated in some DPI devices. NEXThaler® (Chiesi, Parma, Italy), a multi-dose inhaler, exemplifies a device incorporating a novel BAM and dose protector that restrain dose release until the pressure drop across the device is approximately 1.8 kPa. As air is drawn through the device the BAM mechanism triggers, the dose protector translocates and the metered dose is aerosolised using the energy provided by the patient's inhalation, under highly consistent conditions.

Here we report results from experimental studies designed to investigate the effect of BAM pressure and inhalation flow rate on the controlled dose delivery achieved.

STUDY 1: INVESTIGATING INFLUENCE OF BAM PRESSURE

To investigate the impact of trigger pressure for a BAM, four DPI variants (NEXThaler, Chiesi) were produced, each with a BAM different release pressure. The control variant had a pressure drop of ~1.8 kPa which is representative of the marketed device; two further variants were constructed to release at ~0.6 kPa and ~4.0 kPa, respectively. A final device was manually pre-triggered before firing, so that the dose was unprotected and free to evacuate into the airflow immediately, so effectively mimicked the action of a DPI with no BAM.

All device variants were assessed using the 90th percentile inhalation profiles of asthmatic patients,[5] generated using a BRS 3000 breath simulator (Copley Scientific, Nottingham, UK). Dispersion performance was assessed using a Fast Screening Impactor (FSI) (Copley Scientific) containing a 5 µm cut-off plate, and operating at a constant flow rate of 100 L min^{-1}. The FSI was attached to a BRS 3000 breath simulator using a mixing flow inlet to allow the application of different flow profiles over the device while keeping a constant flow through the impactor.

A flow rate of 100 L min^{-1} was selected to prevent backflow of powder-laden air into the breathing simulator and to match the P90 inhalation profile. A modified USP induction port containing the LiveShot rig[6] was used to record dose evacuation kinetics from each device.

Each device was filled with 1.5g ± 5% of lactose carrier based formulation containing approximately 4.7% w/w beclomethasone dipropionate (BDP) and then stored at 20°C 40% RH for at least 24 hours. Prior to measuring dispersion performance analysis, five waste shots, around 10 mg each, were actuated from each device into a waste dose uniformity sampling apparatus tube operated at 60 L min^{-1}. All measurements were conducted in triplicate. BDP was recovered from the apparatus using an appropriate diluent and analysed using ultra-performance liquid chromatography (UPLC) with Single Quad (SQ) Detector (Waters Acquity).

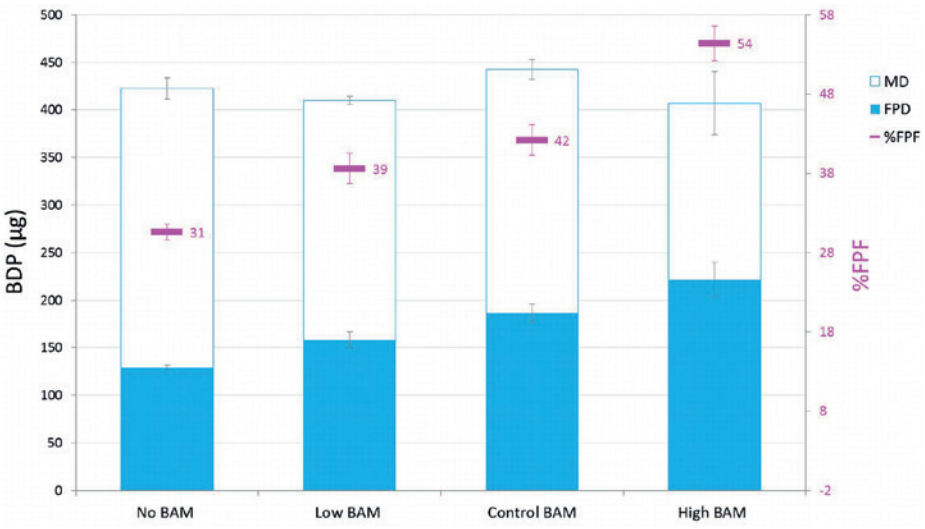


Figure 1: Impaction data shows that dose dispersion performance improves with increasing BAM set pressure; mean values (n=3); error bars ±SD.

	No BAM	Low BAM	Control BAM	High BAM
Shot weight (mg)	9.7 ± 1.0	9.2 ± 0.1	10.0 ± 0.6	9.1 ± 0.3
Metered dose (µg)	423 ± 11	410 ± 4	443 ± 10	407 ± 33
Fine particle dose <5µm (µg)	129 ± 2	158 ± 9	187 ± 9	222 ± 18
Fine particle fraction <5µm (%)	31 ± 1	39 ± 2	42 ± 2	54 ± 2

Table 1: FSI dispersion performance from the four DPI variants; mean values (n=3).

Results and Discussion

With increasing BAM pressure, the dispersion performance, as quantified by the fine particle dose (FPD <5 µm) improves, with the no BAM variant producing the lowest FPD in comparison with a much higher FPD from the high BAM variant (see Figure 1 and Table 1).

However, with the high BAM variant, data variability is also higher – the dose evacuation kinetics data from the LiveShot rig reveal a possible explanation (Figure 2 and Table 2).

The LiveShot data shows that altering the BAM trigger point impacts dose evacuation kinetics, in particular, the time taken to reach peak powder discharge (Obs_{peak}) and the flow rate at which Obs_{peak} occurs. Discrepancies between the BAM opening pressure and the pressure drop at Obs_{peak} arise because of the formulation residence time as it passes through the device.

In comparison with the control variant, the low BAM device reduces the time taken to reach peak flow and, as a result, the powder is released into a slightly lower airflow rate. Removal of the BAM causes a similar effect, but of much greater magnitude. Conversely, increasing the BAM trigger pressure delays the time taken to reach peak powder discharge ensuring release of the powder into a higher airflow

rate. The correlation between enhanced dispersion and BAM set pressure suggests that releasing the powder into an increased airflow velocity may be advantageous in terms of DPI performance.

STUDY 2: INFLUENCE OF BAM AT DIFFERING FLOW RATES

To investigate the impact of inhalation flow rate on dose delivery, two devices containing a BDP 100 µg/dose formulation were actuated according to the patient instruction leaflet. One device had BAM functionality, the other did not. The 10th, 50th and 90th percentile inhalation profiles (P10, P50 and P90, respectively) from asthmatic patients were applied using a breathing simulator coupled with a FSI and flow-mixing inlet exactly as described in the first study. This flow rate through the FSI was set at 60 L min^{-1} for the P10 and P50 profiles and 100 L min^{-1} for the P90 profile.

The LiveShot rig enables the recording of device evacuation profiles as a function of pressure drop at a sampling flow rate of 1000 Hz. For the purposes of this study, the requirement was to analyse the LiveShot evacuation traces in detail, as a function of flow rate, and so pressure drop was converted into volumetric flow rate. The device resistance of the DPI was calculated to be 0.110 cm $H_2O^{1/2}$ L^{-1} min^{-1} at 58 L min^{-1}, the test flow rate required to achieve a 4 kPa pressure drop across the device.

The volumetric flow rate corresponding to a certain pressure drop was therefore calculated by dividing the overall pressure drop (converted into comparable units) by the device resistance. Prior to analysis, five waste shots were actuated from each device into a waste Dosage Unit Sampling Apparatus (DUSA) operated at 60 L min^{-1}. All other aspects of testing were carried out as in the first experimental study.

Results and Discussion

Dispersion performance results are displayed in Figure 3 and Table 3. Without a BAM the delivered dose is higher with all three inhalation profiles. However, the inclusion of a BAM results in a higher and more consistent FPF on average across all three profiles: 51% ± 3% and 37% ± 6%, respectively.

A possible explanation for this is that the removal of the BAM, as discussed above, causes the dose to be released into a slower airflow velocity, meaning that larger carrier particles are less likely to impact

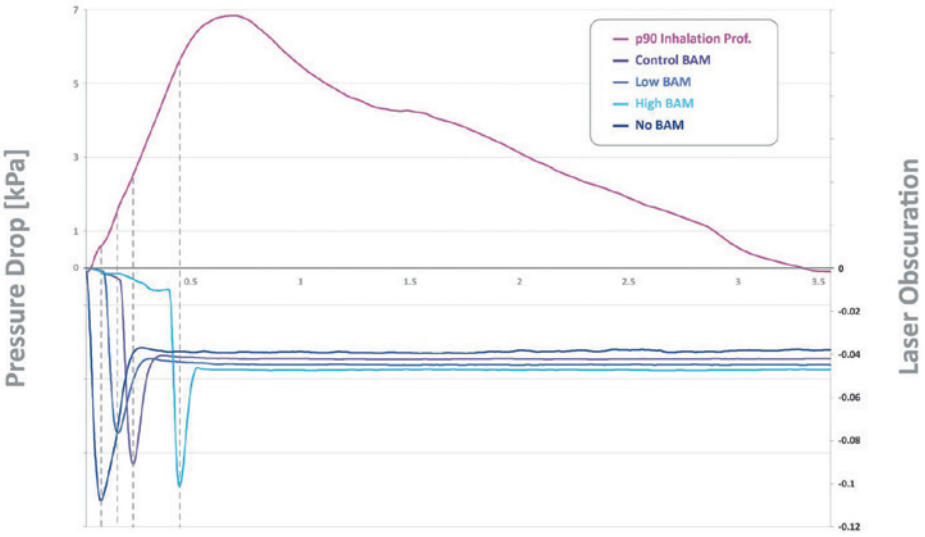


Figure 2: LiveShot dose evacuation kinetics, showing both laser obscuration and differential pressure, provide insight into the enhanced dose dispersion delivered by higher BAM set pressures (n=3).

Device variant	BAM opening pressure (kPa)	Time to Obs_{peak} (s)	Pressure drop at Obs_{peak} (kPa)	Flow rate at Obs_{peak} (L min^{-1})	Peak duration (s)
No BAM	N/A	0.068 ± 0.003	0.6 ± 0.0	22.0 ± 1.0	0.215 ± 0.010
Low BAM	0.6	0.196 ± 0.021	2.2 ± 0.2	42.6 ± 2.1	0.250 ± 0.010
Control BAM	1.8	0.223 ± 0.005	2.5 ± 0.1	46.3 ± 0.6	0.177 ± 0.005
High BAM	4	0.466 ± 0.005	6.7 ± 0.1	75.0 ± 0.0	0.170 ± 0.006

Table 2: Key characteristics identified from the LiveShot dose evacuation kinetics; mean values (n=3).

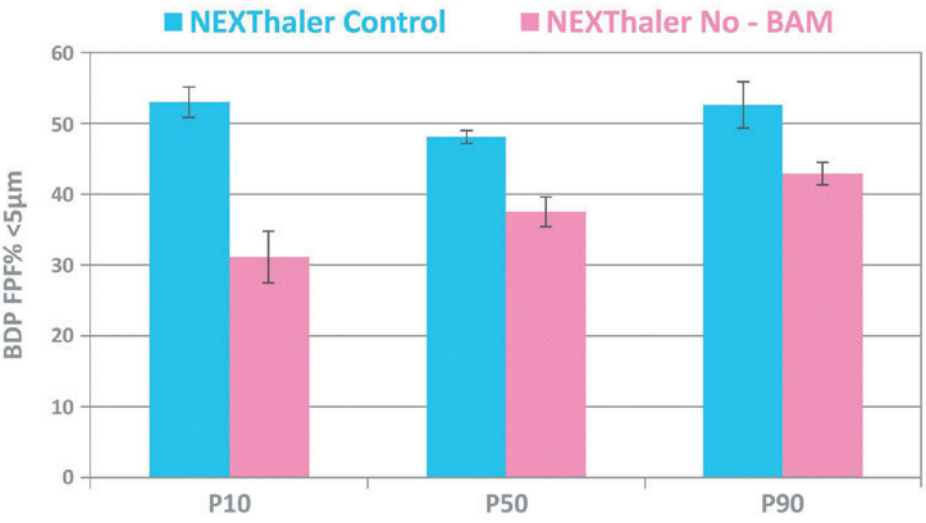


Figure 3: Incorporating a BAM in the DPI device improves the magnitude and consistency of the FPF% across a range of flow rates (n=3).

	P10		P50		P90	
	Control	No-BAM	Control	No-BAM	Control	No-BAM
Delivered dose (µg)	79	81	67	79	78	83
Fine particle dose <5µm (µg)	42	25	32	30	41	36
Fine particle fraction <5µm (%)	53	31	48	37	53	43
Shot weight (mg)	8.2	8.4	8.1	8.7	8.6	8.7

Table 3: Incorporating a BAM in the DPI device improves the magnitude and consistency of the FPF% across a range of flow rates (n=3).

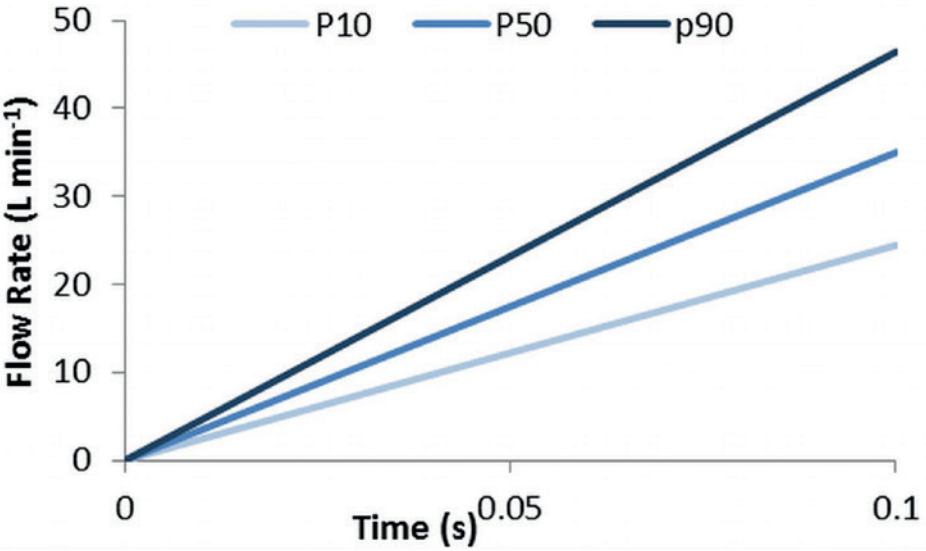


Figure 4: Increase in flow rate between 0 and 0.1 secs for the P10, P50 and P90 inhalation profiles; P90 is associated with the fastest acceleration rate.

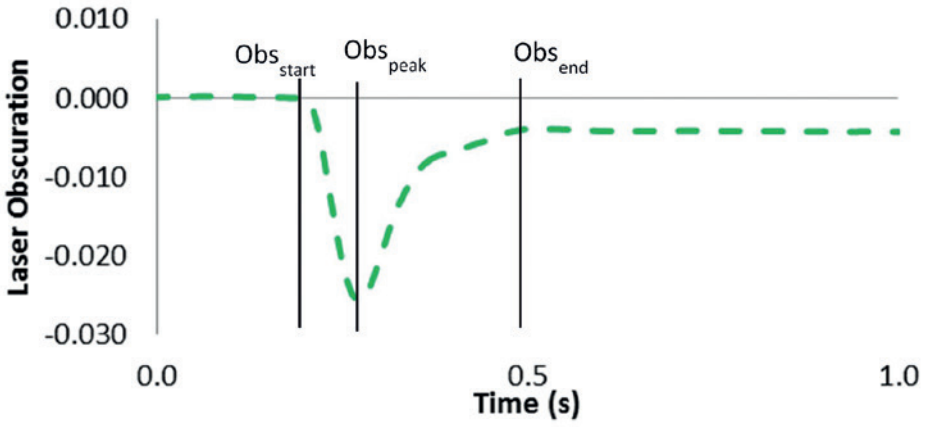


Figure 5: Dose evacuation data using the No-BAM device with the P50 inhalation profile demonstrating the start (Obs_{start}), peak (Obs_{peak}) and end (Obs_{end}) of the laser obscuration, which characterise the dose dispersion event.

within the device, increasing delivered mass. However, a lower airflow velocity may also reduce the mass of fine API detaching from the carrier particles, thus reducing the FPF% and FPD. Releasing the dose into a higher velocity, more turbulent airflow promotes more effective detachment of the fine API from carrier particles, facilitating drug delivery.

An additional observation is that varying the inhalation profile has a greater influence on the FPF % measured with the No-BAM device; this may be attributable to the differences in the initial acceleration rates associated with the different profiles (Figure 4). The greater acceleration rate of the P90 profile produces a higher airflow velocity with more energy to shear fine API from the carrier particle. This energy is substantially reduced at lower initial acceleration rates and without the BAM to promote dispersion it becomes a less energetic and effective process.

The LiveShot data provides further insight into these effects. With the No-BAM variant, the dose releases at the same point regardless of the inhalation profile, and the Obs_{peak} is consistent). However, with a BAM in place the dose only releases when a pressure drop of approximately 1.8 kPa is reached. This difference means that the dose is released into a different airflow rate regime, depending on the device used (Figure 5 and Table 4).

This effect means that the device with a BAM begins to release the dose at a flow rate of between 36-37 L min^{-1} whereas the No-BAM variant releases the dose into a significantly lower flow rate, 9-11 L min^{-1} at all inhalation profiles. Flow rates at the Obs_{peak} and Obs_{end} are also lower with the No-BAM variant; indicating that the dose leaves the device at a slower rate. Average dose duration (Obs_{end} minus Obs_{peak}) of the three inhalation profiles increased from 51ms ± 2ms for the device with a BAM to 72ms ± 6ms for the No-BAM variant, confirming that in the absence of a BAM dose dispersion is a slower, less energetic process.

CONCLUSION

For effective treatment of chronic obstructive lung disease, the delivery of APIs to the lung must be controlled. DPIs are relatively easy to use, as they do not require co-ordination of inhalation and actuation, but can be less effective than MDIs because de-aggregation of the dose to a respirable size is driven

Device	Inhalation profile	Obspeak		Obspeak		Obspeak		Dose duration (s)
		Time (s)	Flow rate (L min^{-1})	Time (s)	Flow rate (L min^{-1})	Time (s)	Flow rate (L min^{-1})	
NEXThaler control	P10	0.44	36	0.49	37	0.49	37	0.52
	P50	0.35	36	0.40	38	0.40	38	0.51
	P90	0.30	37	0.35	43	0.35	43	0.49
NEXThaler No-BAM	P10	0.18	9	0.26	23	0.26	22	0.79
	P50	0.20	11	0.27	27	0.27	27	0.68
	P90	0.20	10	0.27	30	0.27	30	0.68

Table 4: LiveShot data measured at P10, P50 and P90 inhalation profiles (n=3 ± RSD) shows that in the absence of a BAM the dose is released more slowly into a lower air flow.

only by the inhalation profile applied by the patient. This can be compromised either as a result of poor lung function or inadequate training.

The use of a BAM improves the drug delivery efficiency of DPIs and has the potential to ensure more consistent performance, for a wider range of patients. The results presented here confirm the ability of BAMs to enhance FPF and FPD by controlling release of the formulation, and entraining the dose into higher velocity airflow. They illustrate how BAMs can be used to ensure that patients receive the maximum dose of APIs, and receive better treatment.

REFERENCES

1. *Brambilla G, Church T, Lewis D and Meakin B, "Plume temperature emitted from metered dose inhalers". Int J Pharmaceutics, 2011, Vol 405 pp 9–15.*
2. *Azouz W, Chetcuti P, Hosker H, Saralaya D, Stephenson J, Chrystyn H, "The inhalation characteristics when they use different dry powder inhalers". J Aerosol Med and Pulmonary Drug Del, 2014, Vol 27, pp 1–8.*
3. *Chrystan H, "Effects of device design on patient compliance: comparing the same drug in different devices". Resp Drug Del Eur, 2009, Vol 1, pp 105-116.*
4. *Ronmark E, "Correct use of three powder inhalers: Comparison between diskus, turbohaler and easyhaler". J Asthma, 2005, Vol 42 (3), pp 173-178.*
5. *Casaro D, Bramilla G, Pasquali I, Sisti V, "In vitro aerosol performances of NEXThaler® using representative inhalation profiles from asthmatic patients". 2014, In Proc Resp Drug Del, pp 375-380.*
6. *Tweedie A, Keegan GM, Lewis DA, "DPIs – A LiveShot Experience". Drug Delivery Australia, 2013, 23-24 October, Sydney.*

Download the **2016** Media Pack for more information!

ON drugDELIVERY

2016/17 EDITORIAL CALENDAR

Publication Month	Issue Topic
May 2016	Injectable Drug Delivery: Devices Focus
June 2016	Connected Drug Delivery Systems
July 2016	Novel Oral Delivery Systems
Sept 2016	Wearable / High Volume Injectors
Oct 2016	Prefilled Syringes
Nov 2016	Pulmonary & Nasal Delivery
Dec 2016	Delivering Biotherapeutics
Jan 2017	Ophthalmic Drug Delivery
Feb 2017	Prefilled Syringes
March 2017	Skin Drug Delivery: Dermal, Transdermal & Microneedles
April 2017	Pulmonary & Nasal Drug Delivery

COMPANY PROFILE: NOBLE

Noble®, the leader in onboarding and device training, is a full-service, patient-centred product development and manufacturing company. Noble works closely with the world's leading pharmaceutical and biotechnology companies to develop educational and training solutions designed to provide positive patient onboarding experiences, reduce errors and improve patient outcomes. Cross-disciplinary designers and engineers provide fully customised solutions from the first concept sketch through to production, in both regulated and non-regulated environments. ISO 9001 and ISO 13485 supply chain and manufacturing.

PATIENT ONBOARDING

The first 30-, 60- and 90-days, commonly referred to as onboarding, are the most important regarding patient adherence. This is the time when a patient is expected to self-administer medication based upon prescribed regimen. While a patient's first exposure to a drug delivery device typically consists of training with a healthcare professional onsite at a medical facility, a patient will most often perform their medication administration alone outside of a health care facility and healthcare provider supervision. Nonetheless:

- 45% of patients avoid injections due to anxiety[1]
- 93% of patients use their inhaler incorrectly[2]
- 40-80% of information provided by a HCP is forgotten immediately.[3]

While many variables contribute to patient adherence and therapy acceptance during onboarding, patient factors including needle anxiety for injections, confidence, memory and understanding correct administration technique (see Figure 1) can detrimentally influence attitudes and perception toward medications and drug delivery devices, resulting in training gaps and treatment barriers.

INJECTION & RESPIRATORY DEVICE TRAINING

As the number of patients required to self-administer medication increases, so does the need for patient-centric training and education including training devices such as auto injectors (AI), prefilled syringes (PFS), wearable injectors and respiratory platforms.

Noble has developed a wide variety of patient-centric onboarding products to help patients administer correctly and improve adherence and patient outcomes. Noble's offerings range from mechanical training devices to smart error-correcting training platforms, assistive devices and even patient support including travel packs and training instructions for use (IFU).

These devices have been designed to mimic actual commercial drug delivery devices while being a low-cost, reusable solution to onboard users safely and effectively.

> "If I am doing it incorrectly, I would want to know."
> – Cynthia

PRODUCT FEATURES

MDI and DPI trainers:

- Off-the-shelf and customisable solutions, including proprietary technologies
- Technologies range from resettable mechanical to smart features, such as sensors, audio and error-correcting
- Trainers designed to mimic actual device characteristics such as: shape and design; inhalation forces; and sequences.

AI and PFS trainers:

- Off-the-shelf and customised solutions, including proprietary technologies
- Technologies range from resettable mechanical to smart features, such as sensors, audio and error-correcting
- Trainers designed to mimic actual device characteristics such as:
  - Shape and design
  - Needle insertion simulation
  - Forces: cap, unlock, actuation, breakout and glide
  - Sound replication
  - Plunger replication
  - Post injection safety.

TRAINING SUPPORT PRODUCTS

Designed to create a complete training program and solution, Noble offers:

- Angle aid tools
- Administration assistive tools
- Smart injection pads
- Smart packaging
- Training packaging
- Training IFU
- Travel assets.

Noble
121 South Orange Avenue
Suite 1070 North
Orlando
FL 32801
United States
T: +1 888 933 5646

www.gonoble.com

Figure 1: Noble's offering comprises novel training technologies such as mechanical and smart, error-correcting auto injectors, prefilled syringes and pulmonary delivery devices, angle aid tools, auditory packaging and other multisensory solutions.

DEVELOPMENT & PRODUCTION

Noble's proven repeatable process takes client's needs from concept to distribution. Our team is meticulous in defining a client's needs, working with our clients to develop solutions, and then being able to produce the approved product design with high-volume production.

Our in-house design facilities provide Noble with the ability to produce prototypes and conduct extensive engineering and benchmark testing. Our quality control procedures are in place from development to production, ensuring design requirements and specifications can be efficiently transferred to optimised high-volume manufacturability, with quality assurance involved at every level of a project realisation.

Noble's dedication to delivering quality products extends beyond our corporate headquarters. Our ISO 90001 and 13485 certified global manufacturing partners use a systematic approach to perform in-line functionality testing including 100% verification testing of critical product features and functionality before delivery.

Noble manufacturing capabilities include:

- Tooling
- Injection molding
- Electronic/PCB assembly
- Assembly
- Packaging.

CHOOSE NOBLE

As the number of patients being required to self-administer medication via drug delivery devices continues to grow, training and education will remain a critical success determinant of a patient's ability to use these devices safely and effectively and adhere to therapy. Novel training technologies such as mechanical and smart, error-correcting auto injectors, prefilled syringes and pulmonary delivery devices, angle aid tools, auditory packaging and other multisensory solutions help empower patients to lead healthier lives (Figure 1).

In the modern era of patient-centric care, products that are able to provide superior onboarding and patient experiences will be well positioned and benefit by reducing patient errors, while improving patient satisfaction and outcomes.

Noble's focus is to bring value to our clients, driving innovation in onboarding and device training.

STUDIES REINFORCE THE SIGNIFICANCE OF DEVICE TRAINERS[4]

• Patients who use a trainer are more compliant
• 90% of patients value a trainer 7 or higher
• Patients who use a trainer are less likely to discontinue treatment

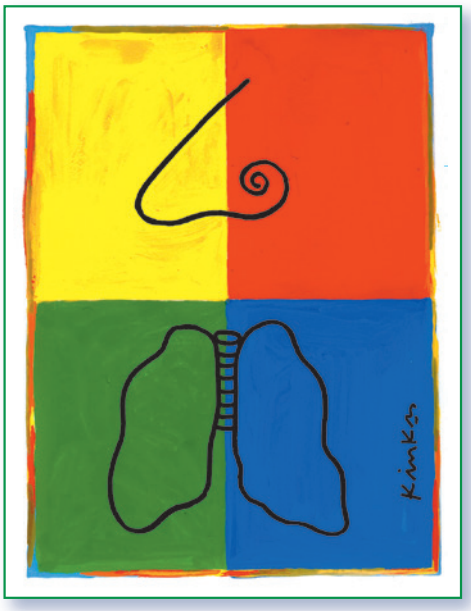
REFERENCES

1. *Zambanini A, Newson RB, Maisey M, Feher MD, "Injection related anxiety in insulin-treated diabetes". Diabetes Res Clin Pract, 1999, Vol46(3), pp 239-246. (Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10624790).*
2. *Bonds R, Asawa A, Ghazi A, "Misuse of medical devices: a persistent problem in self-man- agement of asthma and allergic disease". Annals Asthma, Allergy & Immunol, 2015, Vol 114(1), pp 74–76(e2). (Retrieved from www.annallergy.org/article/S1081-1206(14)00752-2/fulltext).*
3. *Kessels RP, "Patients' Memory for Medical Information". J Royal Soc Med, 2003, Vol 96(5), pp 219–222. (Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC539473).*
4. *"The link between device training and patient compliance". Noble Company Poster at PDA Universe of Prefilled Syringes & Injection Devices Conference, 2015, Vienna, Austria.*

ATTEND ▪ PRESENT ▪ EXHIBIT ▪ SPONSOR

RDD EUROPE 2017

Respiratory Drug Delivery



APRIL 25 - 28, 2017

Palais des Congrès d'Antibes

Nice, **FRANCE**

DEADLINES:

Workshop Proposal Submission
June 16, 2016

Podium Abstract Submission
August 1, 2016

Scientific Poster Abstract Submission
January 6, 2017

rddonline.com/rddeurope2017

Nice - Art Deco - Palais de la Méditerranée

RDD Europe is a conference jointly organized by

RDD Online
Respiratory Drug Delivery

Aptar pharma

Device training happens here.

There's life beyond chronic conditions. Distractions, anxiety and understanding correct administration technique can all affect compliance. Studies suggest 61% of patients don't completely read the IFU[1] and 12% of patients have proficient health literacy.[2]

Will your patients correctly administer their drug delivery device?

noble®

Onboarding and Device Training

GONOBLE.COM 888.933.5646

Come see us at RDD '16 | April 18-19th

Reference: 1. Noble. (2015, November). The link between device training and patient compliance. Poster session presented at PDA - Universe of Prefilled Syringes 2015, Vienna, Austria. 2. Kessels, R. P. (2003, May). Patients' Memory for Medical Information. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC539473/

PRESSPART

MODIFYING MDI CANISTER SURFACES TO IMPROVE DRUG STABILITY & DRUG DELIVERY

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

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

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

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

> "The unique combination of process equipment design and precursor monomer means the technology is now scalable to handle the throughput and commercial demands of the global MDI market."

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

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

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

www.presspart.com

cause degradation, resulting in increased impurity levels. In both cases the interaction leads to a reduction in the drug content in the formulation, resulting in the patient receiving less than the prescribed dose.

RANGE OF COATINGS

Applying a suitable surface coating to the MDI components improves the stability of the formulation as well as the product performance, and helps to extend the product's shelf life. A range of coatings have been developed that can be applied to both the canister (Figure 1) and valve components to protect the contents from deposition and degradation.

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

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

COATING TECHNIQUES

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

Figure 1: MDI canisters.

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

PLASMA PROCESSING TECHNOLOGIES

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

The process creates an ultra-thin layer that protects against degradation, deposition and corrosion. It is a low-temperature

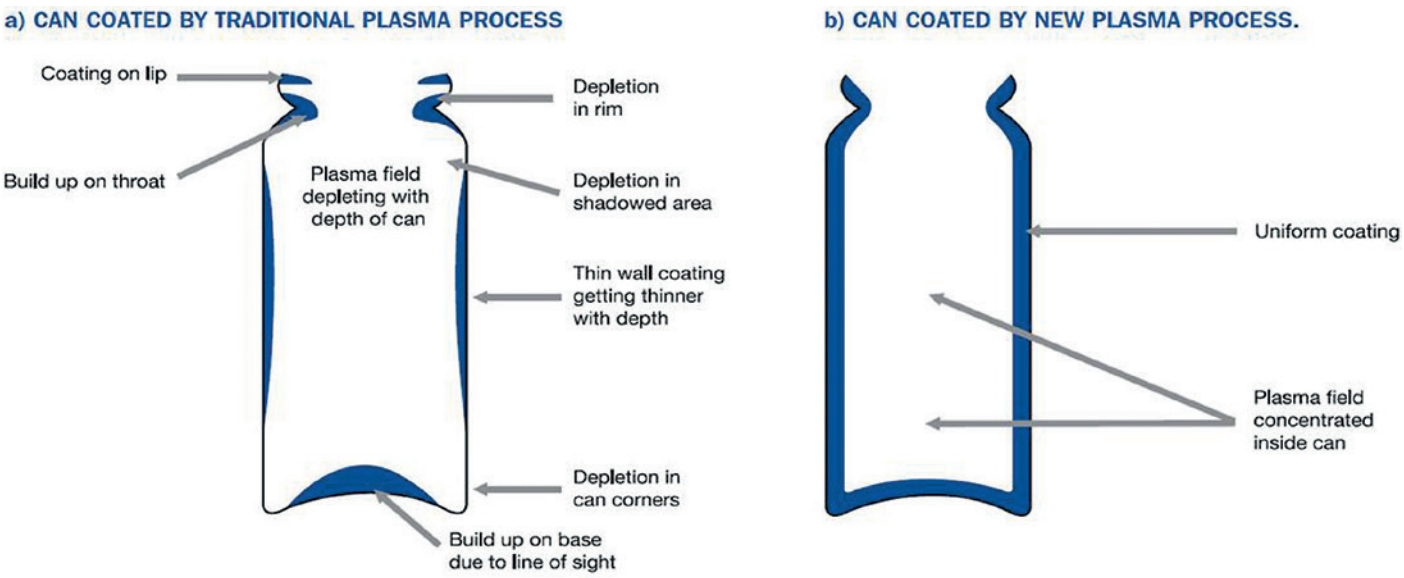


Figure 2: a) Traditional plasma processing does not ensure a uniform coating to internal wall of the canister whereas b) the new plasma process gives a uniform coating to canisters.

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

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

OPTIMISING THE PLASMA PROCESS

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

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

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

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

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

More recently, an improved process has been developed that eliminates the issues associated with typical plasma system designs. Using proprietary gas/monomer delivery configurations and electric field control (designed specifically for can coating geometry), uniform coatings can be deposited (Figure 1b).

Dedicated system design configurations mean constant, high deposition rates with extreme reproducibility in terms of coverage, chemical speciation and product performance. The unique combination of process equipment design and precursor monomer means the technology is now scalable to handle the throughput and commercial demands of the global MDI market.

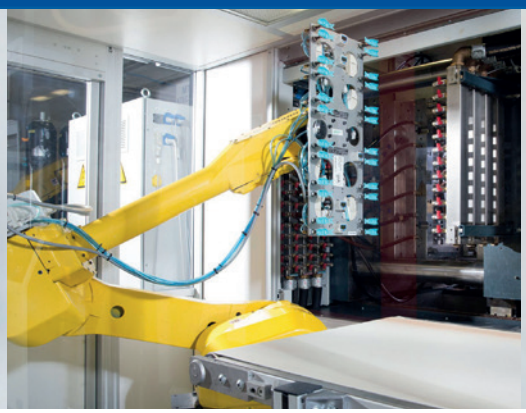
This process has been used to develop several different plasma coating options that successfully prevent drug deposition on the can walls, and prevent drug degradation in solution or suspension. Examples include surface treatments for budesonide, formoterol, fluticasone proprionate and beclomethane dipropionate,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

CONCLUSION

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

PRESSPART

Living and breathing drug delivery



Presspart, the world's leading manufacturer of metered-dose inhaler canisters and actuators. With over 40 years' experience in the design and manufacture of bespoke drug delivery, we help the customer create the ideal medical device component, whatever their needs.

www.presspart.com | info@presspart.com | +44 (0) 1254 582233

Chimera Consulting: Combination Product Training Institute®

FDA ISSUES FINAL GUIDANCE ON MEDICAL DEVICE HUMAN FACTORS STUDIES

In this, the third in their series of articles for ONdrugDelivery Magazine covering quality system requirements for medical devices used to deliver drugs and biologics, and combination/borderline products, Michael Gross, PhD, RAC, Principal Consultant, Chimera Consulting, and Adam Shames, MBA, Chief Executive Officer, Core Human Factors, discuss US FDA draft recommendations on human factors validation which are part of the design validation requirement of device design controls.

INTRODUCTION

In the first article in this series,[1] the authors summarised quality systems, design control and design validation regulations[2,3] and draft guidance[4] for combination products and borderline products. In February 2016, the US FDA issued three guidance documents[4, 5, 6] that recommend approaches and methods for the identification, assessment and mitigation of hazards related to the use of medical products that utilise a medical device. In the second article in this series[7], the authors summarised the draft guidance, "Human Factors (HF) Studies & Related Clinical Study Considerations in Combination Product Design & Development". In this third article in the series, the authors summarise the other two recently released guidance documents. One is a final guidance, "Applying Human Factors & Usability Engineering to Medical Devices", and the other is a draft guidance, "List of Highest Priority Devices for Human Factors Review".[8]

SIMULATED-USE & ACTUAL-USE HF EVALUATIONS

HF evaluations should facilitate the analysis of use error and identification of their root cause. They are often conducted under simulated-use conditions but when simulated-use test methods are inadequate to evaluate the user-device interface, in addition to design validation testing, actual-use evaluations may be conducted under actual-use conditions, or as part of a clinical study as an addition to simulated-use studies.

However, in a clinical study, participants are generally trained differently and/or are more closely supervised than users would be in real-world use, so HF observations and interviews obtained during a clinical study should be viewed in this context. For clinical studies involving self-administration in the home, patient reported HF data should be supplemented with observational data.

FORMATIVE HF EVALUATIONS

Formative HF evaluations are used to refine the results of preliminary empirical/analytical analyses, and are used to identify and determine the nature of any required design modifications. They are conducted as the device design evolves on mock-ups and prototypes following implementation of risk- mitigation strategies intended to address use-related hazards.

Formative HF evaluations can be conducted with varying degrees of formality

Dr Michael Gross
Principal Consultant

Chimera Consulting
T: +1 215 316 8394
F: +1 215 545 6028
E: michaelgross.chimera@gmail.com

www.chimeraconsultingna.com

Mr Adam Shames
Chief Executive Officer

Core Human Factors (USA)
T: +1 610 668 2673
F: +1 610 668 2674
E: info@corehf.com

www.corehf.com

and sample sizes. The critical task list used in formative evaluations may change as the device design and risk analyses evolve. If formative HF evaluations are not conducted during device development, and design flaws are discovered during HF validation, then the HF validation becomes a formative evaluation.

RISK MITIGATION

When considering implementing risk mitigation strategies, risk severity is more important than risk probability. Hazards may be mitigated through design changes, incorporating protective safety features/mechanisms, or by providing information or training. Design modifications are generally the most effective means for mitigating use-related hazards.

If design modifications are not possible or not practical, it may be possible to implement protective measures. Labelling and training, are important hazard mitigation strategies, but are least preferred because they rely on memory and reference to information and labelling that may be unavailable during real world use; and knowledge gained through training can decay over time.

HUMAN FACTORS VALIDATION

Human factors validation is conducted to demonstrate that the evolved device can be used by its intended users for its intended uses, under expected conditions of use, without serious use errors or problems that could produce serious harm that could be eliminated or further reduced through modification of the design of the user-interface.

The final critical task list is tested in the human factors validation. Test participants should reside in the country or geographical region where the device will be commercially available. The labelling and, if applicable, training materials to be evaluated should also correspond with those to be used in the country or geographical region where the device will be commercially available. Protocols should describe the number of times participants will use the device and its extent of use, identify critical tasks to be evaluated and describe data collection methods and evaluation methods.

Observational and knowledge assessment data collected during testing should, starting with the overall device and later focusing on each critical task or use scenario, be supplemented with data collected in interviews with participants after use scenarios are completed. Questions should be open-ended and neutrally-worded.

Participants should provide their subjective assessments of use difficulties. All use errors identified in the interview should be discussed determine how and why participants believe the use error occurred. FDA encourages manufacturers to submit for feed-back a draft of the human factors validation protocol before it is implemented.

> "Insight into FDA's thinking about risk assessment, risk mitigation and the design and conduct of human factors evaluations during engineering development of drug delivery devices and systems that include a medical device can be gained from recommendations contained in three recently published human factors guidance documents."

USER GROUPS IN HF TESTING

Human factors validation testing should involve at least 15 representative participants in each user group. Participants should represent the range of characteristics within their user group. Participant characteristics (e.g. age, occupation, education, literacy level, and sensory or physical impairment) are likely to affect device-user interactions.

Based on task characteristics, certain users may use the device in ways that may be expected to produce responses that are different from those expected of other users. If the device is intended to treat patients with medical condition(s) that cause functional limitations, users with a representative range of these limitations should be included as a distinct user group. Different user groups may perform tasks differently or have different knowledge, experience or expertise that could affect their interactions with the device interface, or have different potential for use error. These users should be separated into a distinct user group.

Healthcare providers and intended lay device users should be treated as distinct user groups. All of these characteristics should be considered when establishing user groups. The labelling to be evaluated in a human factors validation should explain user capabilities needed for safe and effective device use.

USER TRAINING IN HF TESTING

The test protocol should describe the content, mode(s) of training delivery and dwell time between training and testing. To simulate learning decay, testing should not occur immediately after training. The design and extent of training needed for safe device use that will be evaluated in a human factors validation should reflect real world training that will be used commercially. If intended users will receive little or no training before using the device, then the participants in the human factors validation should not be trained. If training is used to mitigate identified risks, then data should be provided in the HF/Usability Report that demonstrates its effectiveness in reducing risks to acceptable levels.

HF DATA ANALYSIS

Analysis of use-related risk should be used to determine how use errors occurred, if design modifications are needed, or are possible, and how they may be effective at further reducing risks to an acceptable level. The results of human factors validation testing should be analysed qualitatively to determine if the device design, labelling and, if applicable, training, should be modified to reduce use-related risks to acceptable levels. The root causes of all use errors and problems should be considered to determine their potential to produce harm and to determine their priority for implementing additional risk management measures. If human factors validation testing results indicate that serious use errors persist, this is not acceptable unless it can be demonstrated that further reduction of the residual risk is not possible, or practical, and that the benefits of device use outweigh its residual risks. True residual risk is beyond practicable means of elimination or reduction through modifications of the user

interface, labelling, or training. Residual use errors or problems associated with high levels of residual risk should be described, including their relationship to the device design, and justified in the HF/Usability Report.

HF/USABILITY REPORT

The results of the overall HF evaluation program, including results and methods of risk management and HF/usability testing, and design optimisation should be summarised and documented in an HF/Usability Report, which may be included in pre-market applications.

The report should discuss safety-related HF engineering and usability engineering issues, materials, processes, risk analyses focusing on the device-user interface, resolutions, results and conclusions.

The report does not need to include test data. Its level of detail should be sufficient to communicate to marketing application reviewers how all serious use-related hazards were identified, evaluated and mitigated. FDA recommends the following order and content for a HF/Usability Report:

1. Conclusion
2. Description of intended device users, uses, use environments, and training
3. Description of user interface
4. Summary of known use problems
5. Analysis of hazards and risks associated with use of the device
6. Preliminary analysis/evaluations summary
7. Description/categorisation of critical tasks
8. Details of HF evaluations testing.

HIGH-PRIORITY MEDICAL DEVICES

The draft guidance that provides a list of devices for which FDA believes it is important to conduct and report HF evaluations to marketing applications, is based on Medical Device Reports (MDR) and product recall data. The devices listed in the draft guidance were selected on the basis of their potential to cause serious harm resulting from use error. The following drug delivery device general types are the only ones identified in this list:

- Auto injectors
- Implanted infusion pumps
- Infusion pumps
- Insulin delivery systems.

CONCLUSION

Well-designed HF usability evaluations have become an essential part of the device engineering development process used in part to demonstrate the safe and effective use of devices intended to deliver pharmaceuticals. Insight into FDA's thinking about risk assessment, risk mitigation and the design and conduct of HF evaluations during engineering development of drug delivery devices and systems that include a medical device can be gained from recommendations contained in three recently published human factors guidance documents. One is a final guidance on medical devices, one is a draft guidance on combination products that contain a medical device constituent part, and one is draft guidance that identifies the drug delivery devices for which FDA is most concerned about hazards associated with use-errors.

REFERENCES

1. *Gross M and Shames A, "Quality & Systems Usability Requirements for Drug Delivery Devices & Systems". ONdrugDelivery Magazine, Issue 64 (February 2016), pp 54-56.*
2. *US FDA, Final Rule-Current Good Manufacturing Practice Requirements for Combination Products (§21CFR4).*
3. *US FDA, Final Rule-Quality System Regulation (§21CFR820).*
4. *US FDA, "Draft Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products". FDA Office of Combination Products 2015.*
5. *US FDA, "Draft Guidance for Industry and FDA Staff: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development". FDA Office of Combination Products 2016.*
6. *US FDA, "Guidance for Industry and FDA Staff: Applying Human Factors and Usability Engineering to Medical Devices". FDA Center for Devices and Radiological Health, 2016.*
7. *US FDA, "List of Highest Priority Devices for Human Factors Review". FDA Center for Devices and Radiological Health, 2016.*
8. *Gross M and Shames A, "US FDA Issues Guidance on Human Factors Studies for Combination Products". ONdrugDelivery Magazine, Issue 65 (March 2016), pp 32-35.*

THE COMBINATION PRODUCT TRAINING INSTITUTE

In 2016, the Combination Product Training Institute® is conducting two identical three-day training programs that address quality system and design controls requirements for combination and borderline products in the US and EU, and the conduct of human factors studies. These programs cover requirements for both newly developed and legacy products as well as quality system obligations of device constituent part manufacturers. The first of the two training programs took place on March 29-31, 2016 in Philadelphia, PA, US. The second program will take place on June 14-16, 2016 at the NH Barbizon Palace (Amsterdam, The Netherlands). Throughout the year, the Combination Product Training Institute will offer other venue-based training programs on various combination product topics. In-house training programs are also available. For additional details please visit the Combination Product Training Institute website at: www.CombinationProductTraininingInstitute.com.

ABOUT THE AUTHORS

Michael Gross is the Principal Consultant of Chimera Consulting®, specialising in quality assurance, regulatory affairs and technical development of drugs, biologics, medical devices and combination products. He also heads the Combination Product Training Institute®, which provides professional training programs on combination product topics. Michael holds a PhD in Organic Chemistry and conducted post-doctoral research in biochemistry at the National Institutes of Health. He is a former FDA reviewer and inspector. Michael worked for 30 years in senior quality, compliance and regulatory affairs roles for a number of large and small pharmaceutical and medical device companies. Today, he provides an influential industrial perspective on the regulation of combination products and is a frequent speaker on combination products topics and has published numerous articles in regulatory and scientific publications.

Adam Shames is a recognised human factors expert and consultant and is the Founder and Chief Executive Officer of Core Human Factors, Inc, a leader in human factors and usability engineering consulting services with over 12 full-time employees. Adam holds an MBA in international business and a BS in human factors engineering and psychology. He received the De-Florez Prize in Human Engineering and holds a Certificate in Applied Ergonomics Training from the United States Army Center for Health Promotion and Preventive Medicine. Adam has over 15 years of human factors research experience and has served as the Principal Investigator on hundreds of IRB reviewed usability studies involving thousands of participants in cities around the world.

Controlled Release Society Annual Meeting & Exposition

July 17–20, 2016 • Seattle, Washington, U.S.A.

Don't miss the must-attend event in delivery science and technology.

- Collaborate with 1,200 colleagues from 55 countries
- Learn about cutting-edge research and innovation
- Showcase your company in the Exposition

Register Now!

controlledreleasesociety.org

CRS
Leading Delivery Science and Technology

At Phillips-Medisize We're All About Process

We know process is the absolute key to assuring that we deliver upon our customers' expectations, **the first time and every time**. That's why our people are all about process. In fact, our process requirements apply not only to manufacturing and quality SOPs, but also to our customer facing operations such as Program Management and Design and Development engagements, ensuring our customers benefit from a repeatable and scalable model.

So, when you work with Phillips-Medisize, you can be certain we'll exceed your highest expectations **the first time and every time**.

MANAGEMENT FORUM

We are at

Dry Powder Inhalers Annual Conference

16-17 June 2016, London, UK

Phillips Medisize

Partnerships Built on Innovation

Contact Phillips-Medisize: phillipsmedisize.com / eu_sales@phillipsmedisize.com