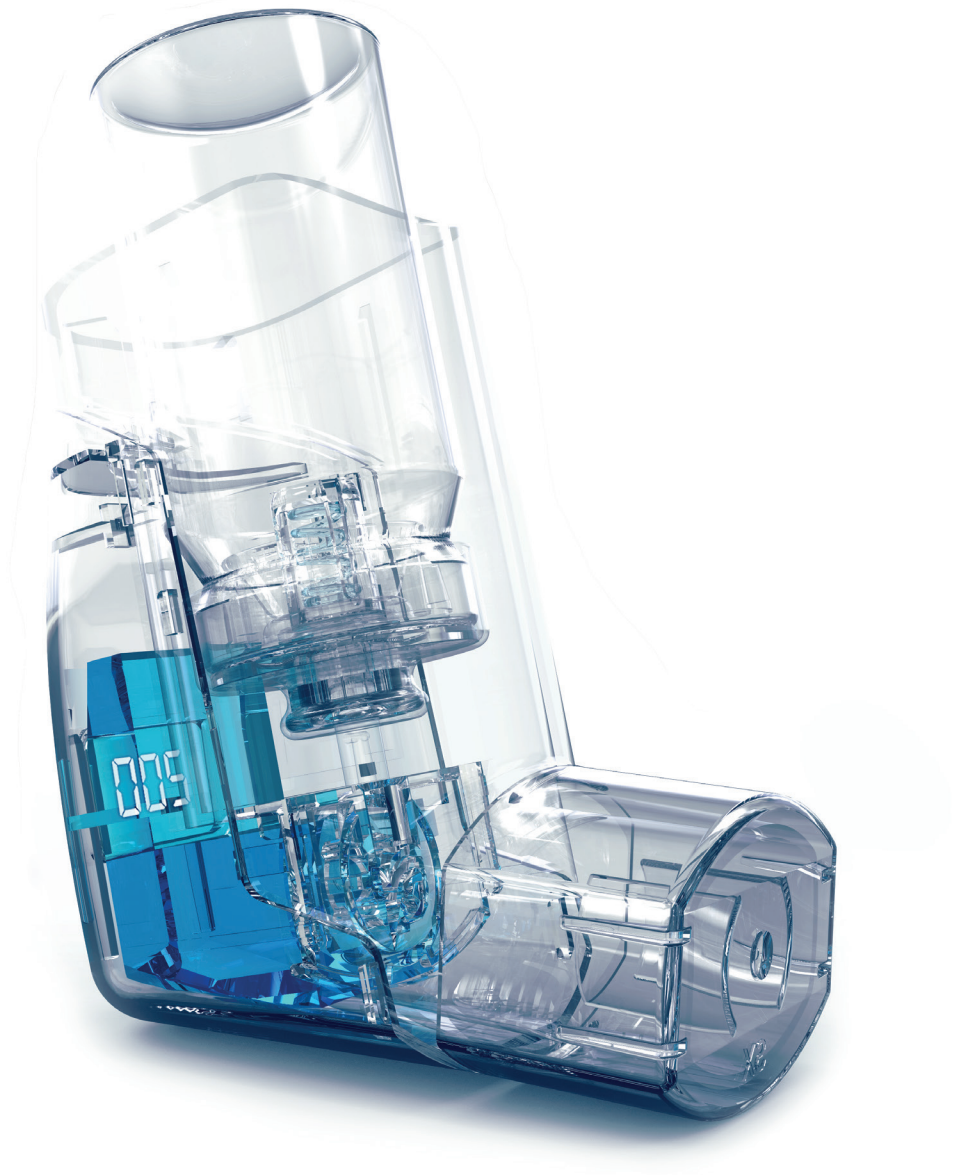
PULMONARY & NASAL DELIVERY

ON drugDELIVERY



APRIL 10TH 2017 • ISSUE Nº 74

Aptar pharma

BAUMANN 125 FOUNDED 1886 IN SWITZERLAND

BIOCORP

H&T PRESSPART

Nemera

noble®

Phillips Medisize a molex company

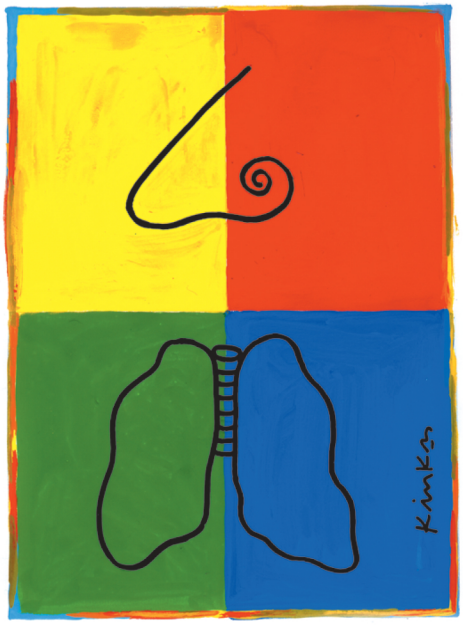
proveris SCIENTIFIC

Qualicaps Engineered to perform

ATTEND • PRESENT • EXHIBIT • SPONSOR

RDD EUROPE 2019

Respiratory Drug Delivery



MAY 7-10, 2019

Estoril Congress Center

Lisbon, PORTUGAL

rddonline.com/rddeurope2019

Palace of Pena - Sintra-Cascais Natural Park

RDD Europe is a conference jointly organized by

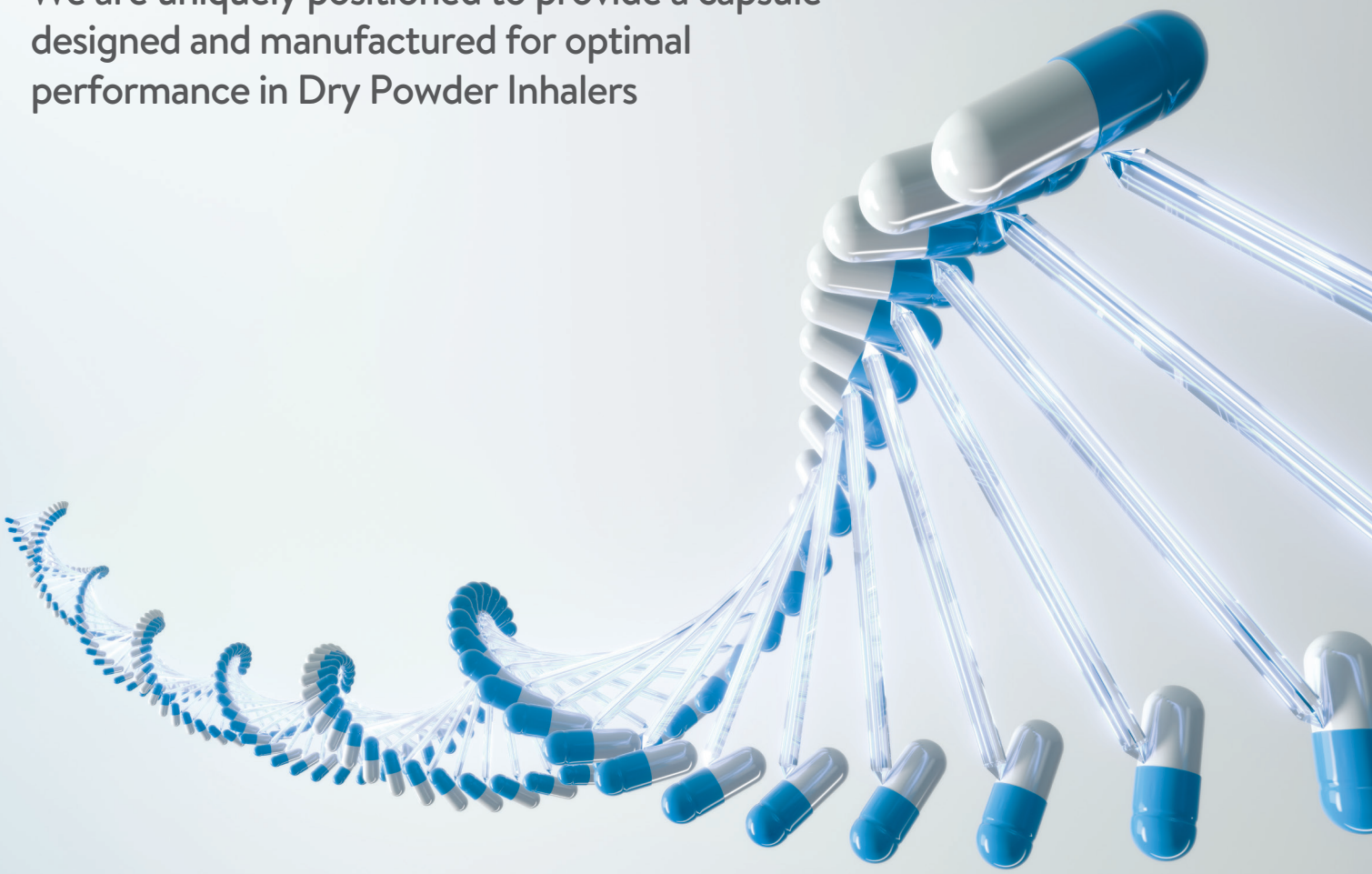
RDD Online Respiratory Drug Delivery

Aptar pharma

WHAT WE DO
WHAT WE ARE

CAPSULES ARE THE VERY ESSENCE OF QUALICAPS®

We are uniquely positioned to provide a capsule designed and manufactured for optimal performance in Dry Powder Inhalers



Quali-V®-I capsules for inhaled drug delivery

- *Strict Microbiological Control*
- *Better Aerosolization*
- *Inner Surface Control*
- *Reduced Powder Adhesion*
- *Superior Puncturing Properties*

Qualicaps *Engineered to perform*

REDISCOVER QUALICAPS® at www.qualicaps.com

ONdrugDelivery Issue N° 74, April 10th, 2017

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
Jan '18	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: "eDose Counter for MDIs" courtesy Aptar Pharma. Reproduced with kind permission.

BAUMANN MEDICAL

SPRINGS AND STAMPINGS FOR MEDICAL DEVICES

www.baumann-group.com

For more than 125 years, BAUMANN Group has been a symbol of Swiss precision and quality. We are known worldwide as a leading company in spring and stamping manufacturing. The family-owned group, now in its fifth generation, employs more than 1,500 people at eleven production sites around the globe. Its dedicated medical divison with medical mindset complies with ISO 13485 and addresses the specific customer needs of the medical and pharmaceutical industries in the fields of drug delivery, syringes, blood collection, diagnostics, and airway products.

For further interest and information contact BAUMANN MEDCIAL: medical@baumann-group.com

WHAT IS QUALITY BY **DESIGN** AND WHY SHOULD YOU CARE?

Quality by Design (QbD) is a scientific approach that formalises product design, automates manual testing, and streamlines troubleshooting. A QbD approach is an indispensable tool for successfully developing inhaled and nasal drug products as well as critical to creating effective manufacturing processes for released products. Proveris Scientific explains how this approach works.

Traditional process development is often an empirical approach that relies on frequent end product testing and inspection to determine quality. The processes that create the end product are seen as fixed, any changes are not allowed and the focus is on process reproducibility.

> "Instead of relying on finished product testing alone, QbD provides insights upstream throughout the process by identifying all critical quality attributes and process parameters..."

This approach ignores most real-world variability in materials and processes along the way. Consequently, any future efforts to discover the root cause of an out-of-specification (OOS) or out-of-tolerance (OOT) event either devolve into a trial-and-error hunt for clues, or result in a late-stage attempt at QbD for a product that is already being manufactured.

QbD, on the other hand, is a systematic approach that ensures quality by developing a thorough understanding of the sensitivity of a finished product to all the components and processes involved in manufacturing that product. Instead of relying on finished product testing alone, QbD provides insights upstream throughout the process by identifying all critical quality attributes and process parameters, and determining the extent to which any variation can impact the quality of the end product. The more information on the sensitivity – or insensitivity – of a process on a product's quality, safety or efficacy, the more business flexibility QbD provides.[1] Therefore, any quality issue can be deciphered and its root cause quickly identified.

Getting to market with an orally inhaled or nasal drug product (OINDP) is a difficult and complicated undertaking. Each OINDP includes a miniature machine or medical device packaged with the formulation to create a complete drug delivery system. The fact that each product is a complete delivery system rather than a simple dosage form adds more complexity at every stage of development.

These complexities can result in longer approval times, multiple regulatory submissions, and more time responding to queries from regulators, such as the US FDA.[2] Following a well executed QbD approach helps to reduce the development complexity and get a product to market more quickly.

Proveris Scientific Corporation
290 Donald Lynch Boulevard
Marlborough
MA 01721
United States

sales@proveris.com
www.proveris.com

Proper implementation of QbD provides three main benefits:

1. Saves time developing a product and preparing FDA submissions
2. Reduces approval times and minimises queries from the FDA
3. Provides rapid insights into any OOS or OOT disruptions to manufacturing.

FDA GUIDANCE FOR QUALITY BY DESIGN

The FDA sees QbD as the way to enhance the quality of generic drugs for the benefit of everyone involved. Manufacturers will save time and money developing and producing drugs, and gain better control of their supply chains with more rigorous scientific standards for incoming inspections. Regulators will save time and resources approving drug applications, doing inspections and troubleshooting any severe quality issues. Patients will be assured of more consistent, high-quality generic drugs that perform as advertised.

In the eyes of the FDA and the many adherents of QbD, this approach truly represents a way to do more with less and gain a win-win outcome. When fully implemented, QbD means that all critical sources of process variability have been identified, measured, and understood.[3]

The FDA defines QbD as "a systematic approach to development that begins with predefined objectives and emphasises product and process understanding . . . based on sound science and quality risk management."[4] The same guidelines go on to describe the aim of pharmaceutical development as designing a quality product and manufacturing process that consistently delivers the intended performance. And they emphasise that "quality cannot be tested into products . . . quality should be built in by design."[4]

Even after a drug product has gained FDA approval, routine QC testing may detect an OOS result. Without a rigorous test system, test results can be inconclusive, questions are difficult to answer, and long delays are possible due to the absence of reproducibility and traceability. QbD minimises these risks by mapping all the possible variables of the product components into a known control space.

This means that if any quality issues occur, scientific methods can be used to quickly zero in on the specific variables that are most likely causing those issues and not have to resort to trial and error. This will result in less frequent occurrences of lost batches, manufacturing deviations and inspections, and will result in a more reliable supply of product.

The QbD components the FDA expects to see in all submissions include:

- Quality target product profile (QTPP)
- List of critical quality attributes (CQAs)
- List of critical material attributes of drug and excipients (CMAs)
- List of critical process parameters (CPPs)
- A control strategy that ensures the product reliability meets its predefined objectives.

KEY COMPONENTS OF QUALITY BY DESIGN

The systematic approach of QbD contains four key components that are performed as a series of steps:

1. Defining the goal
2. Discovering the design space
3. Understanding the control space
4. Targeting the operating space.

After defining the product goals, each of the following steps creates a progressively more exclusive set of statistically defined parameters that can be visualised as a multidimensional space.

1. Defining the goal

In this step, the development team identifies all the CQAs for an inhaled or nasal drug product. CQAs and process control variables can be determined using:

- Literature directing the CQA's design space
- Experimental results that discover variables that can be controlled.

For these drug products, actuation matters. Regulators provide the following guidance:

- Drug products administered by devices should be tested in a manner that mimics the intended use
- Automation is the preferred method of testing.[5]

Therefore, a goal for an inhaled or nasal drug product development project using QbD could be: "How do we mimic human actuation with an automated system?"

Literature from the FDA and major manufacturers has established that both actuation parameters and formulation properties influence critical quality attributes. Four CQAs controlled by actuation are:

- Shot weight
- Spray pattern
- Droplet size
- Plume geometry.

Defining the goals for a product forces a development team to study deeply and understand the processes and CQAs. This understanding ultimately eliminates the multi-year process of endless corrective action/preventive action (CAPA) and OOS/OOT observations.

2. Discovering the design space

The key to understanding your processes is in discovering and defining the design space for the product. Critical formulation attributes and process parameters are identified by determining the extent to which any variation can affect the quality of the drug product.[1] The ICH Q8 defines design space as an "established multi-dimensional combination and interaction of material attributes and/or process parameters demonstrated to provide assurance of quality".

By accurately defining a design space, a development team can anticipate the issues and plan for controlling the manufacturing process – rather than reacting to OOS/OOT observations on poorly defined specifications. Since actuation parameters (i.e. stroke length, actuation velocity and hold time) are known to influence the delivered dose and spray characteristics, the design space for a drug product should include measurements of hand actuation and the effect on outputs (i.e. delivered/metered shot weight), as shown in Figure 1.

It is also useful to assess formulation choices along with the device selection. A matrix of devices, formulation choices and actuation parameters can serve as the basis for development across a range of nasal or pMDI products. With this design space envelope defined, you are ready to understand the sensitivity of your CQAs to changes in process variables (e.g. formulation, actuator design, pump or valve design).

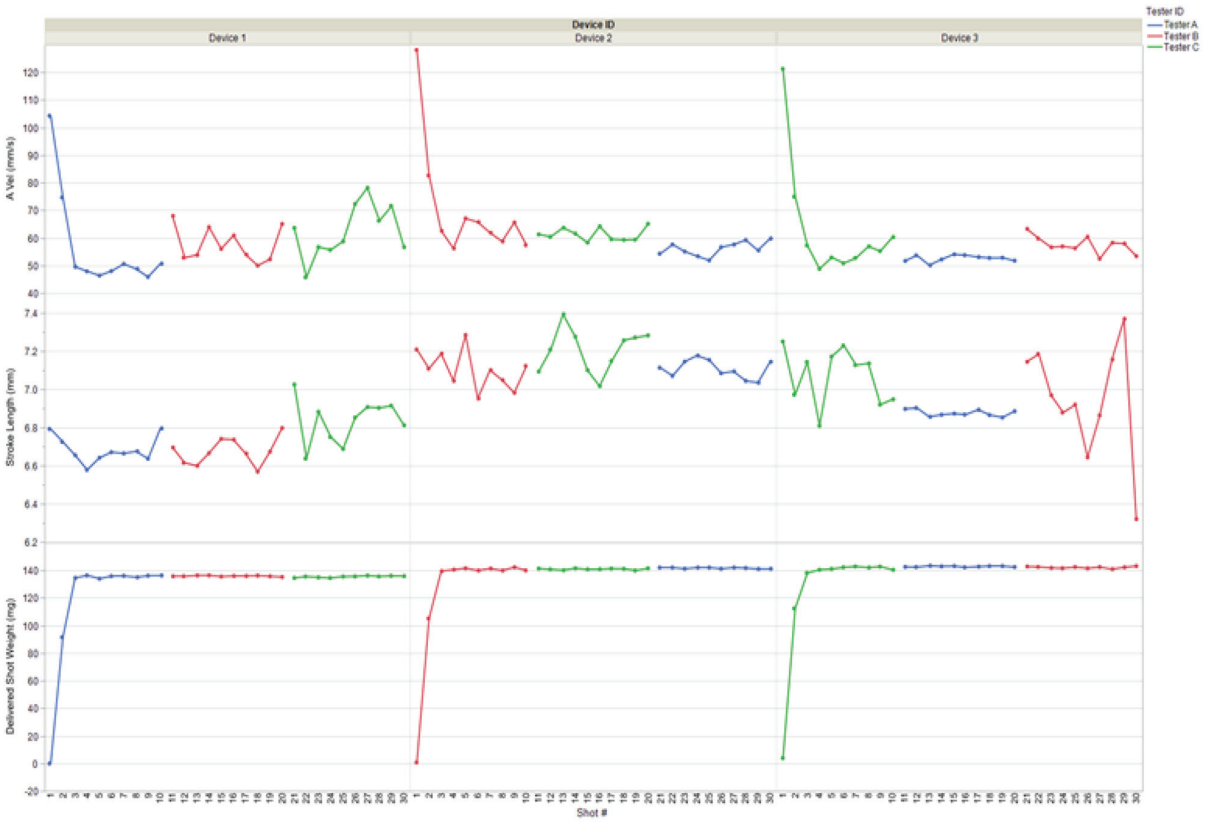


Figure 1: Example design space for a nasal spray product showing delivered shot weight performance with corresponding stroke length and actuation velocity ranges from consecutive actuations collected from three devices and three testers. The outer bounds of this data (i.e. the maximum and minimum value for each parameter excluding priming shots) defines the design space.

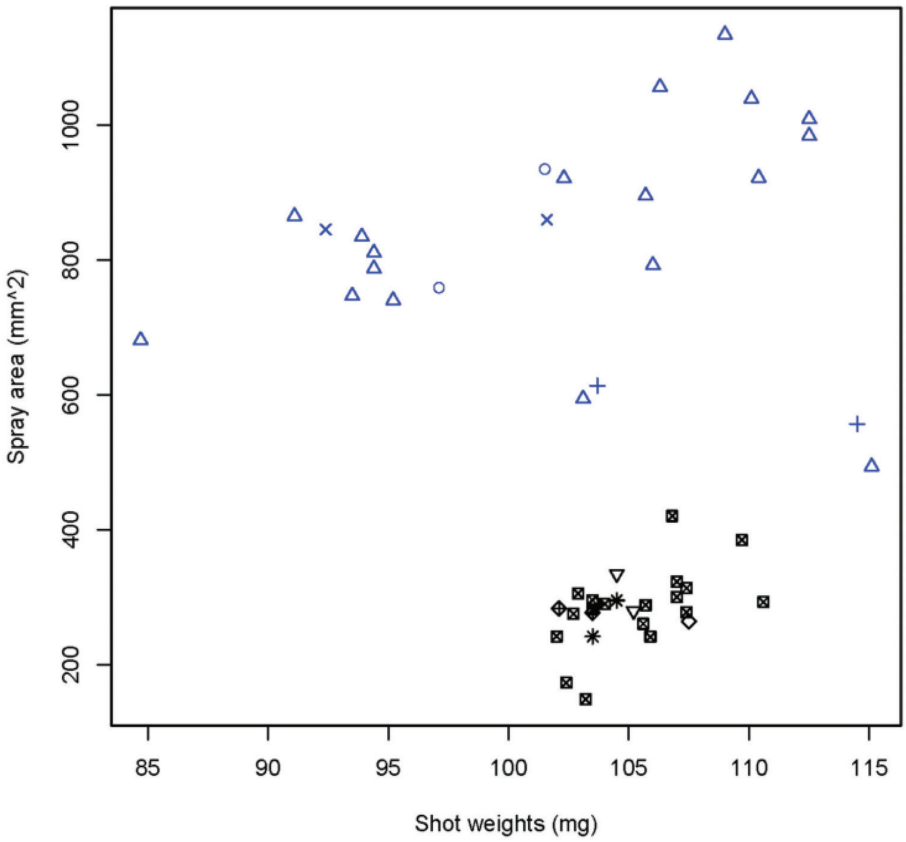


Figure 2: Example of two non-equivalent products that were developed independently – a QbD study was undertaken only prior to filing. This represents a multimillion dollar mistake. Test results in blue and reference results in black were collected at different actuation velocities.

Most importantly, if a manufacturer understands the product control space, method changes can then be handled by reporting them to the FDA in an annual report. The guidance is clear that the manufacturer must know if "the proposed change would present a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product". The simplest way to obtain this knowledge is through QbD during the development process. A QbD control space provides a scientific basis to identify any non-critical variations in input materials or processes that can be safely accommodated within the stated goals for the product.[6]

3. Understanding the control space

Using the design space as a starting point, a set of control space scenarios can be defined and executed. The results of these experiments enable a team to understand their processes in a way that shields product quality from the ordinary variability in the production process.

Figure 2 illustrates the difference between a test product (blue symbols) and a reference product viewed from a control space scenario analysis. Clearly, there are significant differences between the products. Additionally, the reference product data is tightly clustered, representing very consistent spray performance, which is normally the result of a consistent manufacturing process. The test product data is dispersed widely, representing low consistency (i.e. low manufacturing process control). If a QbD study had been performed on the reference product to begin the process, a better matching test product design could have been selected and much wasted effort could have been eliminated.

4. Targeting the operating space

The operating space is the statistically best set of parameters that enable you to accommodate any natural variability in processes and formulations. For generic products, the operating space should be within the control space and should allow the reference product to be tested with the same set of actuation parameters.

For innovator products, the operating space should be within the design space and compliant with FDA and EMEA guidelines. Innovators can gain a competitive advantage by thoroughly exploring the design space, including testing multiple batches of formulations to truly refine their product and make it difficult to reproduce.

The Proveris by Design process leverages QbD principles by:

- Providing a solid, scientific basis for method establishment and assisting with regulatory requirement compliance.
- Measuring how representative people in the drug product's age and gender range use the product. These measurements are used as the basis for programming the actuation systems to ensure efficacy and patient safety as recommended by the FDA.
- Establishing an optimised range of actuation parameters that can be used in spray performance testing for the life of the product.
- Reliably determining the length of a spray drug's conical region and the plume angle, using precise machine vision.
- Providing a scientific basis for distances employed for spray pattern, plume geometry and droplet/particle size distribution.

REFERENCES

1 *Erni F, "Design Space and Control Strategy," EFPIA PAT Topic Group presentation, October 2006, p 19.*

2 *DiMasi JA, Faden L, "Factors associated with multiple FDA review cycles and approval phase times". Drug Information Journal, March 2009, 43(2), p 205.*

3. *Neway JO, "Process Excellence: Five Critical Elements of Quality by Design". BioProcess International. May 2008, p 22.*

4. *FDA. Guidance for Industry, Q8(R2) Pharmaceutical Development. November 2009.*

5. *Guo C, Stine KJ, Kauffman KJ, Doub WH, "Assessment of the influence factors on in vitro testing of nasal sprays using Box-Behnken experimental design". European Journal of Pharmaceutical Sciences, 2008, 3(5), pp 417–426.*

6. *"Guidance for Industry: CMC Postapproval Manufacturing Changes Reportable in Annual Reports". US FDA, March 2014.*

ASSURE INHALER SAFETY & PERFORMANCE: POLYMERS, COLOUR & ADDITIVES

Here, Stephen J Duckworth, Global Head, Healthcare Polymer Solutions, Clariant Plastics and Coatings, describes some of the application of polymer colourants and additives in respiratory drug delivery devices, highlighting the strict regulatory environment.

According to WHO studies, chronic respiratory diseases (CRDs) affect more than 300 million people. In many cases, these diseases are incurable, but their symptoms can be treated by patient-administered medications, orally inhaled and nasal drug products (OINDPs), that use hand-held delivery devices such as dry powder inhalers (DPIs) and metered dose inhalers (MDIs). As the market for inhaled medications continues to grow, the inhaler segment of the medical device market will continue to be an important consumer of plastics.

> "Device manufacturers have come to realise that any material or formulation change during the lifetime of the product, or at any point in a complex materials supply chain, can invalidate product approvals while introducing the risk of leaching or contamination. Thus, the demand for change control over every ingredient in the manufacturing process becomes a formidable challenge."

The plastic components used in inhalers for OINDPs are often manufactured using a wide range of polymers and additives to achieve vital visual, physical, mechanical, and performance properties. For example, a DPI may be comprised of a combination of polymers such as polypropylene (PP), ABS, polycarbonate (PC) and modified acetal (POM) polymers and the like.

While there are more polymer and additive options available than ever before, the choices open to medical device manufacturers can be circumscribed by strict regulatory demands. The US FDA and relevant EU authorities, for example, require detailed information on material components, formulations, packaging, and manufacturing processes, backed by extensive supporting data with respect to physical and mechanical properties, biocompatibility and toxicity. Once this extensive documentation is complete, device manufacturers can use the specified materials and ingredients in their products with the confidence that they meet with regulatory and application requirements.

However, such documentation is a "point-of-time" submission, covering only the specified materials and formulations. Device manufacturers – and their supply chain managers – have come to realise that any material or formulation change during the lifetime of the product, or at any point in a complex materials supply chain, can invalidate product approvals while introducing the risk of leaching or contamination. Thus, the demand for change control over every ingredient in the manufacturing process becomes a formidable challenge, and one that often is assumed rather than actual.

It becomes essential, then, for device manufacturers not only to select materials that meet necessary criteria and offer complete and appropriate documentation, but also to select material suppliers with great care. Ideally, manufacturers will select suppliers whose facilities, manufacturing processes, and operations are dedicated to ensuring uninterrupted, change-controlled, and continuously compliant material supplies from the early phases of product design and development phases through the lifecycle of the product.

Stephen J Duckworth
Global Head, Healthcare
Polymer Solutions
T: +41 61 469 61 71
E: steve.duckworth@clariant.com

Clariant Plastics and Coatings AG
Rothausstrasse 61
CH4132 Muttenz
Switzerland

www.clariant.com/mevopur

DEMANDING REGULATIONS

There are two major classes of inhalation devices for OINDPs. MDIs (Figure 1) emit a metered dose of medication, carried by an aerosol charge, into the user's mouth and lungs. DPIs (Figure 2) dispense a small amount of a finely powdered drug formulation into an outlet chamber, which is then inhaled by the user through the mouthpiece.

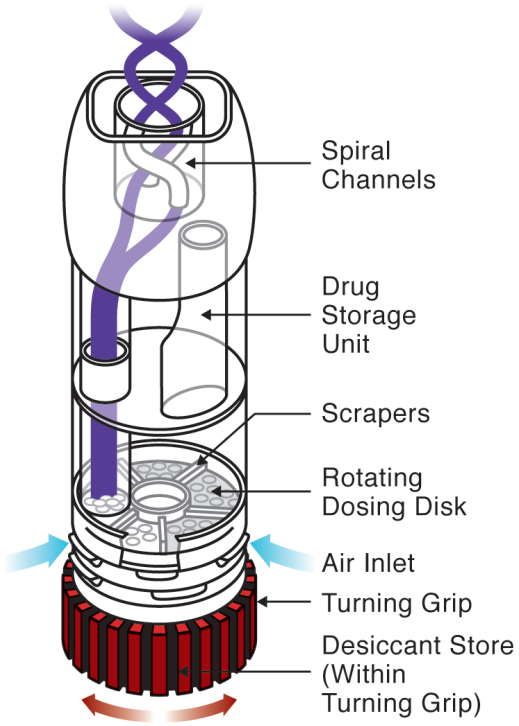


Figure 2: Main components of a typical dry-powder Inhaler.

Concern about the potential risks of materials, additives, and leachables or other contaminants in inhalers is magnified by several factors:

- The FDA rates oral inhalation (together with injection) as the drug administration method associated with the highest concern for risk. This administration method puts the inhaled dosage into direct contact with mucous membranes so it is rapidly absorbed into the body (Table 1).
- The design of both MDIs and DPIs puts plastic components into direct contact with active pharmaceutical ingredients, thus generating the risk of extractables or leachables. MDIs are thought to pose a somewhat higher risk because their aerosols contain solvent compounds that could react more aggressively with polymer components (Table 1).

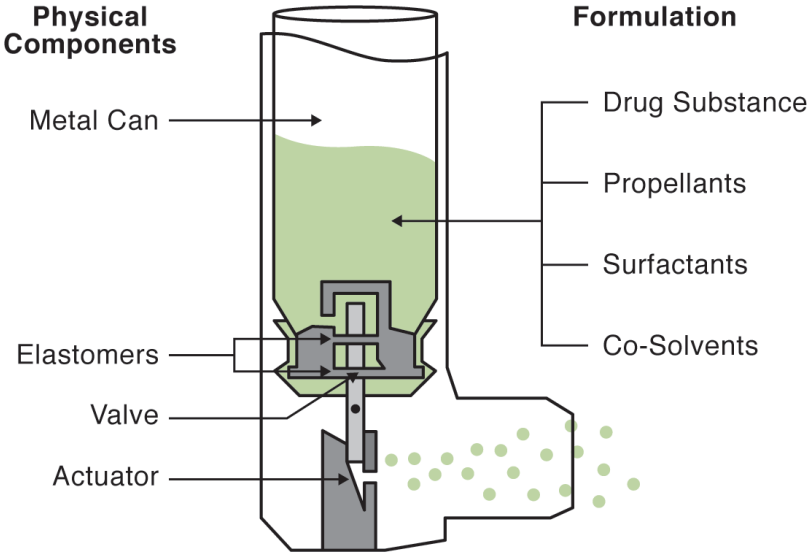


Figure 1: Main components of a typical metered-dose inhaler.

Degree of concern associated with the route of administration	Likelihood of interation (packaging component / dosage form)		
	High	Medium	Low
High	Inhalation aerosols and solutions; injections and injectable suispensions	Sterile powders; Powders for injections; inhalation powders	
High	Ophthalmic solutions and suspensions; Transdermal ointments and patches; nasal aerosols		
Low	Topical soljutions and suspensions; topical and lingual aerosols; oral solutions and suspensions	Topical powders; oral powders	Oral tablets and oral (hard and soft gelatin) capsules

Table 1: Drug Administration, Dosage, and Packaging Interactions. Detail excerpted from "Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics." Published by U.S. Food and Drug Administration, 1999. Found at: https://www.fda.gov/downloads/drugs/guidances/ucm070551.pdf

- Inhalers are designed for repeated usage, so patients may be exposed to inhaler contents 30, 60, or even more times.

To maximise safety, standards and regulatory bodies worldwide are working continuously to update material testing and compliance requirements. For example, the US Pharmacopeia (USP) is in the process of tightening key standards governing plastic packaging materials (USP <661.1>), plastic packaging systems (USP <661.2>), plastic in manufacturing systems (USP <661.3>), and drug delivery devices (USP <661.4>) between now and 2020. These will apply to all materials used in pharmaceutical packaging, including so-called combination devices.

Another international group, the International Pharmaceutical Aerosol Consortium for Research and Science (IPAC-RS) has been working on new, more rigorous testing and control recommendations specific to materials and ingredients used in OINDPs. Published in February 2017, these "Recommended Baseline Requirements for Materials used in OINDPs" make clear that manufacturers

and suppliers must be prepared to implement even higher levels of change controls or risk increased product delays and testing costs. (Full text can be found at: http://ipacrs.org/news-events/news/ipac-rs-updates-recommended-baseline-requirements-for-materials-used-in-oindps.)

COLOUR AND ADDITIVES

This increased regulatory scrutiny comes at a time when – or more likely because – OINDP manufacturers are actually trying to do more and more with colour, functional additives, and other materials in their devices.

Increasingly, treatments are self-administered where compliance to a regular regime is important. US studies indicate only 28% patient-adherence to treatment programs. The cost of wasted medication and follow-on treatment is significant, leading companies to seek out new ways to make their devices more attractive and easier to use. This has led many manufacturers to begin applying techniques perfected in consumer-product design. Colour, for instance, can be used to make OINDPs more appealing to patients so that they are more likely to carry the devices with them and feel comfortable using them as prescribed.

As the market expands, device makers also need to ensure that inhalers are easy to identify and select. Several industry groups have begun recommending that inhalers be colour-coded to indicate the types of medication that they contain. More subtle colour differences can be used to indicate different dosages or other variations. Table 2 shows a coding system typical of those being considered.

Just about any colour imaginable can be developed for OIDNPs and other medical devices, provided that the material properties, regulatory requirements and change management are addressed in the design phase. Suppliers have developed specific product ranges that offer a palette of "standard" or customised colourants already biologically evaluated to ISO10993-1 and USP23 chapters <87> and <88> (Class VI) and, as mentioned in the IPAC-RS guideline, all manufactured with strict quality- and change-control procedures already in place. The same applies to special-effects pigments, which have been used for many years to enhance the look and market appeal of personal-care and consumer goods. When added to plastics, special-effect pigments can give product surfaces a pearlescent, sparkly, or metallic look. Testing has been completed to confirm that the ingredients in these new materials conform to medical and pharmaceutical norms.

Inhaler Colour	Medication Type
Blue	Bronchodilator
Aqua/Green	Long-acting, β_2 agonist
Grey	Muscarinic antagonists
Brown	Corticosteroids
Purple	Compound preparations

Table 2: Example colour coding system for different OINDPs.

> "Though estimates vary widely, the WHO has estimated that more than 8% of the medical devices in circulation are counterfeit, posing not only a significant liability to their manufacturers, but also a risk of harm to patients or healthcare providers."

At the same time, inhalers are mechanical devices. They depend on mass-produced moving parts that must fit together consistently, actuate easily, and reliably deliver a precise dosage of medication anywhere, under any extreme of weather or environment. Achieving and maintaining this level of part-to-part consistency and performance often requires manufacturers to utilise specialised polymer additives. A growing number of functional additives are now available to manufacturers, including:

- Lubricants, which are used to reduce the surface friction between plastic components. These may be part of the original design, or to solve problems encountered during scale-up. Friction reduction plays a vital role device reliability and ease of use in OINDP devices.
- Stabilisers, which prevent certain polymers from losing mechanical properties or prevent the yellowing/discoloration due to gamma or e-beam sterilisation.
- Nucleating agents, which limit the degree of dimensional change in components that can occur when different colours are used. Nucleating agents, which affect how some plastics harden during processing, can help prevent warping due to differential shrinkage. In addition, they can help speed up the process cycle or reduce weight of the component, reducing costs.
- Laser-friendly additives make plastic materials more receptive to laser marking so that the technology can be used for precise, permanent marking even on small, nearly inaccessible surfaces. This type of marking will become increasingly important as unique device identification (UDI) programs are rolled out in both the US and Europe over the next few years.

UDI helps protect patient safety by providing traceability, but is only one weapon to combat the growing problem of counterfeiting, which impacts not only high-value drugs but consumable medical devices like inhalers. Though estimates vary widely, the WHO has estimated that more than 8% of the medical devices in circulation are counterfeit, posing not only a significant liability to their manufacturers, but also a risk of harm to patients or healthcare providers.

One of the most effective ways to protect a reputable product brand is to use multiple level security. This involves the use of covert (hidden) and visible coding on medical devices and their packaging. For plastics, the covert approach employs taggants – unique ingredients that are incorporated into plastic components to provide immediate and incontrovertible proof of the genuine article. Taggants, like other ingredients, are subject to compliance and change-control regulations. Fortunately, solutions are available to meet this challenge.

MOISTURE PROTECTION

Quite often, the medications dispensed through inhalers, particularly DPIs, are moisture-sensitive. Keeping these medications dry, or at a particular relative humidity, is essential not only to maintaining product stability and prolonging shelf life, but to the reliable functioning (e.g. accurate dosing) of the device.

To meet this need, Clariant manufactures a range of controlled atmosphere packaging solutions, including pharmaceutical desiccants, equilibrium sorbents, adsorbent polymers and pharmaceutical closures and containers with these products built in. These products help to protect the drug from moisture even under the severe temperature and humidity conditions used in accelerated shelf-life stability studies.

For example, Clariant's sorbents can maintain humidity equilibrium in pharmaceutical packaging where specific relative humidity conditions are needed, such as in DPI packages. In these packages, equilibrium products perform simultaneously as humectants (desorbers) and desiccants (adsorbers) to maintain an ideal equilibrium relative humidity (ERH). Other desiccant products may be incorporated as washer- or wafer-shaped inserts within inhaler parts, such as the turning grip shown earlier, in Figure 2.

MINIMISING RISK

Device designers, developers, and manufacturers can employ an array of options to add colour and performance to plastic components used in inhalers for OINDPs and other medical devices. The key to successfully employing these options is to understand and manage the regulatory and supply-chain risks that are involved in selecting, sourcing, and controlling these materials through the lifecycle of the product.

Approximately 10 years ago, Clariant Masterbatches recognised supply-chain challenges confronting the healthcare industry and reorganised its approach to the medical device and pharmaceutical packaging markets to help its customers rationalise their approach to risk. This involved creating a network of three global manufacturing plants (one each in the US, Europe, and Asia) and managing them under the ISO13485 quality system with change-control protocols. This is important because, firstly, production of a medical device may be required in different regions or be transferred and, secondly, back-up supply is normally a requirement.

Then came standardisation of raw materials in terms of chemistry and supplier. This process involved the technical, product stewardship and supply chain functions that assess each raw material not only on performance characteristics, but on regulatory criteria such as RoHS, REACh, BSE/TSE and so on, and whether the supply was available in each of the three sites. Each plant uses the same defined raw material ingredients, the same formula, and the same key product quality parameters. The measurements not only include typical tests such as colour and physical properties, but also ISO 10993 part 18 extraction, biological evaluation (ISO10993 and USP <87>, <88>) and batch comparison to a chemical "fingerprint" of a reference product.

CONCLUSION

Whether the issue is regulatory compliance, change control, UDI, counterfeiting prevention, patient acceptance, or usability, there are polymer and additive solutions readily available to help manufacturers get a better OINDP to market more quickly. Once some of the uncertainty that is part of the global material sourcing process has been eliminated, manufacturers can concentrate more on making devices that are more functional, more attractive and, thus, more effective at giving patients around the world greater access to better and safer treatment.

ABOUT THE AUTHOR

Stephen Duckworth is a graduate in Applied Chemistry with over 30 years spent in the polymers and compounding industries in R&D, marketing and operations functions in the US, Europe and Asia, with leading international companies such as Raychem, General Electric (now SABIC), DSM, PolyOne and also as an independent consultant for market analysis, M&A, and Asia entry strategies. He joined Clariant in 2007.

In 2008, Mr Duckworth initiated and led a global project to address the medical, pharmaceutical and healthcare sector that radically changed how Clariant approached this market, and the creation of a new brand MEVOPUR®. Since January 2011, he is the head of a newly formed segment focused on Healthcare, and leads a team of dedicated specialists based in the US, Europe and Asia. This global team initiates and manages developments with pharmaceutical and medical devices companies and their supply chain in areas such as drug packaging and delivery devices, IVD, and invasive devices, focused around an approach of minimisation and management of risk of changes.

Mr Duckworth is Vice-Chairman and Executive Board Member of the cross-industry group MedPharmPlast Europe, and member of the regulatory affairs committee of this association. MedPharmPlast monitors and analyses potential legislation and provides expert insights to the European Commission / legislators, and to the membership.

CONTROLLED-RELEASE SYSTEMS FOR PROTEINS & PEPTIDES: 3RD-GENERATION INTRANASAL ANTHRAX VACCINE-DELIVERY SYSTEM

By S. Mohan Mohanraj, PhD, and Meir Kende, PhD

ABSTRACT

The objective was to develop microsphere-based delivery systems (MDS) for controlled and pulsed-release delivery of recombinant anthrax vaccine via intranasal immunisation. Microsphere-based recombinant protective antigen (RPA) delivery systems for intranasal immunisation were successfully developed, wherein the MDS formulations produced extremely high antibody titres (over 150,000) in mice after 65 days of immunisation compared with the aqueous RPA vaccine system (at 15,900).

Selected MDS systems were challenged with anthrax toxin. The MDS systems, on two intranasal doses, showed 100% protection against anthrax toxin challenge in mice, compared with <17% that were protected by the aqueous RPA vaccine system and none in the non-immunised control group.

OBJECTIVES

The general objective of the work was to develop and evaluate microsphere-based antigen delivery systems to enhance the efficacy of the RPA vaccine via intranasal immunisation. To demonstrate that effective protection against anthrax can be achieved by alternative needle-free vaccination, PolyMicrospheres developed and evaluated novel antigen-adjuvant delivery systems.

The efficacy of vaccination can be considerably improved not only by incorporating the antigen in a matrix, but also incorporating potent adjuvants in the matrix to provide long-term delivery of antigen together with an adjuvant for further potentiation of the immune response.

Depending on the composition, the matrix delivery system releases the incorporated RPA/adjuvant at many distinct time points, stimulating primary and many booster responses for better immunity and protection. The controlled-release kinetics and the consequent multiple antibody peaks assure a long-persisting immunity and protection for at least one year.

> "The platform technology of this intranasal delivery system is also suitable for other human and veterinary vaccines including simultaneous intranasal delivery of multiple immunogens."

BACKGROUND AND SIGNIFICANCE

The possibility of biological warfare and bioterrorism is an increasing threat in today's world. Among these weapons, anthrax has become the most prominent threat. It is only prudent to take steps to minimise the damage from such an act of bioterrorism. One of the most effective precautions will be a two-dose immunisation with an effective vaccine delivery system, which can be easily administered.

The *Bacillus anthracis* organism can be very easily produced in bulk quantities and disseminated as stable, long-lasting spores which can infect a large population via inhalation or contact.[1-2] The most serious route of infection is pulmonary. The spores germinate and quickly disseminate in the hilar and tracheal lymph nodes; the ensuing bacteraemia produces over 80% mortality within a short period. An RPA vaccine has been developed and immunisation with this protein has offered significant protection against pulmonary anthrax.[3-7]

In a combat situation, logistics of vaccine administration, compliance and time are of essence. Vaccination with the first

Dr. S. Mohan Mohanraj
Director of Technology
T: +1 317 549 3764
E: mohan@polymicrospheres.com

PolyMicrospheres
Division of Vasmo Inc.
4101 East 30th Street
Indianapolis
IN 46218
USA

www.polymicrospheres.com

Dr Meir Kende
Dept of Molecular Biology,
Integrated Toxicology Division

US Army Medical Research Institute of Infectious Diseases (USAMRIID)
1425, Porter Street
Fort Detrick
MD 21702
United States

www.usamriid.army.mil

generation of anthrax vaccines, after the initial injection, requires five parenteral booster doses in 18 months. Furthermore, side effects occur, which can range from local soreness to fever and illness, with increased chances of occurrence after a booster injection. The second-generation vaccine, RPA with alum adjuvant, requires three or four vaccinations over an 18-month period.

Thus there is a need for a vaccine delivery system which is convenient and offers long-term protection without multiple boosters. In this applied research, we developed and evaluated microsphere-based antigen-adjuvant intranasal delivery systems to enhance the efficacy of RPA vaccine via two doses. This platform technology could be utilised not only against inhalation anthrax but also against other microbes.

Mucosal surfaces of the nasal passages and the gastrointestinal tract are the major portals of entry of infectious agents and microbial toxins. Therefore, the mucosal surfaces constitute the first line of defence. Intranasal vaccination strategies that enhance mucosal immunity have practical significance to protect military personnel and civilian populations against various microbes and toxins.

Most importantly, mucosal immunisation elicits a broader immune response, and an enhanced systemic and topical protection. The efficacy of the vaccine is substantially enhanced by a mucosal adjuvant; consequently, a powerful systemic and mucosal immunoglobulin response is stimulated, thereby providing a very potent first-line protection against intranasal entry of microbes and toxins.

Controlled release of antigens from polymer microparticles has been of particular interest in the development of vaccine delivery systems.[8-10] The efficacy of vaccination can be improved not only by incorporating the antigen in the polymer matrix, but also by incorporating potent adjuvants in the matrix to provide long-term delivery of antigen together with a vaccine-adjuvant for further potentiation of the immune response.

Many modern vaccines are composed of highly purified or recombinant proteins or synthetic peptides. The use of potent adjuvants to enhance immune response to these antigens is an attractive method for improving their immunogenicity. Such adjuvants include CpG motifs, lipopolysaccharide, polyIC and monophosphoryl lipid A.[11-12] Other potent adjuvants include LTR72 and LTK63.[13-14] The biological activity of LTR72 and LTK63 is by cytokine-stimulated robust enhancement of both the humoral and the cellular immune response.

METHODS

The MDS were designed and developed as follows: in order to achieve full protection by a two-dose intranasal immunisation, the delivery system needs to be optimally designed using appropriate microencapsulation methods and finely tuned release kinetics.

A correct combination consists of the following: the second-generation RPA, most potent mucosal adjuvant (Adj), RPA-Adj ratio, poly(lactide/glycolide) ratio for the right half-life, microsphere particle diameter to have the proper drug load and to penetrate into the mucosal epithelial cells, and the process parameters to achieve the stability and integrity of the conformation of RPA (see Figure 1).

The matrix of the antigen/Adj-incorporated microspheres may be further coated with a bioadhesive to promote adhesion to the antibody producing M cells in the mucosal membranes of the respiratory tract. For these reasons and due to the extreme high cost of RPA, it was essential to develop, evaluate and refine the delivery systems in multiple stages. We were able to develop, test and refine the formulations as we progressed through each stage with the results from the animal studies.

The novel RPA/Adj delivery systems were designed to provide controlled- and pulsed-release delivery of the recombinant anthrax vaccine equivalent to multiple immunisations. A mucosal adjuvant such as LTK-63 was also incorporated into the microsphere matrices to provide a long-term delivery of a vaccine adjuvant for further potentiation of the immune system.

In these MDS, both the RPA and the Adj are incorporated into the same microsphere matrices. Depending on the optimal combination of the RPA/Adj in the polymer matrix, the molar ratio of lactide-glycolide, drug loading, particle diameter and the microencapsulation methods and process techniques, the content is released in a controlled manner at multiple time-points stimulating antibody peaks several weeks apart, thereby a long-lasting (at least one year) immunity and protection is stimulated.

The delivery systems were designed such that the antigen can reach the mucosal antigen processing cells in its native conformation for induction of an effective protective immunity.

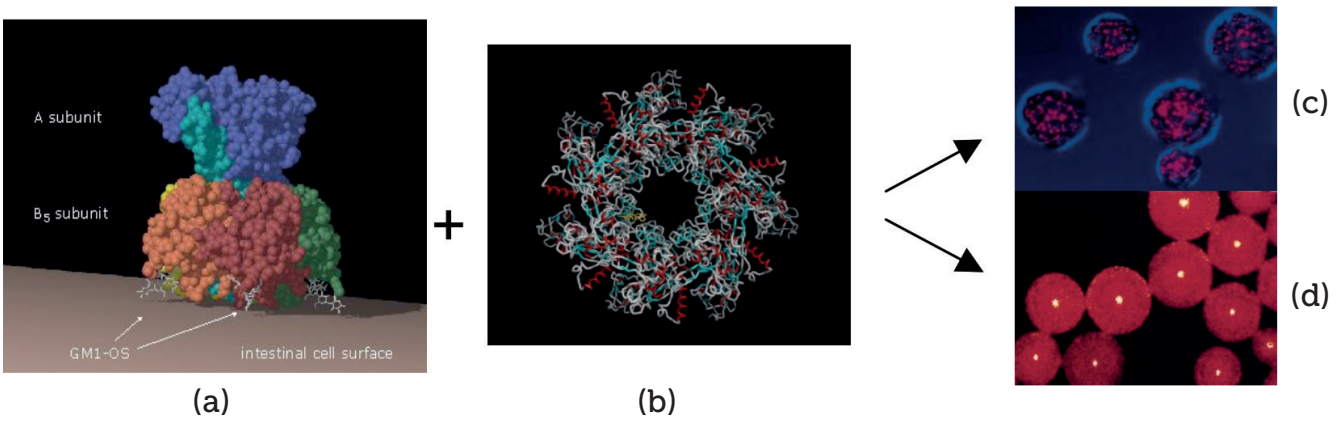


Figure 1: RPA (a) bound to an adjuvant (b) incorporated into heterogeneous microspheres (c) or homogeneous microspheres (d) with controlled-release kinetics over a period of 15 weeks stimulating antibody response at many distinct time points. The released RPA/adjuvant binds to the cell surface by the B subunit of the adjuvant. After entering the antibody producing cells, a long-lasting and enhanced immune response and protection is stimulated.

A. Preparation of the MDS formulations:

- Polymers poly(dl-lactide-co-glycolide) and poly(dl-lactide)
- Microsphere Mean Diameter range: 9-16 µM
- RPA of anthrax (from List Biological) Loading: 0.8-1%
- Adjuvant (LTK63 from Chiron) Loading: 0.04-0.08%

MDS formulations were prepared using established protocols currently in use at PolyMicrospheres.[15] A modified complex coacervation process was used.

Processes include heterogeneous (Process I leading to Type I products) and homogeneous (Process II leading to Type II products) water-in-oil primary emulsions leading to different matrix-formulations to release the antigen and adjuvant at different rates.

Preparation of MDS coated with a bioadhesive:
These formulations were prepared using established protocols currently in use at PolyMicrospheres. Briefly, a dispersion of MDS microspheres was coated with a solution of a bioadhesive polymer. The coated microspheres were centrifuged or filtered, and dried under vacuum or lyophilised.

B. Analytical methods for the characterisation:
The MDS formulations developed were characterised as to mean particle diameter, size distribution, antigen and adjuvant loadings using established protocols currently in use at PolyMicrospheres.[15] Briefly, the analytical instruments and techniques are summarised as follows:

a) Particle size and size distribution analysis using Shimadzu Laser Diffraction Particle Size Analyzer SALD-1100 and/or Coulter N4MD Multi-angle Sub-Micron Particle size Analyzer.
b) Particle aggregation, uniformity, shape, and surface morphology analysis using a Nikon-Diaphot high resolution inverted microscope.
c) Measurement of antigen/adjuvant loadings in the microparticle delivery systems: A known weight of the microparticle sample was dissolved in a suitable volume of solvent and extracted with a known volume of PBS. The concentration of protein was determined using a Bio-Rad Protein Assay Kit.

C. Protocols for vaccination of mice and efficacy:
Selected formulations were tested for their ability to induce a systemic antibody response in mice following a two-dose intranasal administration. The immune response was assessed by an ELISA assay of periodic test bleeds for anti-RPA antibodies.

Mouse immunisation protocol:
Groups of 8 AJ mice were immunised with 3-3.4 mg each of MDS incorporated with both RPA and Adj by intranasal administration. The second dose was administered after 20 days of the first immunisation with the same dosage of each MDS. Control groups include aqueous RPA system and non-immunised control. Mice were bled from the retro-orbital sinus under light anesthesia over a 15-week period after second immunisation. Serum was prepared and assayed for anti-PA antibodies by ELISA.

ELISA assay for mouse anti-PA antibodies:
Individual serum samples bled at various time points (10, 30, 65 and 108 days after immunisation) were assayed for anti-PA IgG, IgG1, IgG2a, and IgG2b immunoglobulins using standard ELISA protocols. Horseradish peroxidase-labelled anti-mouse antibody directed against the appropriate Ig class of interest was used. The amount produced was determined spectrophotometrically. A standard curve was prepared using known amounts of purified mouse anti-PA antibodies, obtained from USAMRIID as a positive control, and the amount of anti-PA antibodies in the samples were determined.

Anthrax-toxin challenge studies in mice:
Selective MDS formulations were tested for efficacy in inducing protection against a lethal challenge of anthrax toxin. Control groups include an aqueous RPA system and a non-immunised group. Mice were bled as described above from the retro-orbital sinus for 15 weeks. The serum was tested for antibody titre to assure that animals receiving the vaccine have responded. The anthrax-toxin challenge was performed after 110 days of the second immunisation. This challenge consists of iv mixture of lethal factor (1.5 mg/kg) and protective antigen (3 mg/kg) in a combination equivalent of approximately five LD_{50} in non-immunised mice. On day 42 after toxin challenge, experiments were terminated.

D. Safety & histopathology studies:
Four to six weeks after the second immunisation of selected MDS formulations at the dose used in the immunisation protocol, five mice at each time point were sacrificed for complete organ histopathology to rule out toxic side effects. At these time points, blood samples were collected prior to sacrificing the mice for routine serum chemistry, including liver and kidney function tests, creatinine kinase, and for complete haematology parameter determinations. Evaluation criteria were to compare the histopathology, and serum chemistry including kidney and liver function tests with normal untreated animals.

MDS Product code	Mean Diameter	Drug loading		Type (see Methods)
		RPA	Adj	
MDS-I	9 µM	0.96%	0%	I, coated w/bioadhesive
MDS-V	12 µM	0.88%	0.08%	I
MDS-VI	13 µM	0.87%	0.08%	I, coated w/bioadhesive
MDS-VII	9 µM	0.82%	0.04%	I
MDS-VIII	10 µM	0.81%	0.04%	I, coated w/bioadhesive
MDS-X	16 µM	0.81%	0.04%	II, coated w/bioadhesive

Table 1: MDS incorporated with both RPA and ADJ in the same microspheres.

RESULTS AND DISCUSSION

The RPA-adjuvant delivery systems were designed, developed and crafted at PolyMicrospheres in many stages. Each stage consists of a group of optimal formulations with various diameters, polymer matrices and drug loadings to provide controlled and pulsed-release of the anthrax vaccine. As the formulations were developed, they were tested systematically in mice (as described above).

The antibody titres of immunity stimulated with MDS were determined in mice. Based on the results, formulations were refined, redesigned and the process conditions were altered to obtain formulations with the desired integrity, antigen/adjuvant content and release kinetics required to stimulate full protection against the anthrax toxin challenge. Development and evaluation were done side-by-side and stage-by-stage. We developed more than 40 MDS formulations using established protocols currently in practice at PolyMicrospheres to achieve the best release rates. Only selective MDS formulations with significant results are reported here.

A. Development and optimisation of MDS for RPA vaccine

Significant effort was focused on the design and development of the RPA- and Adj- incorporated MDS, wherein both the RPA and the Adj were incorporated into the same microspheres (Table 1). We have also developed MDS systems coated with a mucoadhesive to promote the adherence and retention of the microparticles into the mucosal membranes of the respiratory tract.

B. Studies on immunisation of mice with MDS via intranasal administration

We have immunised mice via two-dose intranasal administration with the MDS systems. The second dose was administered after 20 days of the first immunisation. The MDS products were tested for their efficacy to induce an antibody response in mice.

Figure 2 shows the antibody (IgG) response in mice immunised with selected MDS systems via two-dose intranasal administration. Figure 3 shows the antibody IgG Subclass (IgG1, IgG2a, and IgG2b) titres in mice immunised with selected MDS systems.

The MDS systems, MDS-V to MDS-X, all produced high antibody titres. MDS-V and MDS-X showed extremely high antibody titres on days 30-108. Thus, it is very likely that the MDS immunised mice were already fully protected 30 days after the second immunisation.

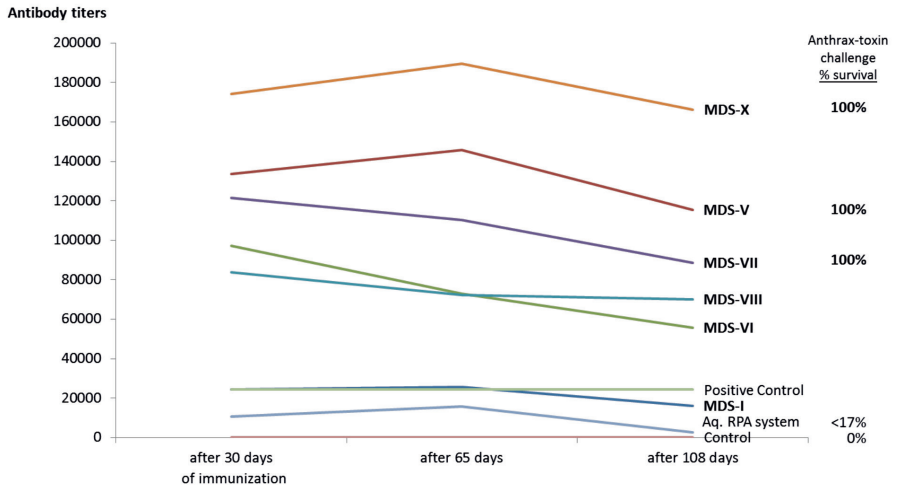


Figure 2: Immune response to selected MDS systems in mice via two-dose intranasal immunisation: antibody (IgG) titres (at dilution X).

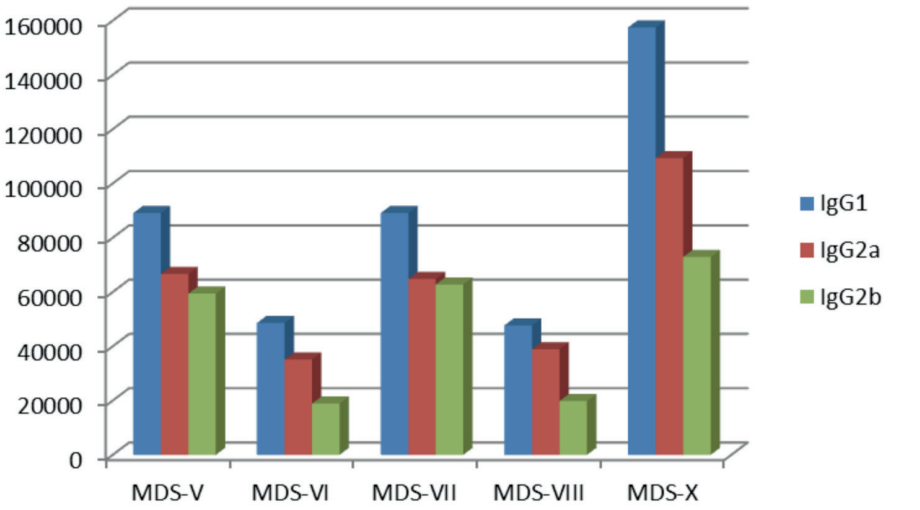


Figure 3: Antibody IgG subclass titers of selected MDS systems in mice via two-dose intranasal immunisation after 65 days (at dilution X).

Among the Type I (Table 1) systems, MDS-V and VII are the most effective. Among all of the delivery systems, MDS-X (Type II) is by far the best, exhibiting a 12-fold increase (on 65 days) over the aqueous RPA system. The IgG titres induced by the MDS systems remained high over the testing period of 108 days, indicating a continuous controlled release of the RPA and Adj over 3.6 months, while the IgG titre of the aqueous RPA system declined almost completely by 108 days.

The MDS systems, MDS-V to MDS-X, all produced high IgG subclass titres. MDS-V, MDS VII and MDS-X showed very high IgG subclass titres.

Among the Type I systems, MDS-V and VII are the most effective. MDS-V and MDS-VII, with different Adj loadings, exhibited similar IgG1, IgG2a, and IgG2b titres.

Among all of the delivery systems, MDS-X (Type II) is by far the best, exhibiting extremely high IgG Subclass titres.

Although IgG correlated well with protection (Figure 2), it is important to identify the protective antibody subclasses. The IgG2a response (which is believed to be the principal protective antibody against tumour cells and tumours, trypanosoma and hepatitis B virus infection) correlates well with the resistance to anthrax toxin challenge. IgG1, IgG2a and IgG2b effector activity is complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC). CDC and ADCC are directed against tumour or viral antigen expressed on the cell surface.

C. Challenge of immunised mice against anthrax toxin

Mice immunised with selected MDS products showing high antibody titres were challenged with anthrax toxin. Figure 2 includes toxin challenge studies on selected MDS systems against anthrax toxin. Anthrax-toxin challenge was performed after 110 days of the second immunisation. On day 42 after the toxin challenge, experiments were terminated. All control (non-immunised) mice died within the first three days, demonstrating that the challenge was correctly administered to the mice.

The median survival time of mice immunised with two-dose of aqueous RPA system is <12 days (5 died in <6 days, and one survived), showing <17% protection against the toxin challenge. Mice immunised with MDS-V, MDS-VII and MDS-X groups had all survivors. The MDS systems MDS-V, MDS-VII, and MDS-X showed 100% protection against the anthrax toxin challenge on the 42nd day when the experiments were terminated. These vaccine delivery systems afforded good protection against anthrax toxin while the aqueous vaccine system did not.

These results indicate a viable intranasal delivery system for anthrax vaccine. Microsphere-based intranasal RPA/Adj delivery system inoculated to mice substantially augmented the RPA-specific ELISA IgG titres for more than 108 days compared with the aqueous RPA system titres. Unlike with the aqueous RPA system, mice vaccinated intranasally with two doses of MDS system resisted challenge with anthrax toxin.

D. Histopathology studies on immunised mice

Preliminary histopathology studies indicate that the heart, lungs, liver, spleen, kidneys and small intestine are normal in mice immunised with the delivery systems MDS-V and MDS-X, and they did not show any toxic effects.

CONCLUSION

In this applied research, PolyMicrospheres has successfully developed a viable intranasal microsphere-based delivery system (MDS) offering an effective delivery of recombinant anthrax vaccine via two-dose immunisation. MDS-V and MDS-X systems delivered over 100,000 antibody titres throughout 108 days, compared with less than 3,000 for the aqueous RPA system. In addition, the novel MDS showed 100% protection against lethal anthrax toxin challenge, while the aqueous RPA system was ineffective.

Preliminary histopathology studies of the MDS did not show any toxic effects. Even three weeks immunisation time with two doses of our MDS is a significant reduction of the current parenteral immunisation protocol of 18 months with the RPA-alum adjuvant, plus the added benefits of reducing the cost of the immunisation and logistics.

The platform technology of this intranasal delivery system is also suitable for other human and veterinary vaccines including simultaneous intranasal delivery of multiple immunogens.

ACKNOWLEDGEMENT

Research Support: US Army Medical Research, Contract Number: DAMD17-02-C-0018

REFERENCES

1 *Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Friedlander AM, Hauer J, McDade J, Osterholm MT, O'Toole T, Parker G, Perl TM, Russell PK and Tonat K, "Anthrax as a biological weapon: Medical and public health management". Journal of the American Medical Association, 1999, Vol 281, pp 1735-1745.*

2 *Scorpio A, Blank TE, Day WA and Chabot DJ, "Anthrax vaccines: Pasteur to the present". Cellular and Molecular Life Sciences". 2006, Vol 63, pp 2237-2248.*

3 *Gu ML, Leppla SH and Klinman DM, "Protection against anthrax toxin by vaccination with a DNA plasmid encoding anthrax protective antigen". Vaccine, 1999, Vol 17, pp 340-344.*

4 *Demicheli V, Rivetti D, Deeks JJ, Jefferson T and Pratt M, "The effectiveness and safety of vaccines against human anthrax: a systematic review". Vaccine, 1998, Vol 16, pp 880-884.*

5 *Friedlander AM, Pittman PR and Parker GW, "Anthrax vaccine: Evidence for safety and efficacy against inhalational anthrax". Journal of the American Medical Association, 1999, Vol 282, pp 2104-2106.*

6 *Friedlander AM and Little SF, "Advances in the development of next-generation anthrax vaccines". Vaccine, 2009, Vol 27, pp D28-D32.*

7 *Robert J, Cybulski J, Sanz P and O'Brien AD, "Anthrax vaccination strategies". Molecular Aspects of Medicine, 2009, Vol 30, pp 490-502.*

8 *Hanes J, Cleland JL and Langer R, "New advances in microsphere-based single-dose vaccines". Advanced Drug Delivery Reviews, 1997, Vol 28, pp 97-119.*

9 *Igartua M, Hernandez RM, Esquisabel A, Gascon AR, Calvo MB and Pedraz JL, "Enhanced immune response after subcutaneous and oral immunization with biodegradable PLGA microspheres". Journal of Controlled Release, 1998, Vol 56, pp 63-73.*

10 *Yan C, Rill WL, Malli R, Hewetson J, Naseem H, Tammariello R and Kende M, "Intranasal stimulation of long-lasting immunity against aerosol ricin challenge with ricin toxoid vaccine encapsulated in polymeric microspheres". Vaccine, 1996, Vol 14, pp 1031-1038.*

11 *Klinman DM, Klaschik S, Tomaru, K, Shirota H, Tross, D., Ikeuchi, H., Immunostimulatory CpG oligonucleotides: effect on gene expression and utility as vaccine adjuvants". Vaccine, 2010, Vol 28, pp 1919-1923.*

12 *Baldridge JR, Yorgensen Y, Ward JR and Ulrich JT, "Monoposphoryl lipid A enhances mucosal and systemic immunity to vaccine antigens following intranasal administration". Vaccine, 2000, Vol 18, pp 2416-25.*

13 *Giuliani NM, Del Giudice G, Gianelli V and Dougan G, "Mucosal adjuvanticity and immunogenicity of LTR72, a novel mutant of Eschericia coli heat-labile enterotoxin with partial knockout of ADP-rybosyltransferase activity". Journal of Experimental Medicine, 1998, Vol 187, pp 1123-32.*

14 *Kende M, Del Giudice G, Rivera N and Hewetson J, "Enhancement of intranasal vaccination in mice with deglycosylated chain A ricin by LTR72, a novel mucosal adjuvant". Vaccine, 2006, Vol 14, pp 2213-2221.*

15 *March KL, Mohanraj S, Ho PPK, Wilensky RL and Hathaway DR, Circulation, 1994, Vol 89, pp 1929-1933.*

VIRGINIA COMMONWEALTH UNIVERSITY

RDD 2018 ARIZONA
Respiratory Drug Delivery

JW MARRIOTT STARR PASS HOTEL & SPA
TUCSON, AZ

APRIL 22-26, 2018

CALL FOR PAPERS

Podium Deadline • August 1, 2017
Poster Deadline • January 8, 2018

CHARLES G. THIEL AWARD

Nomination Deadline
November 30, 2017

VCU RDD PETER R. BYRON GRADUATE STUDENT AWARD

All graduate student poster presenters attending RDD 2018 are eligible

RDDONLINE.COM

BILL WELCH, PHILLIPS-MEDISIZE

Bill Welch has over 25 years of contract design, development and manufacturing experience, primarily serving customers in the drug delivery, health technology and diagnostics markets. In his current capacity as Chief Technical Officer at Phillips-Medisize, he leads a global, over-500 person development, engineering, tooling, program management and validation organisation with more than 75 concurrent schemes. He has been with Phillips-Medisize since 2002.

In this interview, Mr Welch gives ONdrugDelivery Magazine an exclusive preview of Phillips-Medisize's forthcoming workshop, "Realizing the Benefits of Connected Health in Respiratory Drug Delivery", at RDD Europe, which takes place on April 25-28, 2017, in Nice (Antibes), France. In the context of recents major acquisitions by and indeed of Phillips-Medisize, he explains the company's strategy around connectivity and electronics in respiratory delivery systems and highlights the importance of a coherent value proposition when developing connected or electronics-enabled products.

Q We've seen several strong trends in the industry over the past view years – the emergence of biologics sparking the increase in interest in appropriate delivery systems, especially parenteral devices; an upswing in the attention being given to drug delivery systems as patient-centricity, personalisation and self-administration become increasingly important in healthcare; and of course we've seen the arrival of digital tech and connectivity. Interestingly, across all of these, Phillips-Medisize has been right there on it, or ahead of the curve. Could you tell us how, and describe what the journey so far has been like from Phillips-Medisize's point of view?

> "Adding sensors and Bluetooth or NFC is not the difficult part. The difficult part is creating an overall connected health strategy that is really going to improve the outcomes and thus pay for the expense of adding connectivity with the device. Our thinking on this is clear because it has evolved over time as we have come to understand the marketand what patients and physicians are thinking about."

A This has been a long journey for Phillips-Medsize. We first identified the trend for what we call "smaller and smarter" back in 2009-10 and we've had an evolution of our thought each year since then as the market has changed and the patient needs have changed as well.

So, when we talk about "smaller and smarter", smaller relates to the patient expectation of devices engineered to be compact and portable in order to allow discreet usage and improve adherence. To take a look back 14-15 years at a well-known example, the Exubera dry powder insulin device was considered large and bulky and definitely not discreet. The system failed to gain acceptance among patients and physicians and was discontinued after a short period on the market. Meanwhile, if we take a look at some of the new inhalation devices that are reaching the market today, those that are electromechanical in nature, they are getting down to the size of a deck of playing cards and that is similar to the size of the mechanical-only devices. So there are things in clinical trials today that are in that form factor. Being small in size does not guarantee clinical, regulatory and market success for the entire system, which of course includes the drug. However, getting the device down to the size of a mobile phone, which does have consumer acceptance, may translate into patient acceptance on healthcare devices.

Addressing the "smarter" aspect, there are different dimensions of this to talk about, based on the device and the use needs. The first dimension of "smarter" is the creation of more intuitive devices – not necessarily electronic, but intuitive – that will help decrease patient error while increasing adherence, and also the desirability of the therapy in order to gain patient engagement. The second dimension is to improve the device's primary intended function: more effective, targeted delivery of the drug and greater efficiency of delivery, such that less drug product is required to obtain the desired benefit. So this area provides cost savings that will support improvements in other parts of the system, such as the inclusion of electronics and software.

This leads to the third and fourth dimensions of "smarter". The third is the integration of electronics to improve functionality via a electromechanical delivery system. The big benefit of electromechanical systems, even not connected, is to be able to use sensors and software to time the delivery of a dose, rather than depending on a purely mechanical device with which, study after study show, there are adherence problems even with patients who make a sincere effort to follow the prescribed regimen. So there are inhalers in clinical trials today that use electromechanical systems, and measure the patient's tidal breathing, to potentially gain increased delivery effectiveness while protecting against device misuse.

Then, the final dimension of "smarter" is wireless connectivity that allows the

device to communicate – smart phone apps, cloud databases etc – to share information with both patient and caregivers to improve adherence.

Often, when people think "smarter" they often jump straight to the concept of a connected device whereas, in reality, that's one of what we consider to be four dimensions of a smarter device. It's important to emphasise that simply adding connectivity to a device is not the solution. Success comes through making it about the entire system and considering outcomes, and not just putting Bluetooth or near field communications (NFC) in.

Adding sensors and Bluetooth or NFC is not the difficult part. The difficult part is creating an overall connected health strategy that is really going to improve the outcomes and thus pay for the expense of adding connectivity with the device. Our thinking on this is clear because it has evolved over time as we have come to understand the market and what patients and physicians are thinking about.

What we know is that whether it's an electronics-enabled device or a connected device, there is cost being added *versus* a mechanical-only device, so the question becomes: what is your value proposition to improve the overall therapy, reduce healthcare costs to offset that investment needed in the electronics and software?

Q The company has gone through some major acquisitions over the past year. The two most prominent were first that Phillips-Medisize acquired Medicom Nordic, and then it was acquired itself by Molex. Tell us what these acquisitions mean for the business.

A We've actually had a third acquisition in the past year, which was the acquisition of Injectronics in the North East United States. All of these acquisitions really fit with our strategy around electronics-enabled and connected healthcare.

So starting with Injectronics, that acquisition was really aimed at getting us a location that was close to the biopharma hub of the North East US, and being able to localise our services there.

The acquisition of Medicom on June 1, 2016, was of course highly strategic for us. Two key aspects of this were particularly exciting. Firstly, the offering of a device strategy service to our customers, which relates directly to what we were talking about earlier as one of the big barriers: exactly how are you going to position your device, create the value proposition and reduce overall cost of care in order to fund an electromechanical, connected device? So the Medicom offering positions us very well on the front end, working with the drug owner / biopharma company on a device strategy that will help make a connected solution successful. The second thing, which was equally important, was that in Medicom we acquired a low-volume orphan drug delivery device capability in Denmark, so traditionally Phillips-Medisize has done things globally at volumes of hundreds of thousands at the low end up to tens of millions. Now with Medicom, we've got a great capability to do connected device manufacturing for devices that may require just tens of thousands of units per year. That smaller-volume capability is equally important in serving the broad spectrum of the market.

> "Traditionally Phillips-Medisize has done things globally at volumes of hundreds of thousands at the low end up to tens of millions. Now with Medicom, we've got a great capability to do connected device manufacturing for devices that may require just tens of thousands of units per year."

Molex on the other hand, as a new owner, provides us with global capabilities in electronics manufacturing. Therefore, when we get into production and begin setting up a supply chain, we've got the ability to be vertically integrated in that supply chain. The reason that's important is many of our customers have viewed that ability not only just to engineer and supply-chain-manage as critical, but also to be able to do the manufacturing of the PCBAs [printed circuit board assemblies] and related components as critical too.

So with Medicom we cover the extreme front end of our device strategy, and with Molex we've got the supply chain elements covered. The great news here is that we've got several case studies where we have been able, with the combined Phillips-Medisize and Molex solution, to go back to our customers with new vertically integrated solutions that collapse the supply chain and in some cases reduce the cost of the device *versus* our prior solutions, which were very intensive on an outside supply chain.

Q We touched on the arrival of connected health earlier and this is without doubt one of the most fundamental shifts I've experienced since I began observing the drug delivery sector nearly two decades ago. We'll go on to talk in more detail about your forthcoming RDD Europe Workshop which focuses on Connected Health in Respiratory Drug Delivery but, leading into that, I wondered if you could talk generally about connectivity and the impact the arrival of this technology is having on the world, on healthcare, on pharma and in drug delivery systems?

A In terms of the general impact connected health technology is having on the world, this becomes yet another way of connecting people not only to their healthcare providers but also to others in the community who may be managing the same disease, and therefore being able to create networks where people are not finding themselves alone in the problems that they are facing. So that's some of the soft side benefits of connected devices.

Beyond that we have seen good applications of connectivity technology, obviously with their different challenges with sensors and communication, but we've seen applications in inhalation devices, injectors and indeed across the whole range of drug delivery devices.

The biggest common need, regardless of the type of delivery device, is to come up with a strategy that in the end results in the connected ecosystem. When we start to pursue that strategy, then gathering that data and managing that data becomes crucially important for the success of the therapy. And it is not one size fits all for different therapies, different delivery systems and different indications.

You can start with the basics of what dose was delivered and when. But when you start to conduct in depth strategy work to determine what you need for effective therapy, then you begin to bring in other data that are important to patient care. You can gather and consolidate it with the basic dose and time data and then you can start to do analyses and correlations that were impossible before. Now you gain the

> "This will be an interactive discussion in small groups that is intended to engage people to think about the challenges and, from many different viewpoints, how you go about addressing them. It won't simply be an hour-long presentation with a Q&A at the end."

ability to use true information to develop personalised solutions for individual patients.

Q What are the major regulatory barriers that need to be overcome in order for connected drug delivery system development to progress?

A There are unique requirements in each region and even at the country level that need to be considered when building a connected health system.

As part of our device strategy and development process, we work with our clients to understand which markets will be targeted for the entire connected ecosystem, and ensure we have the right expertise on the joint team to address the requirements in parallel with the device development process. This includes technical requirements (infrastructure being scalable and durable, etc) and ongoing support for selected OS platforms (Android, iOS, Windows, etc).

Q Focusing now on your forthcoming Connected Health in Respiratory Drug Delivery workshop at RDD, as mentioned previously, Phillips-Medisize has been right on the money in identifying digital tech and connectivity as a major area of growth and has already built considerable expertise and know-how. What are the main points you are going to cover in the workshop? What value can those attending the workshop expect to derive?

A In our workshop we are going to be able to start by giving an extremely well informed view of the landscape, describing where things are in the development of connected inhalation devices. From there, we will have three different smaller breakout sessions, and we'll have each of the groups look at some of the challenges in implementation and some of those barriers. We'll be able to draw parallels and start to formulate solutions.

So we'll be able to say, here's the landscape that we have today, here are some of the challenges that we have for the implementation of connected health, how do we go about solving some of those strategies. We'll be able to hear points-of-view from the broad spectrum of attendees at the conference from industry and academia.

In terms of the value those attending the workshop can expect to gain, first, attendees will gain a very concise update as to the current state of the industry as it relates to connected healthcare as well as electronics-enabled healthcare. Secondly, they will be able to get into a very healthy small group discussion on specific issues and how to go about addressing them. So it won't simply be an hour-long presentation with a Q&A at the end. This will be an interactive discussion in small groups that is intended to engage people to think about the challenges and, from many different viewpoints, how you go about addressing them.

> "To boil it down into a simple statement, it is about the industry going from selling a drug, to delivering improved outcomes. Once you start from there, then things begin to flow logically."

RDD is a very interesting conference due to the global nature of the attendees. Going back to the earlier points we discussed about regulatory considerations, each geographic market has its own laws and regulations that have to be met in order to release a product where you're collecting personal data. So it will be interesting to see how these different regulatory environments translate into different approaches, from people who work in those different geographic regions, to overcoming some of the barriers.

Q The point about developing a coherent value proposition seems to be central and links the various other aspects. Perhaps you could expand on this a little more?

A To boil it down into a simple statement, it is about the industry going from selling a drug, to delivering improved outcomes. Once you start from there, then things begin to flow logically. Improved outcomes will be achieved how? By superior devices, improved patient engagement, and getting better therapeutic results. Once you reach that stage, now you are able to start monetising what is the value of that improvement with each new connected device, and that becomes your value proposition as to how you will pay for such a device.

Q To conclude, I wonder if you could tell us what the plans are for the short/medium term and also, more broadly and in light of the current trends in the industry, what the longer-term future holds for the company?

A We continue to be very focused on providing complete solutions to our biopharmaceutical, diagnostics and medical technology customers. With the acquisition by Molex, we add global scale in electronics to our existing capability set. Customer response has already been extremely positive, and we will continue to focus bringing connected health solutions to market for our customers.

Mr Bill Welch
Chief Technical Officer
T: +1 715 386 43203
E: bill.welch@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

Phillips Medisize

a molex company

Harmonised Drug Delivery Device roadmap for efficiency, compliance and speed to market

The use of electronic functional components is becoming a new crucial prerequisite to facilitate the patients' drug administration, to ensure precise dosing quantity and timing, and predominantly to raise drug delivery to higher safety standards. The rise in complexity of a drug delivery device results in exponential growth of important factors which have to be considered when following the individual steps of the entire value-creation chain. Pharma companies need to look for partners who can help turn an idea into a successful complex drug delivery device, as well as coverage of a value proposition and a strategic platform. Further to provide turn-key manufacturing solutions for customers developing electro-mechanical drug delivery systems, correspondingly covering the regulatory requirements which have to be met e.g. for a connected health device, its validation procedures and particular constraints imposed by the responsible authorities in the countries concerned.

During RDD Europe, Phillips-Medisize will discuss in it´s workhop about Realising the Benefits of Connected Health in Respiratory Drug Delivery.
Bill Welch, CTO Phillips-Medisize, Kevin Deane, Executive VP, Front-End Innovation and Bjorn Andersen, Director Front-End Innovation (both Medicom Innovation Partner) will discuss the importance of developping a connected health solution and device strategy to assure future success of connected health tools to improve outcomes for patients and reduce the total cost of care in the respiratory field. Initially the presenters will review how to develop a connected health solution from the perspective of understanding the market and patient needs in line with technical, regulatory and commercial conditions, inclusive of a robust device strategy.

This workshop will also investigate data related aspects, such as:

- what data will be gathered
- by what data platform / interface, will it be shared and with whom?

In addition, connected device development issues such as hardware and software, data management and security as well as manufacturing and regulatory pathways will be addressed.

Outcome for Participants:
The goal is for attendees to obtain an overall understanding of the key elements and challenges that go into successfully developing and realising the benefits of a connected health solution in the respiratory drug delivery arena.

Register for the RDD workshop and visit our table top

H&T PRESSPART

DOSE COUNTERS AND INDICATORS – MEETING A REAL PATIENT NEED

Providing methods for predicting the end of life of pressurised metered dose inhalers (pMDIs) and incorporating mobile Health (mHealth) technology would improve patient safety considerably. Inga Meyer, Global Business Development Manager, and Kyle Wilson, Technical Applications Engineer, from H&T Presspart, explain how their dose counter-enabled inhaler development work has led to the production of a system that accurately indicates the end of life of a device.

Asthma and chronic obstructive pulmonary disease (COPD) are chronic lung disorders responsible for millions of deaths every year. Both diseases are characterised by variable and recurring symptoms and when poorly controlled, can result in severe limitations in quality of life of patients. Controlling and monitoring treatments therefore is not only meeting a real need to reduce healthcare costs related to hospitalisations but a real patient need.

> "The majority of marketed MDIs offer no practical way for patients or doctors to know how many doses are left in their inhaler, specifically in case of emergency."

Patient expectations are for a reliable system to support their correct and timely use of inhalers, without changing the way of using them or adding any steps to their routine: devices need to be intuitive and non-destructive, without much additional weight or change in shape.

Furthermore, in addition to a safety system to help patients know about the filling status of their drug, they would like help with adherence and compliance. The majority of marketed metered dose inhalers (MDIs) offer no practical way for patients or doctors to know how many doses are left in their inhaler, specifically in case of emergency. Furthermore, there is a collective requirement to track adherence or compliance to medication.

To address these requirements, the US FDA published guidance on integration of dose-counting mechanisms into MDI drug products. Under this guidance, devices should offer either clear numeric counting mechanisms or indication functions with colour coding or other means, so patients have clear and unmistakable information on the amount of drug left in their devices.[1,2] The guidance also encourages drug manufacturers to update existing devices, if possible.

Pharmaceutical companies worldwide are working on integrating dose-counting or -indicating mechanisms into their pMDI to both address the patient need and differentiate their products in an increasingly competitive pMDI market space. Available solutions include mechanical and on-can dose counter and indicator systems, and an ever-increasing offering of connected counting and health management solutions.

H&T Presspart has a portfolio of counting and indicating solutions to address the variety of customer and market requirements and is actively supporting a number of global dose counter and indicator programmes for pharmaceutical clients in all types of counting projects (Figure 1).

Inga Meyer
Global Business Development Manager
E: Inga.Meyer@presspart.com

Kyle Wilson
Technical Applications Engineer
E: kyle.wilson@presspart.com

H&T Presspart
Presspart Manufacturing Ltd
Whitebirk Industrial Estate
Blackburn, Lancashire
BB1 5RF
United Kingdom

www.presspart.com

Figure 1: H&T Presspart's end of life indication product portfolio.

INCREASED SAFETY, CONVENIENCE & DIFFERENTIATION

To address the transition towards indication of end of life of the device, H&T Presspart offers a mechanical dose-counting system, a licensed product design from 3M, which is suitable for any generic or new chemical entity (NCE) development and designed to be compatible with all marketed pMDI valves. It is supported by a variety of actuator styles and geometries meeting the performance and regulatory targets for any given formulation.

The dose counter technology was the first integrated dose counter available for third party developments and first to be approved by the FDA in conjunction with a pMDI product.

Development Process

Central to the development process is an understanding of the final design requirements. Such requirements are dictated in part by the specific components and formulation selected as well as any local regulatory requirements, performance requirements of the final package e.g. aerodynamic particle size distribution (APSD) and spray pattern plume geometry (SPPG) or additional customer-specific requests for the product.

Also integral to any component manufactured by H&T Presspart is the quality-by-design promise to avoid undercounting, which is accomplished by understanding the requirements such as general formulation characteristics and preferred component selection.

The remainder of the development process consists of three key activities:

- Valve characterisation
- Actuator customisation (including colour and geometry selection)
- Robustness testing.

Valve characterisation starts with an assessment of the customer-selected valve on crimped and filled canisters. The data generated in this characterisation is used to confirm, or modify as necessary, the overall design in order to avoid undercounting.

Next, the final actuator is ready to be customised. Most important is perhaps the geometry selection process, especially when addressing generics programmes where APSD and SPPG measurements must match the originator. In these cases, factors such as the components selected or measuring equipment may have an impact, for which the geometry selection process can compensate, ultimately ensuring the performance requirements are fulfilled. In parallel, any other preferences are addressed such as colour selection for the body and dust cap as well as any embossing or other customisations desired.

Finally, the product is put through robustness testing. Such testing ensures the full package will withstand the rigour of regular patient use, proving that the design goals were fulfilled. Testing includes, but is not limited to, verification of through-life counting and drop testing and is performed on the full final assembly. The data generated from these activities will then be summarised for submission purposes.

FLUTICASONE – A CASE STUDY OF DEVICE DEVELOPMENT

H&T Presspart has gained invaluable experience in the process of dose counter-enabled inhaler product development and brings this experience to the table with each new development program. Whether through the activities mentioned above or further activities on offer through our Inhalation Product Technology Center (IPTC) Laboratory, we are prepared to support any pMDI program. This is particularly important in the case of generics programs for the US market (Figure 2).

The complexity involved in preparing a generic for the US market is perhaps best illustrated by examining a representative scenario – the development of a generic fluticasone propionate product with an integrated dose counter. Filing into the US will require *in vitro*, PK and PD equivalence. *In vitro* equivalence can, in turn, be broken

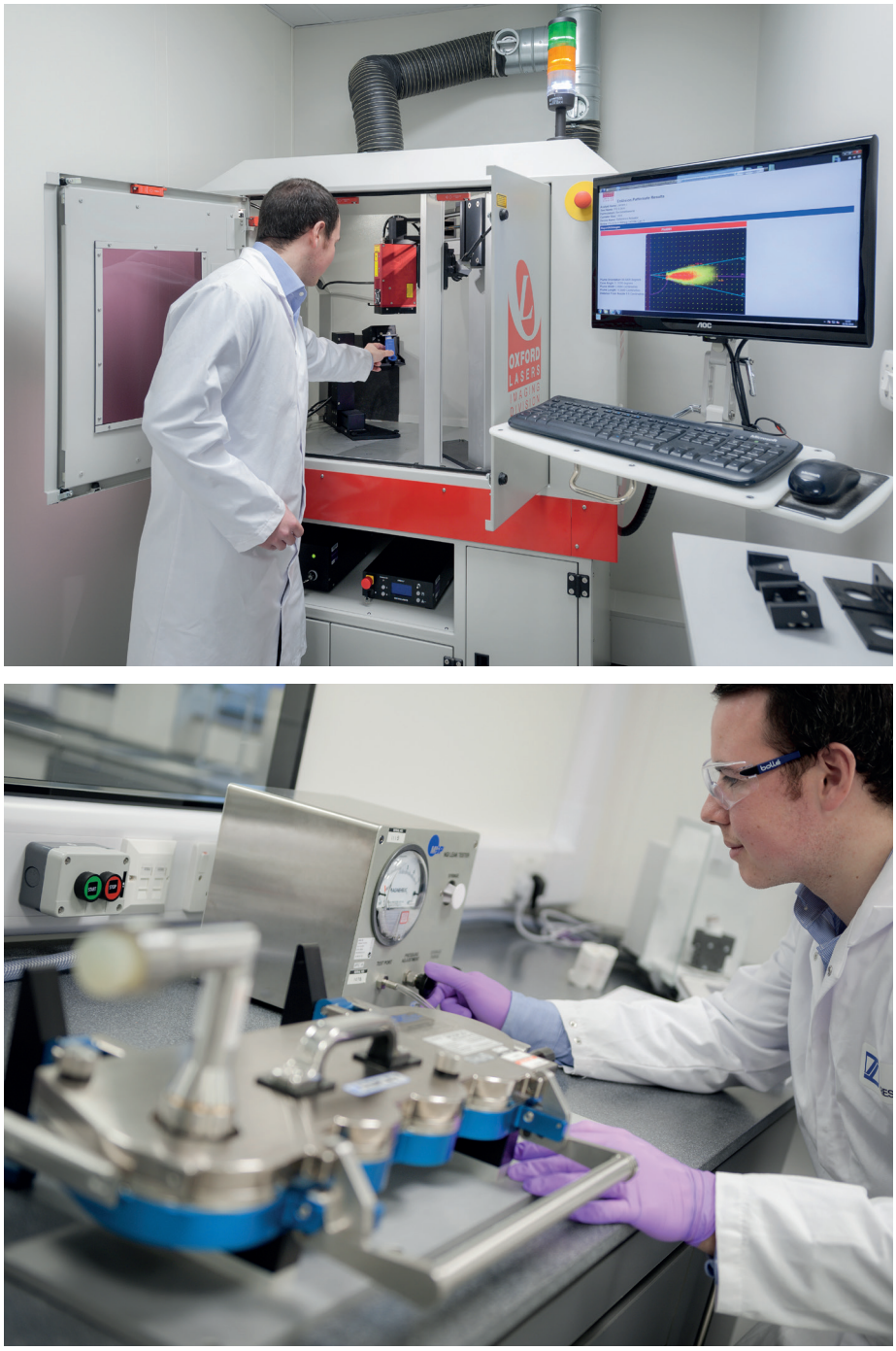


Figure 2: H&T Presspart's Inhalation Product Technology Centre (IPTC) laboratory in the UK.

down into APSD, SPPG, and delivered dose uniformity parameters, all of which must be equivalent for success.

Finalising Dimensions & Target Specifications

The first steps involve finalising the dimensions required as a starting point as well as populating the data for the Reference Listed Drug (RLD) products to establish target specifications. Sourced fluticasone propionate RLD is tomography scanned for overall dimensions as well as critical internal dimensions such as orifice diameter, jet length and sump volume and to establish target specifications via measurements on cascade impactors and laser imaging. In parallel, measurements are taken on placebo canisters with the selected valve as a part of a valve compatibility study. The customer-specific product is developed using the RLD geometries as a starting point.

Design of Experiments

To account for the influence of any differences introduced by the specific parts and formulation selected and developed by the customer, a design of experiments (DoE) is established. This DoE focuses on key dimensions of interest as agreed between H&T Presspart and the customer and also utilises the rapid prototyping and testing capabilities available at IPTC. In this case, two actuators passing the initial screening are finalised and analysed by the customer for confirmation of best fit.

Robustness Testing

In parallel, all other actuator development activities are progressed to ensure colours and other design criteria are met. The design frozen product is run through robustness testing to ensure the final product is consistent with design expectation, namely a design that avoids undercounts, and is ready for filing to the FDA. All necessary data and documentation support is provided by H&T Presspart.

The process outlined above has progressed in a manner that ensures that the final design is robust, will count as expected, and is optimised in terms of *in vitro* performance characteristics. Further, use of a DoE to establish and test the design space has helped avoid costly and time-consuming sequential iterations. The final product is ready for filing with full confidence by means of supporting data.

H&T Presspart mechanical dose counters and indicators are available for generic and NCE formulations and our programmes support pharmaceutical customers from early stage development through scale-up, market launch and high volume commercial supply.

DEVELOPMENT OF QUANTUM

Pharma companies in less regulated markets are looking at ways to differentiate their offer and improve treatment outcomes without adding prohibitive cost to the package. To address those needs, H&T Presspart has developed the first on-can, cost-effective, off-the-shelf dose indication system marketed as Quantum™.[3,4] It provides patients with a simple but intuitive way to indicate that the pMDI canister is coming to its end of life and provides added convenience for patients such as treatment monitoring and compliance management via an optional mobile phone application.

How Quantum Works

The patient has to simply remove the can from its actuator, roll it on a flat surface and read an indicator arrow on the bottom of the can. Thanks to the on-can integrated bias weight, the canister will balance and indicate the remaining drug left in the

can. Compared with other dose indication systems, there is no change to the actuator required and no additional part in the flow path of the device.

Another key advantage is that Quantum always reads what is left in the can even if there is a slowly leaking can, for example. Through rigorous analytical and robustness studies in our labs, a dose-to-arrow angle profile has been developed that provides the basis for reliable feedback to the patient about the remaining fill level in the can and when the pMDI needs to be replaced (Figure 3).

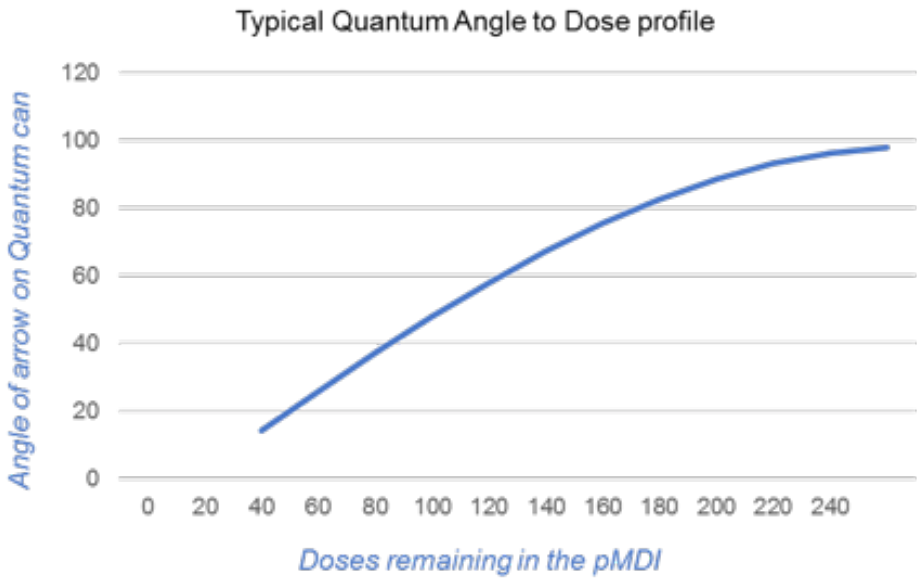


Figure 3: Typical profile dose/angle profile for a 200 dose pMDI.

User Study

To understand usage of pMDIs by nurses and asthma and COPD patients further as well as how Quantum can improve inhaler experience and patient safety, H&T Presspart conducted a user study with a group of 50 participants. In particular, the group was asked how they currently estimate the fill volume of their pMDI can.

Results showed that more than half of respondents simply shake the can to determine if it is empty. The study also showed that patients consistently used pMDIs until no more "puffs" occurred, which could lead to dangerous, potentially life-threatening situations in the event the pMDI turns out to be empty during exacerbations. And this fear was confirmed by the respondents as more than two thirds of patients said they were concerned with their current method.

During the study, participants were asked to estimate the current fill level of a pMDI can by shaking the can to estimate the can fill and alternatively using Quantum to evaluate the fill level. The response given was coded as a "success", a "safe failure" or an "unsafe failure". An unsafe failure occurs when the can is actually empty and the patient believes it is still safe to use or near empty.

Not surprisingly, the study demonstrated a high unsafe failure rate, confirming the unreliability of determining the remaining fill by simply shaking the can. The high unsafe failure rate dropped significantly when the respondents used the Quantum dose indicator to make the decision about the fill level of the can. We could also demonstrate that there was potential for a further decrease of unsafe failures when Quantum was used several times supporting the effectiveness of the system after some initial training compared with simple shaking. Over 80% of participants found Quantum easy and effective to use.

Mobile Connectivity

To enhance asthma and COPD treatment management and patient compliance, Quantum has the option to connect to a mobile phone app which provides instant feedback to the patient on the medication left inside the canister.

The mobile phone app also incorporates adherence and usage-tracking features, reports, dose reminders for multiple medications, prescription re-order reminders, interactive training videos, patient information leaflets and the opportunity to integrate a variety of push notifications to patients. The app can be connected to cloud services to provide pharmaceutical companies, doctors and other stakeholders access to patient and medication data in real time to improve treatment outcomes and optimise the supply chain (Figure 4).

Quantum is applicable to all pMDI products independent of the number of doses. It can be used with all marketed valves and standard actuators and is easily implemented to a pMDI with no additional development time.

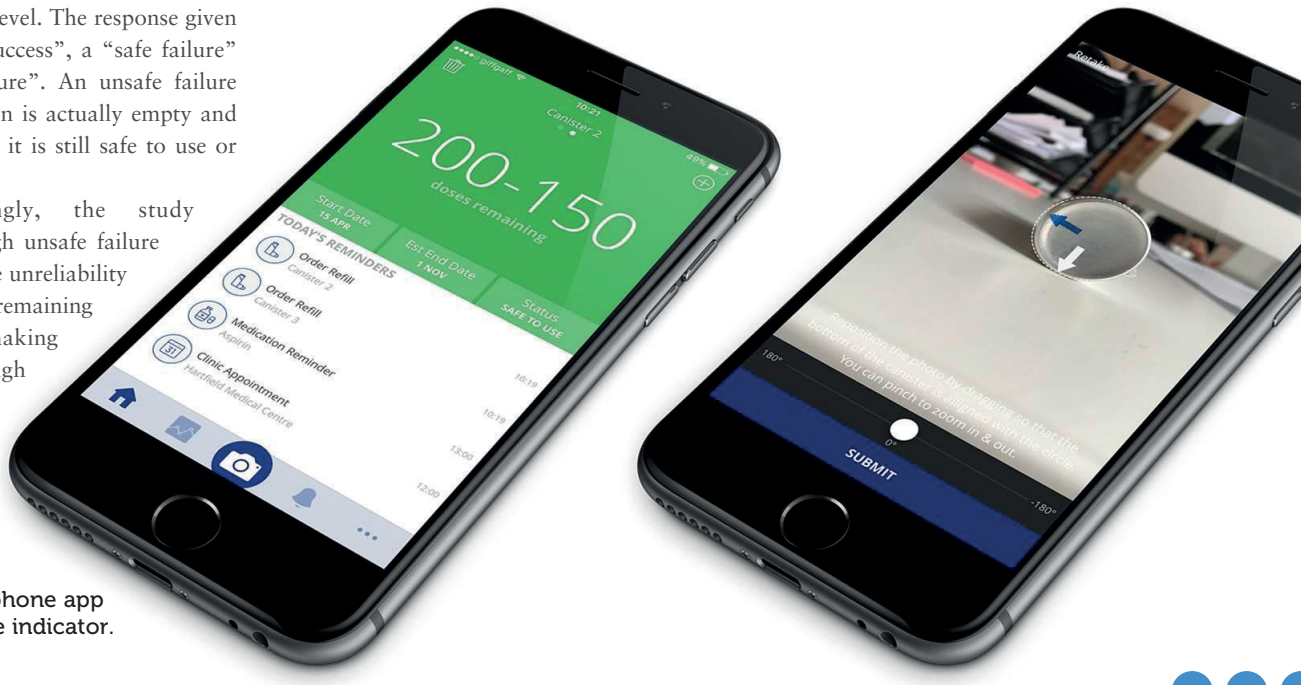


Figure 4: Mobile phone app for Quantum dose indicator.

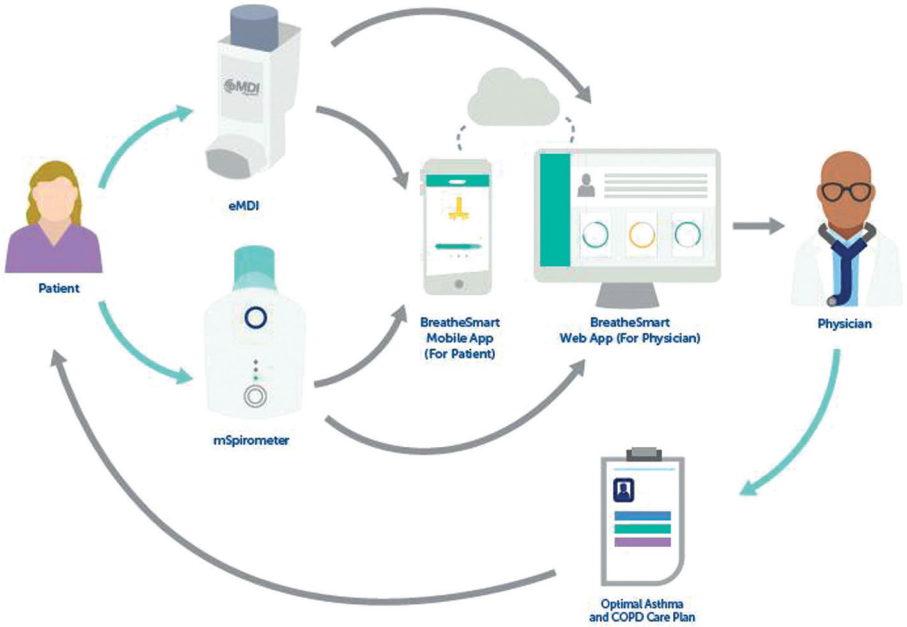


Figure 5: Integration of the eMDI with BreatheSmart in treatment management.

CONNECTED DOSE COUNTING & MHEALTH SOLUTIONS

The increasing development of mobile health solutions on the market[5] has developed one area of focus on solutions for patients with asthma and COPD.[6,7] Over the years, a number of embedded and non-embedded solutions for pMDIs have been presented and/or officially launched to market, many of which have a history of use in clinical environments.

Developments of fully embedded solutions are designed to meet, firstly, the requirements of patients, but also address needs of physicians, health institutions, pharmaceutical companies and payers.

In 2013, H&T Presspart embarked on a strategic development programme focused on real-time pMDI patient data capture and transmission in order to address the requirement of patients and other key stakeholders within the healthcare sector. In 2015, H&T Presspart initiated collaboration with Cohero Health, a digital health company, to bring innovative device and software tools and technologies to improve respiratory care, reduce avoidable costs and optimise medication utilisation.

In December 2016, H&T Presspart and Cohero Health launched the first market-ready, intuitive, fully embedded and connected metered dose inhaler, eMDI™ aimed at improving adherence and enabling continually optimised care of patients with asthma and COPD. The eMDI strongly builds on the existing design of pMDIs, to facilitate intuitive patient operation and ease of manufacturing.

One design option incorporates an FDA-approved mechanical dose counter which allows for quick integration into existing marketed drugs and supports a fast-track approval process for highly regulated markets. The eMDI is the only embedded device solution which integrates seamlessly with BreatheSmart from Cohero Health, a comprehensive respiratory disease management platform that uniquely enables tracking of both controller and rescue medications, along with clinically accurate lung function measurement, in real time (Figure 5).

By tracking, recording and sharing data on the use of both preventer (controller) and reliever (rescue) medications, the eMDI engages and empowers patients in their self-care, leading to improved adherence, while enabling real-time monitoring of medication use and symptom flare-ups by caregivers and the healthcare community. Medication utilisation data from the eMDI can be merged in real-time with lung function data from Cohero Health's mSpirometer – a clinical grade handheld wireless spirometer that precisely measures critical lung function metrics. This allows, for the first time, for the effects of preventer and rescue medication use on lung function to be tracked and analysed.

H&T Presspart is actively working with pharmaceutical companies to make the eMDI available to patient populations for daily treatment management in the near future.

CONCLUSION

With a number of different solutions on the shelf at H&T Presspart and strong background in running programs for drug approval and large volume industrialisation, it is now in the hands of pharmaceutical manufacturers to pick the best solution for their product/market requirement and offer patients additional support in drug adherence and compliance.

REFERENCES AND NOTES

1. *FDA, Guidance for Industry, "Integration of Dose-Counting Mechanisms into MDI Drug Products", 2003, p 1.*
2. *FDA, Jurisdictional Update, "Metered Dose Inhalers, Spacers and Other Accessories, 2016*
3. *Technology is licensed from Trig 1*
4. *Quantum logo is a registered trademark of Presspart Manufacturing Limited*
5. *Monroe N,"Connected Combination Products: Past, Present & Future", ONdrugDelivery, 68 pp 5.*
6. *Asthma UK, "Real-world implementation of connected devices in the UK to reduce asthma attacks", pp 4*
7. *Fortune.com, "Inhaler Makers Want to Watch Every Breath You Take", July 20, 2016.*

ABOUT H&T PRESSPART

H&T Presspart offers pharmaceutical customers high-precision injection moulded plastic components and deep drawn metal cans for respiratory drug delivery systems, with more than 40 years' experience and a worldwide reputation for competence, quality and innovation in pharmaceutical and industrial sectors. H&T Presspart's Inhalation Product Technology Centre (IPTC) supports new product developments and strategic initiatives with its customers. Founded in 1970 and acquired by the Heitkamp and Thumann group in 2002, H&T Presspart has three European manufacturing sites in Germany, Spain and the UK, with Sales offices in China, India, South America and the US.

DDL2017

DRUG DELIVERY TO THE LUNGS

6/7/8 December 2017

Edinburgh International Conference Centre

Edinburgh, Scotland, UK

The Drug Delivery to the Lungs Conference (DDL) is Europe's premier conference and industry exhibition which is dedicated to pulmonary and nasal drug delivery.

The focus is on providing a forum to present through podium and poster presentations recent developments in the field of inhalation therapy.

700+Delegates / Annual DDL Award Lecture / 90+Industry Exhibitors

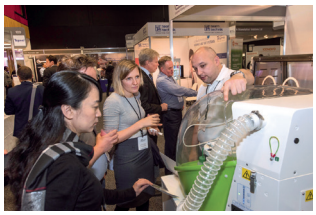
Networking Receptions / Emerging Scientist Award / Poster Prizes

Submissions for podium and poster presentations are now invited from the UK and internationally:

Areas of particular interest for DDL2017 include:

- **Inhaled Therapy in Special Populations**
  Delivery of aerosol medicines to patients at the extremes of life (neonates, paediatrics, the elderly), patients with poor capacity to use inhalers, concomitant diseases, ventilated patients, etc.
- **Emerging Therapeutics and Novel Respiratory Medicines**
  New and repurposed drugs, novel formulations and drug combinations, generic inhalers and innovative inhaled treatments based on advances in clinical science and respiratory medicine.
- **Inhalation Devices and Aerosol Science**
  Novel inhaler technology, new devices and performance enhancements. New or novel methods for aerosol generation, measurement and characterisation.
- **Modelling and Simulations in Inhalation Science**
  The application of in silico methods to any aspects of inhaled drug development, including discovery and lead compound optimisation, molecular and particulate interactions, aerosol dynamics, lung deposition and pharmacokinetics.



Visit www.ddl-conference.com to submit your abstract - Deadline 28.07.2017

Contact the team: sheila@ddl-conference.com / nikki@ddl-conference.com

+44 (0)1275 849019 / www.ddl-conference.com

TECHNOLOGY SHOWCASE: BIOCORP'S INSPAIR™

Figure 1: Inspair™ sensing technology for inhalers.

AN INTEGRATED SOLUTION TO DIGITALISE INHALED THERAPIES

Airflow – caused by lung ventilation – has a critical impact on inhaled particle deposition. Thus, it seems evident that successful dose delivery requires a complex combination of mechanical conditions involving optimal airflows.

This is the reason why Biocorp has developed Inspair™, a sensing technology able to measure inhalation metrics and therefore provide an accurate insight into actual doses consumed. When it comes to obstructive lung disease, this information provides significant benefits both to end users and healthcare professionals.

Any pressurised metered dose inhaler (pMDI) can be enhanced with Inspair's smart sensor (Figure 1) and thus take advantage of this highly effective digital health platform.

READY TO BE QUICKLY ADAPTED TO EXISTING INHALERS

Inspair is a smart sensor that can be attached to pMDIs to track every inhalation. The sensing device has been designed to be very compact with three separate pieces: the sensor part, the plastic mouthpiece and the cap.

Without changing the recommended use of inhalers, Inspair smart sensor is a user-friendly device compatible with a wide range of pMDI. Inspair's modular design ensures a perfect fit with very different mouthpiece shapes: the removable sensing part remains unchanged and only the plastic mouthpiece requires customisation. Thus, Inspair technology can be easily adapted to a large range of inhalers – reducing significantly the time to market.

NEW POSSIBILITIES FOR ASTHMA/COPD CARE

The Inspair inhalation tracking system provides unique insights into inhaled therapy and supports patients, enhancing respiratory disease self-management. It brings numerous advantages, including:

- Better breath-hand co-ordination. Lack of co-ordination is a significant problem among pMDI users and affects the actual dose delivered.

Mr Jean Vuillecard
Product Innovation Manager
T: +33 688 697 285
E: jvuillecard@biocorp.fr

Mr Eric Dessertenne
Head of Business Development
T: +33 608 021 451
E: edessertenne@biocorp.fr

Biocorp
Parc Technologique
Lavaur-La-Bèchade
63500 Issoire
France

www.biocorpsys.com

- Measurement of inhalation depth and speed. This is a major concern for patients with highly constricted airways, so inhalation metrics bring precious support, improving medical decision-making.
- Measurement of inhaled dose. This critical information is needed to improve treatment compliance.

"Treatment data is accessible through Biocorp's proprietary platform. This cloud storage solution offers a very high level of protection. Health data and personal data are stored on separate servers. Only a cryptographic pseudonymisation system can associate health data with a personal ID."

The Inspair tracking system allows patients to access feedback and advice on inhalation technique.

Indeed, using inhalers requires end users to follow complex handling instructions with several operations to be performed in a specific sequence. Inspair can be used as an education tool helping patients improve their inhalation technique, improving therapeutic outcomes and saving time for healthcare professionals.

Treatment data collected in between medical visits is critical for assessing the persistence of and compliance with an inhaled therapy. Hence, Inspair is a valuable solution supporting physicians in the management and monitoring of large patient populations – directly from their mobile phone.

Treatment data is automatically stored in an exhaustive treatment history allowing pharma companies and CROs to streamline clinical trials to achieve more cost-effective clinical development.

CONNECTIVITY & WIRELESS TRANSFER SECURED BY DESIGN

Health data are protected from the collection point – Inspair smart sensor – to the storage platform (Figure 2). Data are encrypted in the sensing device and thereafter transferred – via Bluetooth Low Energy (LE) – to a mobile phone pushing data to a secured platform. For security reasons and for enabling multi-device use, no data is stored on the mobile phone.

Treatment data is accessible through Biocorp's proprietary platform. This cloud storage solution offers a very high level of protection. Health data and personal data are stored on separate servers. Only a cryptographic pseudonymisation system can associate health data with a personal ID.

Biocorp's online proprietary platform is compliant with European data protection law and is certified HDS (the French certification for health data storage, compliant with L'Agence Francais de la Santé Numérique (ASIP) guidelines). Finally, a strong authentication system secures end-users access to health data.

OPTIMISING TREATMENT PERSISTENCE & COMPLIANCE

The main end user interface is a customisable mobile app (iOS/Android) and web-platforms can be designed to let healthcare professionals access their patients' data.

Inspair transforms a smartphone into companion software allowing the patient to provide complementary information like daily symptoms or trigger factors. Reminders and alerts features keep patients and their caregivers informed throughout the treatment period. Coaching services can be added to help patients better manage their condition and motivate them to continue their efforts.

"Inspair technology is more than a smart cap for counting doses. Inspair is an integrated health solution that digitalises inhaled therapies through an open sensing device collecting unique drug delivery metrics and a secured platform protecting patients' health data."

CONCLUSION

Inspair technology is more than a smart cap for counting doses. Inspair is an integrated health solution that digitalises inhaled therapies through an open sensing device collecting unique drug delivery metrics and a secured platform protecting patients' health data. Inspair enables personalised care and actively engages patients and their caregivers with their long-term treatment requiring daily effort and motivation.

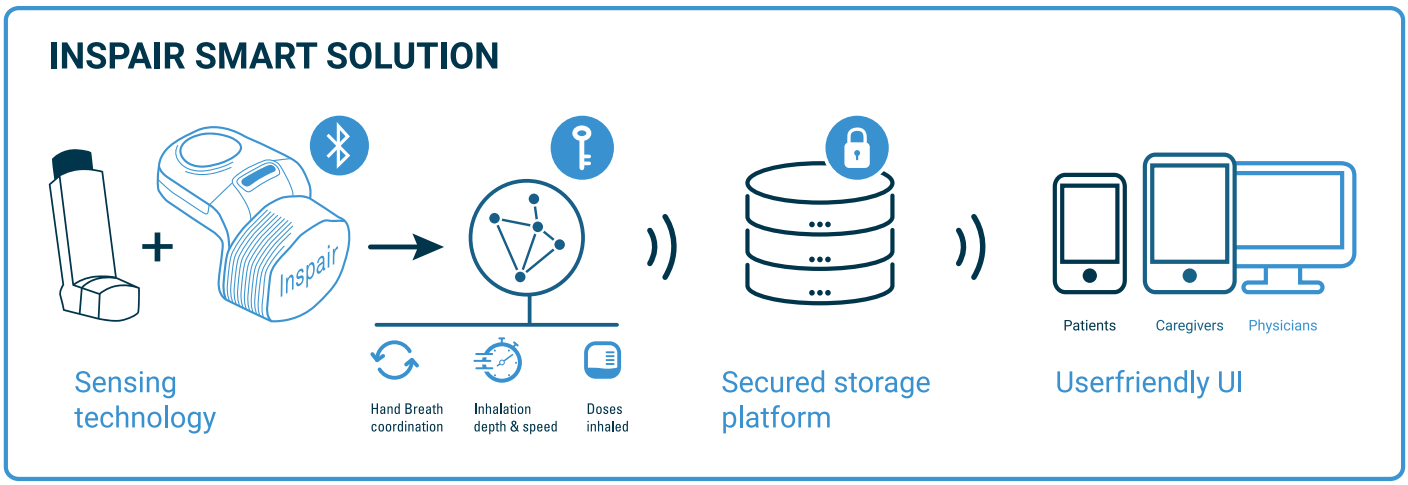


Figure 2: Inspair™ – a smart solution ensuring high data protection standards.

TRAINING DEVICE OPPORTUNITIES AND SOLUTIONS FOR A CHANGING RESPIRATORY MARKET

Building on his previous articles in ONdrugDelivery on training devices and drug delivery device education, here, Joe Reynolds, Research Manager at Noble, outlines the increasing range of options available for helping patients learn how to use their devices correctly and maximise the effectiveness of their treatments.

Pulmonary drug delivery is one of the most common routes of administration for chronic and acute conditions, such as chronic obstructive pulmonary disease (COPD) and severe asthma. As with any device-delivered therapy, the successful use of pulmonary delivery systems depends on a number of intrinsic and extrinsic variables, including the properties of the lung, breathing patterns and delivery techniques.

To realise the full therapeutic benefits of these treatments, patients must first understand how to use their drug delivery devices properly to administer the correct nominal dosage. According to the US National Institutes of Health (NIH), a nominal dose is defined as "the total prescribed dose" of an inhalable therapeutic. When commonly observed, actual deposition rates (amount of medicament effectively reaching the lung) range from 6-60% of the nominal dose. Such incomplete doses can pose safety risks to patients and reduce the overall efficacy of treatments.

IMPROVING PATIENTS' USE OF DELIVERY DEVICES

To understand how to improve patient performance and outcomes, it is important first to understand common treatment barriers and the process patients go through when learning how to use delivery devices.

By definition, autonomous patients are those able to administer a prescribed dose free of error consistently and effectively. In order to reach this level of autonomy, patients progress through a number of learning stage where motor and muscle skills are acquired and confidence is built.

> "Errors experienced during the onboarding process, or the first 30–90 days of treatment, are frequent in nature but can often be avoided through proper education and training."

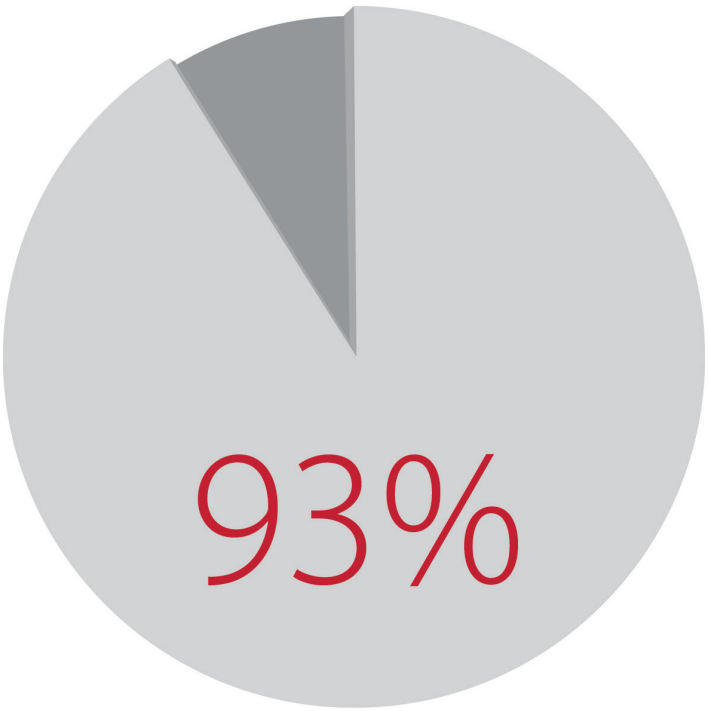
The early stages of this learning process, known as onboarding, is characterised by highly variable outcomes due to patient errors and improper administration techniques. Errors experienced during the onboarding process, or the first 30–90 days of treatment, are frequent in nature but can often be avoided through proper education and training.

Without proper training and support during onboarding, many studies suggest that patients are more likely to incorrectly use delivery systems or discontinue therapy. According to a recent study conducted by the University of Texas Medical Branch in Galveston, 93% of patients who use an inhaler failed to follow proper administration techniques. In addition, only 7% of users demonstrated perfect technique and 63% failed to complete three or more steps correctly (Figures 1 and 2).[1]

Mr Joe Reynolds
Research Manager
T: +1 888 933 5646 Ext. 147
E: jreynolds@gonoble.com

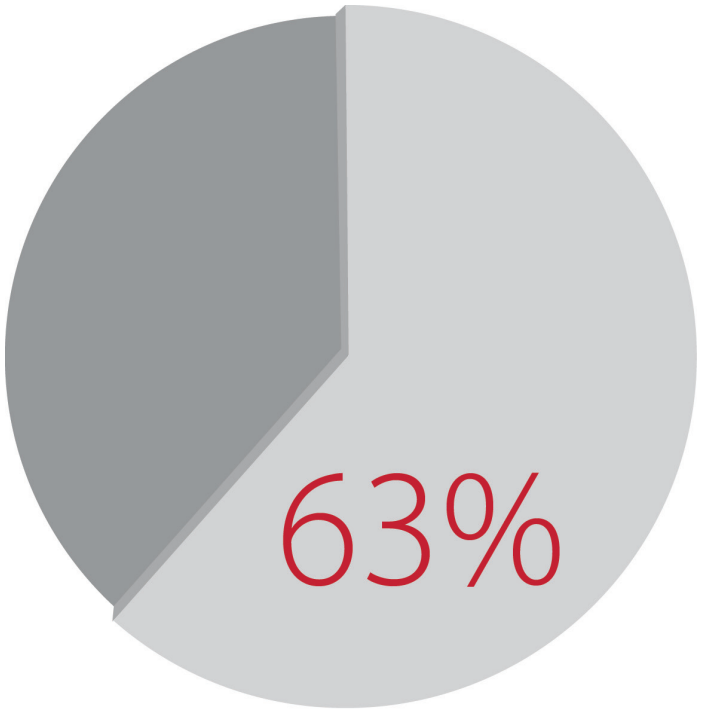
Noble
121 South Orange Avenue
Suite 1070
North Orlando, FL 32801
United States

www.gonoble.com



of patients use their inhaler incorrectly

Figure 1: Percentage of users who failed to demonstrate proper administration technique.



of patients failed to correctly complete three or more steps

Figure 2: Percentage of users who failed to correctly complete three of more steps.

TRAINING DEVICES

As with any form of drug delivery, providing patients with access to proper training and education is often the first step in successfully onboarding them to pulmonary treatments. In recent years the use of training devices that mimic the form, function and behaviours of pulmonary delivery devices have become effective resources for patients when learning how to administer their treatments properly.

These novel training devices are reusable and allow patients to learn how to handle and operate drug delivery devices. For pulmonary systems, this often includes priming, cleaning, actuating and inhaling procedures. Historically, many pulmonary devices require a high degree of hand-lung co-ordination and proper flow rates for medication to reach and deposit in the proper area of the lungs effectively.

Failure to complete these steps successfully can decrease the effectiveness of treatments and result in a number of unintended consequences. To address these risks, pulmonary training devices incorporate novel technologies such as air-flow sensors and calibrated mechanical features to teach patients the proper sequence and flow rates required to administer their treatments successfully. Providing this level of education and training to patients promotes the proper use of drug delivery systems and is an effective strategy to improve outcomes and maximise the value of pulmonary therapies.

Multisensory Technology

Developing optimal pulmonary training devices requires the effective application of human factors considerations and other cognitive methodologies. Modern neurological research suggests that information perception, encoding, decoding and retrieval is influenced by the strength and uniqueness of educational stimuli.

Thus, device-training solutions incorporating multisensory technologies, such as audio, visual and tactile feedback, have been proven to strengthen neurological connectivity between semantic networks of the brain, a principle referred to as cross-modal processing. As a result, training devices that incorporate multisensory technologies can be used to enhance patient training further and create a consistent onboarding experience for all users.

INHALED DRUG DELIVERY DEVICE OPTIONS

Currently, there are a variety of drug delivery device options available to patients with respiratory or related indications. Many of these conditions are characterised by inflammation, constriction or obstruction of airways and the lung. Such factors can

Figure 3: MDI training device designed to be true to form and function of an actual MDI.

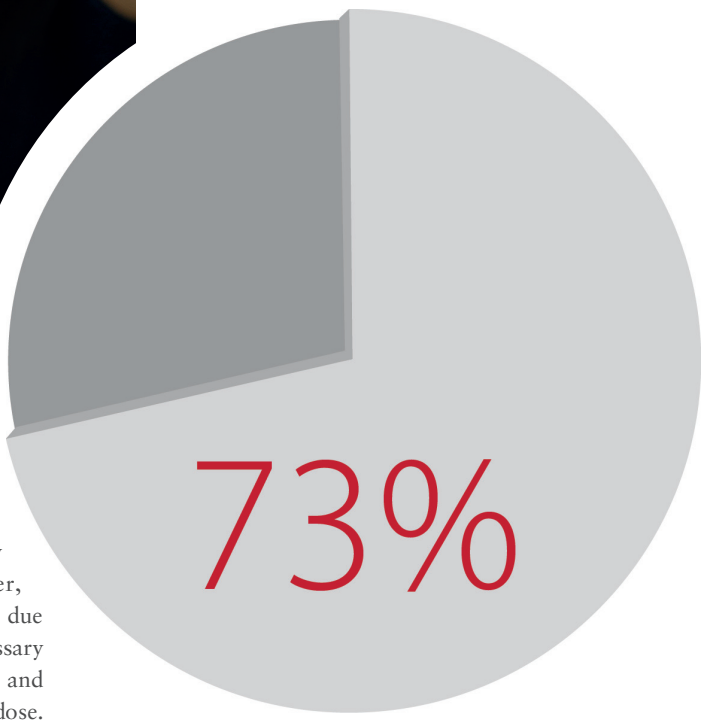
adversely affect the functions of the lung and are commonly treated with targeted therapies such as anticholinergics, beta-agonists or corticosteroids.

The efficiencies of targeted therapies that treat these conditions lie in the localisation and rapid uptake in the lungs. The absorption of medications for systemic delivery has also become an attractive option for future treatments and pipeline molecules due to properties of the lungs and proximity to the cardiovascular system.

The following are drug delivery options that are available for the majority of currently marketed pulmonary treatments.

- Nebuliser – converts liquid medications into a mist to help treat patient conditions. To use the nebuliser, patients inhale the mist through an attached mouthpiece or mask. Nebulisers are historically used by patients at home, limiting the flexibility of their treatment and dosing schedules.
- Metered dose inhaler (MDI) – delivers medication through a pressurised handheld device. Patients use an MDI by pressing on the device while simultaneously inhaling the medication, depositing the medication directly into the lungs. While MDIs are small and easily transportable, patients often fail to inhale the nominal dosage due to a number of issues, including hand/lung co-ordination, confusion in steps, and inspiratory flow or rate of inhalation. An MDI training device is shown in Figure 3.
- Dry powder inhaler (DPI) – also small and compact, making it easily transportable. However, patients often misuse DPIs due to the amount of steps necessary to actuate the medication and administer the nominal dose. DPIs rely on the force of patient inhalation to deposit the medication into the lungs. For this reason, insufficient inhalation flow may cause the patient to receive too little medication. Patients must also properly close the cap in order to prevent the medication from hardening.
- Soft mist inhaler (SMI) – combines the size and portability of MDIs and DPIs with the benefits of a nebuliser. Although SMIs disperse medication through a mist, allowing patients to inhale at their own rate, there are a number of components in the device that can cause confusion for patients and result in preventable errors.

> "Smart technologies provide the opportunity to maximise training value by incorporating sensors, algorithms and multisensory feedback to monitor real-time patient behaviour and detect errors."



of patients reported increased anxiety around injectable treatment therapies when relying on an instruction manual as their only form of training

Figure 4: Percentage of users who reported needle anxiety when relying on only the IFU.

NEW DELIVERY METHODS

Indications such as COPD affect an estimated 11 million patients and is the third leading cause of death in the US.[2] For nearly two decades, the pharmaceutical industry has been evaluating next-generation pulmonary treatments to help in the management of symptoms and to improve patients' quality of life. Many of these pipeline treatments leverage modern science to target and block inflammation through novel mechanisms of action and delivery technologies.

Due to the clinical profile and properties of these treatments, many of them will be administered as subcutaneous injections using prefilled syringes, auto injectors or other parenteral methods. While these injectable compounds will mitigate patient barriers associated with traditional pulmonary devices, they will also introduce new behaviours and training considerations into patients' treatment and onboarding experiences.

Research demonstrates that many patients who self-inject therapies do not read or fully understand the instructions for use (IFU) that accompany their drug delivery device. A study conducted by Noble and researchers from Auburn University surveyed more than 700 patients and found more than half did not read their instructions for use (IFU) document prior to beginning treatment.

In addition to traditional instructions and package inserts, healthcare professionals are often leveraged as learned intermediaries to onboard patients and provide access to training and education. However, patients are often new to medical terminology and therefore do not fully understand medical instructions. Similar to pulmonary devices, patients' inability to recall and utilise information effectively may lead to a higher probability of incorrect administration techniques and errors when using injection devices.

Injection Training Devices

To address the common gaps in patient onboarding for injection systems, training devices are often used to create consistent onboarding experiences for patients through the use of multisensory technologies and mechanisms that fully simulate the mechanical aspects of the injection experience.

In a study conducted by Noble, 73% of patients reported increased anxiety around injectable treatment therapies when relying on an instruction manual as their only form of training (Figure 4). The research also found that providing these patients with training devices that simulate the look and feel of real injection devices and allowing them to practice self-injection prior to beginning helps to decrease anxiety and fear.

CONCLUSION

As the pulmonary market continues to evolve and new injectable treatments are introduced, patients will need to familiarise themselves with using auto injectors, syringes and other forms of injectable delivery. This market need will create opportunities for pharmaceutical manufacturers to establish differentiation through superior onboarding tactics in order to avoid barriers associated to adherence and acceptance.

Due to the success of multisensory device training, smart technologies are now augmenting the training device market. Smart technologies provide the opportunity to maximise training value by incorporating sensors, algorithms and multisensory feedback to monitor real-time patient behaviour and detect errors. This direct feedback further accelerates the learning and onboarding process.

At its core, the ultimate goal of device training is to create value for industry stakeholders by enhancing the patient experience and improving safety. As new products continue to launch and augment markets, brands will continue looking for strategies to differentiate themselves and improve patients' quality of life.

In the modern era of patient-centric care, those able to provide superior product and educational experiences will continue to benefit from the value and utility that they create for patients and society.

ABOUT THE COMPANY

Noble, the leader in patient onboarding and drug delivery device training, develops "True to Form and Function" auto injector, prefilled syringe, wearable and respiratory training platforms to provide biopharmaceutical companies improvements in patient onboarding and adherence. These training platforms are built to brand specifications and are available as off-the-shelf, pre-configured ready-for-launch solutions.

Noble's offerings range from mechanical training devices to smart error-correcting training platforms, which replicate a brand's shape, design and tactile feedback, operational forces and steps needed to administer the drug. These devices have been designed to simulate actual drug delivery devices while being a low-cost reusable solution to onboard users safely and effectively.

REFERENCES

1. *Bonds R, Asawa A & Ghazi A, "Misuse of medical devices: a persistent problem in self-management of asthma and allergic disease". Annals of Allergy, Asthma & Immunology, January 2015, 114, (1), pp 74–76.e2.*
2. *"How Serious Is COPD" (n.d.). Retrieved 03 February, 2017, from http://www.lung.org/lung-health-and-diseases/lung-disease-lookup/copd/learn-about-copd/how-serious-is-copd.html*
3. *Kessels RP, "Patients' Memory for Medical Information". Journal of the Royal Society of Medicine, May 2003, 96(5), pp 219-22.*
4. *Zambanini A, Newson RB, Maisey M & Feher MD, "Injection related anxiety in insulin-treated diabetes". Diabetes Research & Clinical Practice, December 1999, 46(3), pp 239-46.*

ABOUT THE AUTHOR

Joe Reynolds is Research Manager at Noble, where he leverages his knowledge and experience to develop and implement strategies that improve the patient experience and maximise value for stakeholders. His experiences include commercial, managed care and product development initiatives with leading medical device, pharma and biopharma brands.

Mr Reynolds holds a BS in Business Administration from the University of Central Florida, an MS in Marketing from the University of South Florida and an MS in Pharmacy and Master Certificate in Drug Regulatory Affairs from the University of Florida.

THE INTERNATIONAL SOCIETY FOR AEROSOLS IN MEDICINE

ISAM

• INTERNATIONAL SOCIETY FOR AEROSOLS IN MEDICINE •

• 21ST INTERNATIONAL CONGRESS •

ISAM 2017

SANTA FE, NM

• June 3-7 •

TOPICS:

- Translating scientific innovation to inhaled therapeutic strategies
- Emerging formulation, imaging and device technologies for developing respiratory drugs
- Translating novel concepts to inhaled therapeutic strategies

For more information visit: www.isamcongress.com

El Dorado Hotel
Santa Fe NM

Lovelace™

Hosted by the
Lovelace Family
of Companies

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

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/

DIMITRI GRASSWILL Nemera

Following a first R&D experience in automotive industry, Dimitri Grasswill joined the pharmaceutical device area in 2004. He has practiced in various settings, starting from device manufacturing and quality environment to development and industrialisation project management. In 2010, he moved to a innovation lead position, where he started to structure and develop the Innovation Center of Nemera (formerly Rexam Healthcare) with the target to establish a "state of the art" innovation and development organisation for pharmaceutical devices and drug delivery solutions. He has always been convinced that strengthening device R&D activity in healthcare industry would contribute to addressing patient needs better.

Mr Grasswill speaks with ONdrugDelivery Magazine, in the context of the changing market and technology around inhalation devices, about Nemera's strategic decision a few years ago to build design and development capability and integrate that with the company's considerable manufacturing expertise and infrastructure.

Q Nemera's capabilities span a range of drug delivery device classes. Please could you tell us about Nemera's pulmonary drug delivery device offering in the context of the company's overall offering?

A Nemera is a design, development and manufacturing company focusing 100% on drug delivery devices and we operate mainly within five segments, five delivery routes: nasal, ophthalmic, parenteral, inhalation and dermal. We have a large customer-owned-device manufacturing business but over the past few years we have introduced a strong innovation path, where we develop our own products. We operate both models across the five delivery routes, including pulmonary (see Figure 1). Another aspect of our business model is co-development, where we contract develop a product for a customer and then take it on to manufacturing.

So on one side you have the Nemera IP business, on the other you have the pure industrialisation and manufacturing, and in the middle of these you have what we call the co-development business, where we develop products from scratch or continue the development of products whose development has already started.

We have four plants where we industrialise and manufacture devices: two in France, La Verpillière close to Lyon and Le Tréport in Normandy; one in Germany at Neuenburg am Rhein; and one in Buffalo Grove in Illinois, USA. At La Verpillière we have a campus that includes our headquarters and also our development centre, which we call the Innovation Center (see Figure 2). All of our activities on the development side are located in this one area.

We have a team of around 75 engineers and experts who work on designing, developing and qualifying products. We then transfer this to any of these four plants for industrialisation / scale-up and manufacturing.

In terms of plants, we do have plants where we have a stronger history of manufacturing, for example, parenteral devices, and others where nasal devices or ophthalmics have historically been the focus, but there is no barrier between the different segments. It's more a question of the industrial layout, or geography of the different plants than a question of specific know-how at specific plants. We have strong knowledge across the different device types which is centralised and can be co-ordinated amongst our different plants.

Q Focusing on Nemera's pulmonary offering, I wondered if you could take us through each of the three areas: design, development and manufacturing?

A We believe we have a unique approach and we are genuinely able to be a one-stop-shop for our customers because we integrate the whole process of a drug delivery solution – we're able to design it, develop it and manufacture it.

Our approach is a very simple one. We started focusing on our own IP several years ago and by doing that our only objective was to put these devices on the market, which we knew meant

"Nemera, previously Rexam, is a very well-known manufacturing partner in this industry. This is in our DNA. So when we started to develop our own products, we established a new centre of knowledge, additional to the manufacturing. As drug delivery devices are extremely complex, in terms of their mechanical function and in terms of their interaction with the drug, the patient and so on, we think this link we have between development and manufacturing is absolutely crucial."

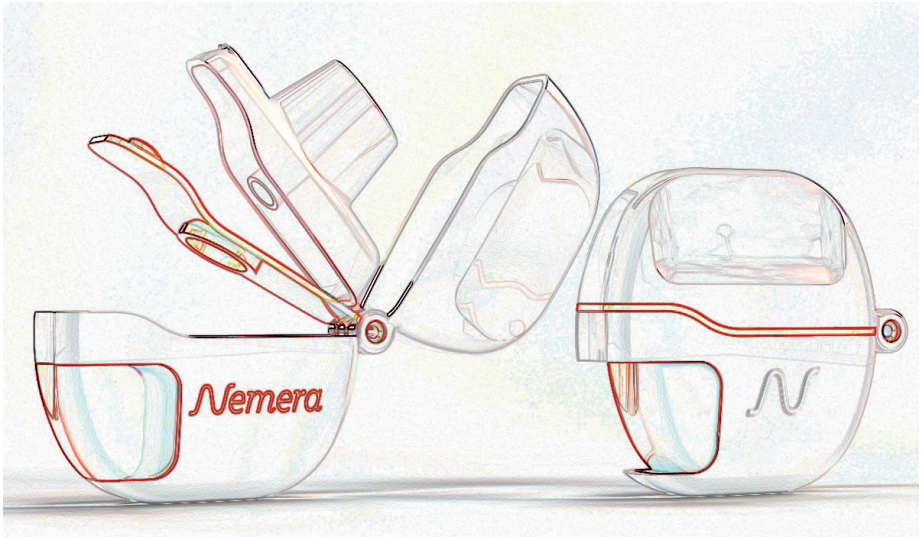


Figure 1: Design sketch of new inhalation device concepts.

> "What we offer clearly is this ability to do this concurrent engineering for industrialisation during design and development in order to be able to move very rapidly to the market. We are able to fine tune the product and the process at the same time, not one step after the other. It is not only fast, it is efficient."

we needed to make a very strong link with our manufacturing. Nemera, previously Rexam, is a very well-known manufacturing partner in this industry. This is in our DNA.

So when we started to develop our own products, we established a new centre of knowledge, additional to the manufacturing. Drug delivery devices are extremely complex, in terms of their mechanical function and in terms of their interaction with the drug, the patient and so on. And with inhalers in particular there is of course complexity arising from the fact that device performance is ultimately really a combination of the device itself and the way the device works with the formulation in terms of preparing the dose and it being inhaled by the patient. Increasingly, we are also talking about connectivity which adds another level of complexity. We think in the context of increasingly complex systems involving the device itself and the formulation, and their interaction patient, all the tiny tolerances that are required on all the materials and moulded parts, that this link we have between development and manufacturing is absolutely crucial.

We do not believe it is an efficient strategy today to develop a device with one partner and then ship the project out to another partner who then begins thinking about the industrialisation. What we offer clearly is this ability to do this concurrent engineering for industrialisation during design and development in order to be able to move very rapidly to the market. We are able to fine tune the product and the process at the same time, not one step after the other. It is not only fast, it is efficient. And by considering the process very early, sitting all the experts around the table from the start, we are also already talking with and preparing our industrialisation colleagues so the design transfer, as it is known in the pharma world, then becomes much easier and avoids all the risks of designing a device to begin with and then when it comes to the industrialisation process having to go back and revise the design because some of the specs were not robust enough in terms of full-scale manufacturability.

Q Are Nemera's clients able to access each category individually (ie design only, or manufacturing only) if they wish?

A We are not dogmatic. Whilst we understand the advantages of considering the manufacturing process from the outset, throughout the design and development stage, and we have built up this capability very successfully, our objective ultimately is to manufacture the device. We are not a design house, we are there to manufacture and so whatever the stage of development we are constantly asking the question, "How is it made?" We see our device design and development capabilities as essential for the rapid and efficient development of the manufacturing process. So if a customer comes to us with a given product, for us to industrialise it, then absolutely we are very happy to do it. Whatever stage it is at, perhaps a partially designed product, for example, we are fully able to interact. We can put around the table all the expertise required to get that product from whatever stage it has reached, to the market.

Figure 2: The Innovation Center at La Verpillière, near Lyon, France.

"We are constantly asking the question, "How is it made?" We see our device design and development capabilities as essential for the rapid and efficient development of the manufacturing process."

Q What do you think are the most significant trends in field of inhalable drug delivery, and how is Nemera positioned in the context of these trends?

A We all feel that connectivity will have a huge impact not only in our field but across all industry. There is a global consensus in the pharmaceutical industry that connectivity will have a significant impact but what is interesting is that nobody really knows exactly how fast or how deep the impact will be.

There is a continual increase in the degree of patient interaction with delivery devices. For example, for inhalation, today you have increasingly intuitive devices, and better instructions and training of how to use them, and you also now have the availability of a means to see how many doses remain in your device – dose counters. Additionally, things like the portability and the general attractiveness of the appearance is improving. But in the end the main driver has to be the quality of the treatment, or therapeutic outcome.

The other major trend, which is not a new one, but one which will continue and likely intensify, is the role of generics. As new chemical entities are becoming rarer every year, for a company such as Nemera the ability to be able to provide delivery solutions for generics will become more important still.

Q Looking to the future, what lies ahead for Nemera – with reference to pulmonary delivery devices in particular, and also more broadly for the organisation as a whole.

A In a way, the future for us started some years ago when we looked forward and began to build capabilities in the design and development area in order to become the global solutions provider we are today, having gone beyond just contract manufacturing. This prescient decision was taken partially to enable us to work more with generics companies, but also to be able to be a real partner of choice for pharma companies as the market evolved.

Another focus is electronics, including connectivity, and for us to be the provider of a mechatronic device. But importantly we are ensuring that we will have the right value proposition in the end. We believe in finding the way that technology brings added value to our devices, and to the patients.

"We believe in finding the way that technology brings added value to our devices, and to the patients."

Everyone is very focused on the fact that connectivity will increase compliance but only a few truly understand the mechanism of how, and connectivity increasing compliance is only one part of it. We are looking at how electronic technology, including but not only connectivity, can bring added value and help improve all aspects of the treatment, not just compliance. Integrating electronic sensors with dose counters, and employing electronic technology to control particle size are examples where this may come into play.

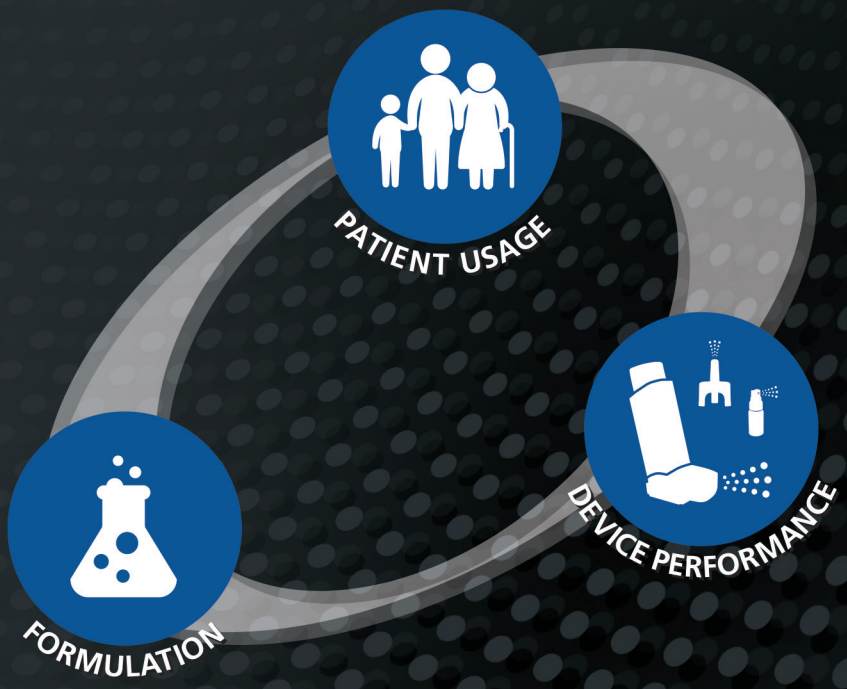
Also, Nemera is proud to contribute to the EU-funded project CUPIDO (Cardio Ultra-efficient nanoParticles for Inhalation of Drug prOducts), that started in February 2017. This project will foster the translation of nanomedical inhalation applications toward the cardiac field. The role of Nemera in this consortium will be the development of the devices for the administration of the nanoparticles by inhalation, to the heart.

Mr Dimitri Grasswill
Global Innovation & Development Director
T: +33 4 74 94 06 54
F: +33 4 74 94 90 60
E: dimitri.grasswill@nemera.net

Nemera Innovation Center
La Verpillière
20 avenue de la Gare
F-38292 – La Verpillière
France

www.nemera.net

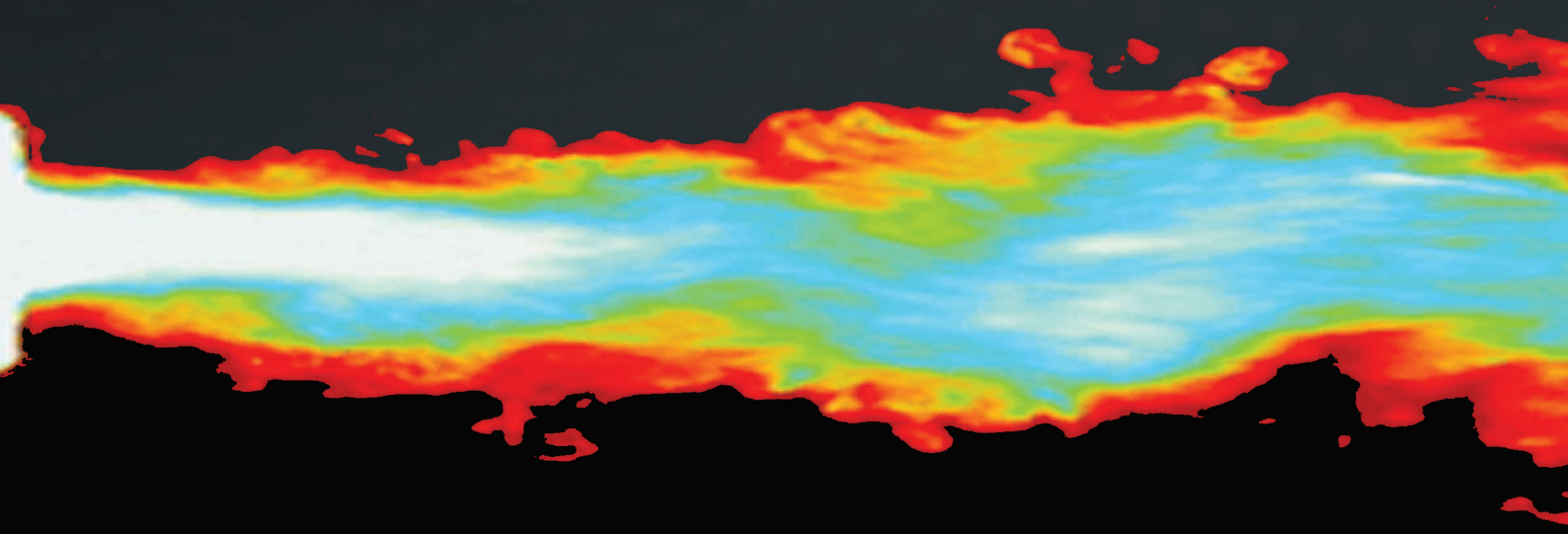
proveris
SCIENTIFIC



Bridging the Gaps between Patient Usage, Device Performance, and Formulation

Proveris by Design™ Lab Studies accelerate development by reducing the time and cost of optimizing the patient-device-formulation combination required for a successful drug product. Our expert lab scientists work one-on-one with customers to bring products to market more quickly utilizing the following services:

- Reference Product Characterization
- Method Development, Transfer, and Validation
- Patient Usage Ergonometric Studies
- Device Component Optimization



Learn more at: goproveris.com/ODD2017

THE 21ST INTERNATIONAL SOCIETY OF AEROSOLS IN MEDICINE CONGRESS

The International Society for Aerosols in Medicine (ISAM) is a scientific society focused on all areas of aerosols including health effects of aerosols and pulmonary drug delivery. ISAM was founded in 1970 with an objective to foster interdisciplinary communication within the areas of aerosols in medicine. Current society membership includes researchers from academia and industry, physicians and regulatory scientists, all of whom are focused on pulmonary research. The society holds a congress every other year to bring its membership together in a dynamic setting to review the current state-of-the-art research and brainstorm new scientific strategies.

BACKGROUND

ISAM was founded in 1970 with the first congresses held in Baden, Austria and Vichy, France. The focus of the society is on the interdisciplinary co-operation and exchange of information in all areas of aerosols in medicine. These include pulmonary drug delivery and the health effects of inhaled aerosols. The society utilises many different venues to communicate the scientific findings including a congress every two years and publication within the ISAM journal, the *Journal of Aerosol Medicine and Pulmonary Drug Delivery* (JAMPDD), which has an impact factor of 3.041.

To foster networking among its membership, ISAM maintains six different focus groups:

- Regulatory Affairs and Standardisation Issues
- New Devices and Emerging Therapies
- Paediatrics and Cystic Fibrosis
- Imaging, Modelling and Physiology of Aerosols in the Lung
- Environmental/Occupational Health
- Plus a networking group for Graduate Students, Post-Docs, Fellows and Junior Faculty.

Membership within ISAM enables participation in the networking groups, subscription to JAMPDD, reduced congress fees, reduced membership to joint organisations (European Respiratory Society), and access to the ISAM *Textbook of Aerosol Medicine*. The textbook, which is on the ISAM website, provides unique and comprehensive coverage of a broad range of topics related to aerosol science and clinical applications of aerosol therapy. It has been written by content experts and provides concise and up-to-date information on various topics of interest to aerosol scientists and clinicians.

Dr Philip Kuehl
Scientist
T: +1 505 348 9745
E: pkuehl@lovelacebiomedical.org

Lovelace Biomedical
2425 Ridgecrest Drive SE
Albuquerque, NM 87108
United States

www.lovelacebiomedical.org

SANTA FE CONGRESS

The 21st ISAM congress will be held in Santa Fe, NM, US from June 3-7, 2017 at the Eldorado Hotel and Spa (www.isamcongress.com). Previous recent congresses have been held in Chapel Hill, NC, US and Munich, Germany. An ISAM congress typically has about 300 attendees from across industry, academia, clinical practice and regulatory sciences. The congress provides an environment that fosters face-to-face interactions within aerosols in medicine.

WORKSHOPS

The 21st ISAM congress will be preceded with three workshops each with a different focus. The workshops will be a full-day (June 3, 2017) immersion into each topic, employing international experts in an interactive setting with the attendees. The three workshops are: "New Frontiers in Inhalation Technology", "Current State of E. Cigarettes and Their Impact on Pulmonary Health", and "A Lab Practical for Inhalation Studies".

The "New Frontiers in Inhalation Technology" workshop is a joint workshop organised by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) and ISAM. The workshop will include presentations on: novel technologies for inhalation products; evolving technologies for monitoring use of inhalation devices; a patient perspective on new technologies; and a review of the current global regulatory status for inhaled therapies. The IPAC-RS/ISAM joint workshop continues to be a cornerstone of the ISAM congress workshops and has always provided a unique dialogue between scientists and regulatory experts. This year's session is sure to provide the same.

With the rapidly changing state of electronic cigarette technology, movement towards regulations and the continued expansion of their use, the workshop on the "Current State of E.Cigarettes and Their Impact on Pulmonary Healt" promises to be well-attended. This workshop will include presentations on the *in vitro*, *in vivo* and regulatory aspects of electronic cigarettes. The *in vitro* presentations will include aerosol characterisation (how to do it and what the results say) and the *in vitro* tolerance findings within multiple different *in vitro* models. The *in vivo* data presentations will include both clinical and non-clinical studies of pharmacokinetics, addiction, and tolerance. With the recent publication of the FDA's Premarket Tobacco Application (PMTA), the presentations on the regulatory aspects will reflect the current interpretation/application of testing to meet the PMTA guidelines.

The workshop on "Lab Practical for Inhalation Studies" will provide a unique hands-on experience for the attendee with experts in operating and conducting inhalation studies. The attendees will have the opportunity to learn about, handle and operate a variety of inhalation products including:

- Nebulisers (compressed air jet, ultra-sonic, vibrating mesh)
- Dry powder devices (clinical and non-clinical)
- Exposure systems
- Particle-sizing devices (impactors and electronic devices)
- Other unique devices.

This workshop will enable attendees to better link the science behind device design and operation with applications in their own research.

CONGRESS PROGRAM

The scientific program for ISAM 2017 will start on June 4, 2017 and conclude on June 7, 2017. Over these three and a half days, a variety of sessions will be presented that are designed to present current/novel/evolving data and technologies to the attendees while also providing the opportunity for scientific dialogue.

Topics will include asthma/COPD, infectious disease, nasal drug delivery, *in vitro* cell models, therapeutic and diagnostic gases, pulmonary fibrosis, personalised medicine, new/emerging aerosol therapy, and electronic cigarettes. Each session will include invited speaker(s) based on their expertise within the focus area and will also include presentation(s) selected from the submitted abstracts. In this manner the congress will include the most current state-of-the-art science within each area.

Additionally, during the scientific program, ISAM will present several awards. These awards include:

- The Thomas T. Mercer Award
- Career Achievement
- Young Investigator
- Student Research
- Jurai Ferin
- Best Oral Presentation.

Details on the criteria for each award and the submission process can be found on the ISAM 2017 congress website.

ABSTRACTS

The organisation committee for ISAM 2017 is seeking the submission of high-quality abstracts for the 21st congress. Abstracts can be submitted via the congress website (www.isamcongress.com/site/index/14) and will be reviewed by the organisation committee for scientific merit. All accepted abstracts will be presented as a poster throughout the congress and are indexed by the JAMPDD.

Additionally, to ensure that the scientific program represents the current state-of-the-art in the designated areas, multiple high-quality abstracts will be selected for oral presentations within the congress program. Therefore, scientists are encouraged to submit high-quality scientific abstracts based on novel research.

SPONSORSHIP AND EXHIBITION

ISAM congresses provide an opportunity for companies to showcase current technologies or products to scientists and clinicians alike. The setting enables an intimate interaction for discussions, product display, and training. Any interested company is referenced to the sponsorship page on the congress website: http://www.isamcongress.com/site/index/16

The 21st ISAM congress will provide attendees with a high-quality meeting to develop scientific knowledge for researchers at all levels. It is with great excitement that the organisation committee encourages anyone interested in aerosols in medicine to consider attendance, abstract submission, sponsorship or exhibition.

Further information, including contact details, is available at the ISAM Congress website (http://www.isamcongress.com/). Hope to see you all in Santa Fe!

THE IMPORTANCE OF SPRING AND STAMPING QUALITY IN INHALER SAFETY

An efficacious and safe inhaler is not only dependent on the drug pharmacology, but also on a well-designed and good quality device. It is also desirable that the devices are small and simple to be used by the patient. The majority of inhalation devices contain springs or related stampings and wire forms, which work as the device's energy source and allow the medication to be released. In this article, Frank Reiss, Head of Business Development, and Bergdis Sigurdardottir, Project Manager, both of the medical division of Baumann, explain how medical competence in spring and stamping manufacturing may prove critical for the developers of inhalers.

> "Each type of metal component assembled in an inhaler brings its unique advantages and in many cases functions as its energy source, allowing the medication to be released."

Respiratory diseases have a severe impact on life, health and productive human activity. Chronic respiratory disorders are becoming a more prominent cause of disability and death. According to the Forum of International Respiratory Societies, chronic obstructive pulmonary disease (COPD) affects more than 200 million people and is likely to become the fourth leading cause of death worldwide by 2030. At the same time, asthma affects about 235 million people around the globe.[1] Furthermore, other related diseases such as cystic fibrosis, allergic rhinitis, idiopathic pulmonary fibrosis and lung cancer affect the life of millions of people.

The inhalation route is a fast, effective, and a convenient way to treat pulmonary diseases. Every year more than 900 million dry powder inhalers (DPIs), metered dose inhalers (MDIs) and nebulisers are used throughout the world. The global pulmonary drug delivery system market was estimated to be worth more than US$30 billion in 2015. These figures are expected to increase continually year after year. This trend is caused by:[2]

- Increasing share of older people in the population
- A growing population of smokers and increasing impact from pollution
- Rising number of patients needing combined therapies
- Strengthened R&D activities for asthma and COPD medication
- Innovations in device development.

What many people do not know is that these trends also affect the business of spring and stamping suppliers because the majority of inhalation devices contain their products. Each type of metal component assembled in an inhaler brings its unique advantages and in many cases functions as its energy source, allowing the medication

Bergdis Sigurdardottir
Project Manager Medical
E: bergdis.sigurdardottir@baumann-group.com

Frank Reiss
Head of Business Development Medical
E: frank.reiss@baumann-group.com

Baumann Springs Ltd
Fabrikstrasse
CH-8734 Ermenswil
Switzerland
T: +41 55 286 81 11

www.baumann-group.com

Figure 1: Illustrative examples of bespoke springs and stampings.

to be released (Figure 1). That being said, specialised companies and subject matter experts must work hand-in-hand, across the supply chain, to optimise the entirety of an inhaler device. Baumann, as one of the worldwide leading spring and stamping suppliers for medical devices, is the partner of choice for key market players in the industry – be it pharmaceutical companies, contract manufacturers or design offices.

BEING A DEVELOPMENT PARTNER

Based on the chosen technology to administer the drug, it is recommended to involve the supplier early on in the R&D stages of the pulmonary device design. When included in the development phase, the supplier can support the design process by providing their manufacturing experience and engineering competence at the first step to verify the feasibility of the design idea.

A well-developed device is one of the key factors in successful pulmonary drug delivery. When Baumann is approached to support projects by supplying bespoke springs and stampings, they can advise on design specifications and production parameters, ensuring manufacturability in the industrialisation phase. This will assist in defining an effective process from development through assembly into high volume series.

Furthermore, functional samples can be provided to verify the design concept. As soon as the design has been formulated, prototypes can be supplied, which can be used for clinical tests and assembly trials, produced on machines representing the same concept and process as used in serial production. Lastly, upon customer approval, validated parts can be manufactured and serial production can begin.

DESIGN VERIFICATION/ CUSTOMISED SOLUTION

Once a spring has been chosen for the device, the next step is the spring design where the main restrictions are the design space constraints. Baumann offers engineering advice when it comes to designing the spring, where the goal is to maximise the spring function within the available design space based on its specification.

With our experience in spring design and the help of analytical calculation or numerical simulation using a finite element model (FEM), we are able to optimise the spring design together with the device developer (Figure 2). The allowable stress in a spring is calculated based on the predicted relaxation and the mechanical properties of the wire. A great emphasis is placed on the coiling index – the proportion of the wire size to the springs outside diameter – since it helps indicate the ease of manufacturing. In the case of a compression spring, the probability of the buckling can be determined based on the relationship between the unloaded spring length and the outside diameter.

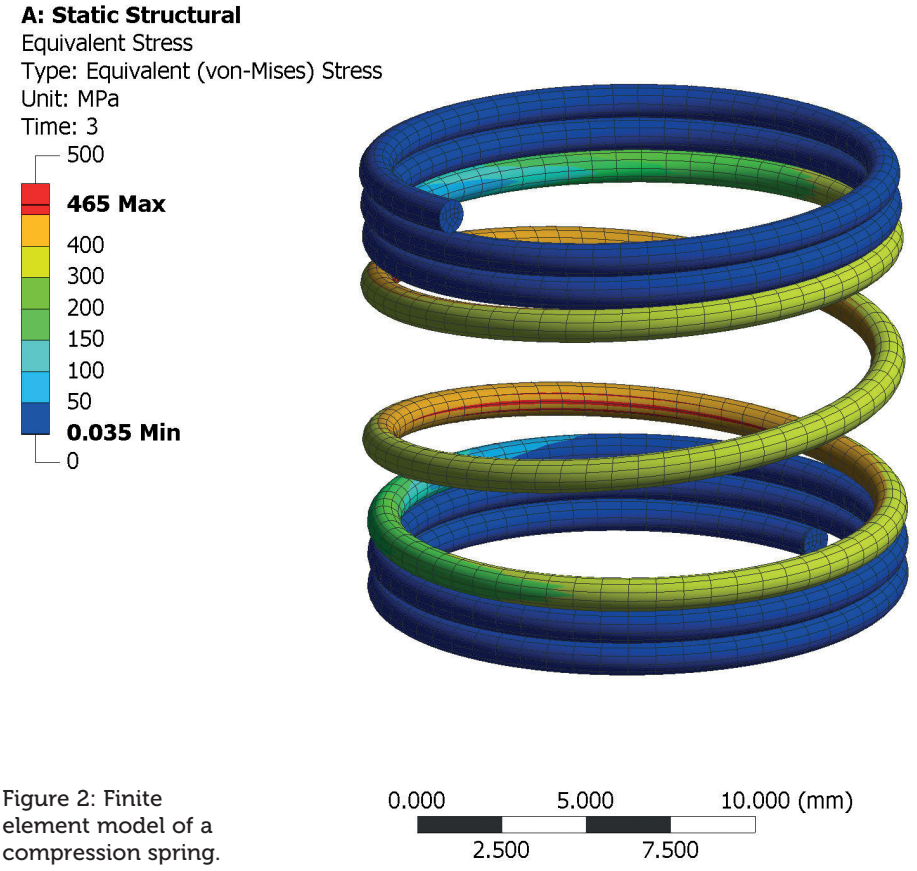


Figure 2: Finite element model of a compression spring.

However, the spring function is only one part of what needs to be considered. Another reason to involve spring manufacturers early in the device design phase is that they also share similar interests in developing a clear and robust design specification in order to avoid undesired complications in future stages of development and production. This includes factors like optimising the spring design to avoid problems in the device's assembly line and making sure it fits the requested process.

To illustrate this, let's consider wire material.[3] The wire supplier needs to be capable of delivering the capacity of the required specification and make sure there is traceability in the supply chain of raw material. This is important because, as a medical production, being able to trace every produced spring batch is critical.

Another important point to consider is the tangling of the spring. The risk of tangling may often be minimised by considering certain features in the design. If that is not feasible, it allows for an early start to find a suitable packaging concept.

> "We want to let device developers become aware of the importance of a close and open collaboration, to prevent problems occurring with supplying of springs and stamping as well as in the assembly of the device."

REALISING THE SOLUTION

After deriving comfort with the spring calculation, prototypes of the springs are created to confirm the design and to evaluate the wire processibility. A particularly important feature is that all prototypes are produced on machine concepts mimicking the one that will be used in future serial production.

It serves the purpose of the product feasibility check and helps identify improvement possibilities at an early stage in the project as well as to evaluate the manufacturability of the chosen concept at a high scale. In addition it ensures stable and robust production processes in later serial production.

The work in the prototyping phase will be performed in close collaboration with the customer. Important aspects will be considered such as whether the technical performances can be met, if the wire material is suitable and the risk of spring tangling. Only then will a clear picture of whether the spring is up to its task be possible.

Another valuable capability is to perform lifecycle tests (for example, relaxation and ageing test) on the springs to verify the features used in the spring calculation. This needs to be confirmed by the device manufacturer with full diagnostic device testing.

In the case of more complex springs or specific requirements from the customers, for example automatic packaging in trays or setting the spring to its compressed length before delivery, Baumann's in-house machine manufacturer can develop customised equipment or tailor-made machine concepts suitable for each project.

GLOBAL MEDICAL PRODUCTION

Baumann has a global medical division (ISO13485 certified), with the mission of providing the same quality in products, service and processes to customers worldwide (Figures 3 and 4). Therefore, the medical division has developed its own validation procedure complying with high medical industry standards.

The validation procedure comfortably accommodates customer requirements. Having these documents readily available

Figure 3: Baumann's global footprint.

Figure 4: Dedicated, ISO 13485-certified medical production area.

Figure 5: Illustration of inhaler device.

accelerates the validation process and reduces the amount of time required from entering the prototyping stage till starting serial production. This validation process is performed for every component manufactured in serial production. It is used to verify that the manufacturing facility and processes for the produced article are capable of generating reliable results which envelop the defined requirements. This includes the component's risk evaluation[4] and all equipment qualifications. The validation report collates the outcome and findings produced in the validation run.

Another important aspect to be applied in all production sites around the globe is complying with Good Documentation Practice (GDP).

RELIABLE BUSINESS PARTNERSHIP

Throughout the clinical trials and approval process of the drug and its device, collaboration should carry on. Hence, the production ramp-up and market introduction of the new product can jointly be prepared. In order to mitigate supply chain risks and avoid a delay in market introduction, it is imperative that commercial terms and conditions are defined, and long-term strategic elements are set in place. This includes capacity commitments, handling of volume fluctuation as well as safety stock build-up, aligned decisions for investments and milestones for global expansion of production.

Baumann has experienced that effective communication, by openly and pro-actively approaching these matters and seeking for timely feedback from involved stakeholders, is highly valued by their business partners. Such a basis of trust is the foundation for a successful, long-term business relation and continuous improvement measures during serial production. It is also the groundwork of supply chain security and optimises the total cost of ownership in the overall project during commercialisation of the product (Figure 5).

CONCLUSION

We want to let device developers become aware of the importance of a close and open collaboration, to prevent problems occurring with supplying of springs and stamping as well as in the assembly of the device. An early involvement of suppliers in the medical device development process is recommended to prevent problems that might occur later on – especially if a customised solution is demanded. It is essential that medical component suppliers understand customer needs and meet medical requirements. At the same time robust and scalable processes must be in place for serial production and to ensure supply chain security.

REFERENCES

1. *Forum of International Respiratory Societies (FIRS), "Respiratory diseases in the world: Realities of Today – Opportunities of Tomorrow". Annual Report 2013*
2. *Transparency Market Research, "Global Pulmonary drug Delivery Device Market". Report, 2017.*
3. *Wright RN, "Wire Technology – Process Engineering and Metallurgy". Elsevier, 2011.*
4. *General Motors Corp, "Potential Failure Mode and Effects Analysis". FMEA 4th Edition, 2008.*

ABOUT BAUMANN

For more than 125 years, Baumann Group has been a symbol of Swiss precision and quality. The Baumann Group is known worldwide as a leading company in spring and stamping manufacturing. The family-owned group, now in its fifth generation, has eleven production sites around the globe, where more than 1,500 people design and produce technically sophisticated products for targeted industries, including the automotive, electrical engineering and medical technology sectors.

In the dedicated, ISO13485-certified medical division Baumann addresses the unique needs of customers in the medical and pharmaceutical industry. Baumann has the know-how to tackle the specific challenges, extraordinary standards, and strict requirements of the industry, and stand as recognized expert and supplier. A specialised team with local professionals in the US, Europe, and Asia will work closely with customer teams, not only to develop the best component for a device, but also to provide a tailor-made solution for a specific customer project. Thus Baumann's partner benefit from this expertise as a long-standing world leader in springs and stampings.

ABOUT THE AUTHORS

Bergdis Sigurdardottir studied at the Reykjavik University, Iceland, and University of Bern, Switzerland. She graduated with a Masters degree in Biomedical Engineering. In 2014 she joined Baumann as a Project Manager in the medical division advising customers in the field of spring and stamping technology.

Frank Reiss, Head of Business Development of the medical division, joined the company in 2014. In his previous career he worked as a Project Manager for the largest Swiss energy company and as a Strategy Consultant for a global consulting firm. He holds a Master of Arts in Economics and Business Administration from the University of Zurich, Switzerland.

PRODUCT SHOWCASE: APTAR PHARMA'S MDI eDOSE COUNTER

Aptar pharma

Aptar Pharma, will unveil its latest innovation, the eDose Counter for metered dose inhalers (MDIs), at the RDD Europe scientific conference in Antibes, France, on April 25-28, 2017.

DOSE COUNTERS IMPROVE ADHERENCE

Asthma and COPD patient adherence is a major health and economic challenge. Several studies report very poor adherence to asthma medication regimens, with measured rates of non-adherence in the range 30-70%.

In the March 2003 US FDA Guidance for Industry, "*Integration of Dose-Counting Mechanisms into MDI Drug Products*", it is recommended that drug manufacturers integrate a dose-counting system into any new MDI drug products marketed in the US.

> "This technology allows for the incorporation of visual MDI priming reminders and feedback on use as well as end-of-product-life warnings."

Patients appreciate dose counters because they are convenient and improve safety by allowing them to identify the number of doses of medication left in their inhalers and to avoid running out unexpectedly.

The global inhalation market has followed the US trend and today multiple MDI drug products with some form of dose-tracking system are marketed outside the US.

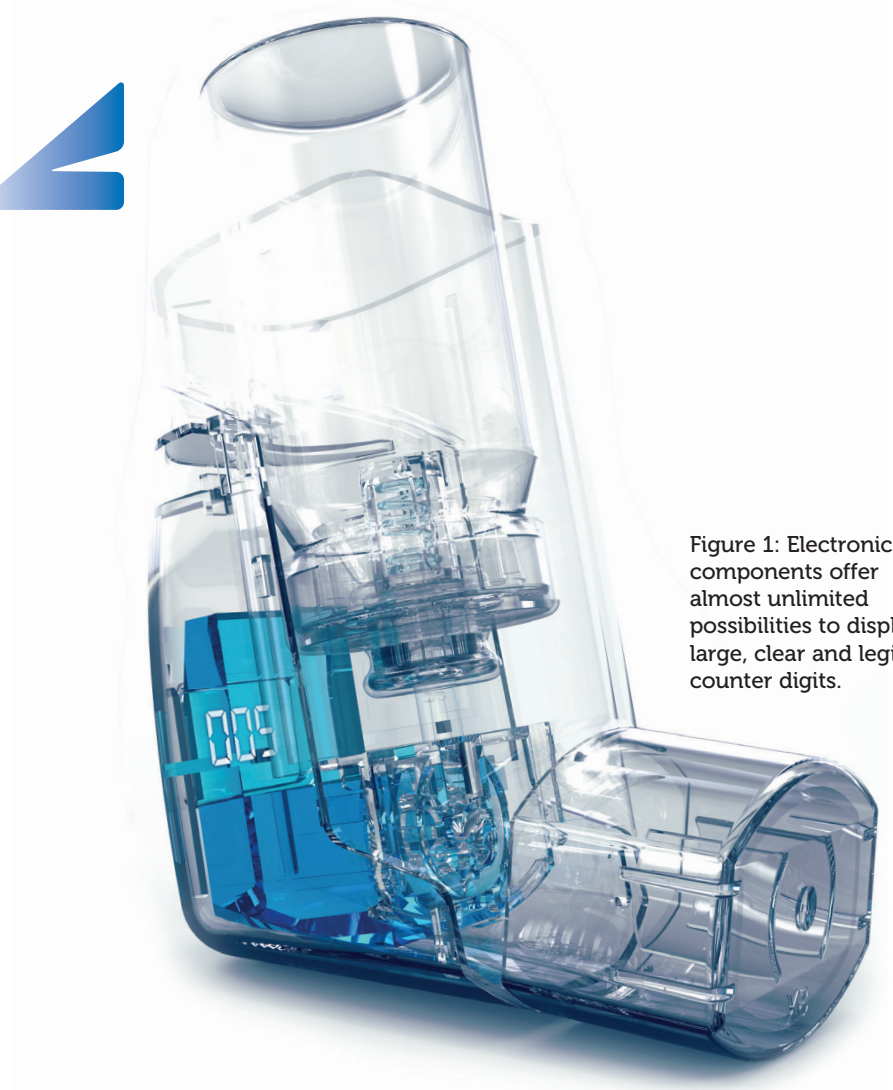


Figure 1: Electronic components offer almost unlimited possibilities to display large, clear and legible counter digits.

ENHANCED PERFORMANCE

Currently, marketed MDI dose indicators and counters are based on mechanical technology. Although this technology offers great opportunities to design simple and cost-effective devices, it does not always meet the expectations of users, regulators and other stakeholders due to poor legibility of the numbers, its effect on MDI user-handling and pharma performance, and the lack of robustness impacting safety (e.g. miscounting events).

Electronic components offer almost unlimited possibilities to display large, clear and legible counter digits required for a wide range of user age segments and medical conditions. In addition, this technology allows for the incorporation of visual MDI priming reminders and feedback on use as well as end-of-product-life warnings. Thanks to the integration of electronic components, these systems not only count doses, but mark a move towards comprehensive connected inhaler solutions.

INTEGRATED UNIQUE SENSING TECHNOLOGY

MDIs are complex systems that integrate several components such as the metering valve, the canister and the actuator. These components must be carefully designed

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

aptar.com/pharma

and manufactured to ensure they work together effectively. This is particularly true for the valve and the dose counter. As the world leading supplier of MDI valves, Aptar Pharma's expertise and experience enables a smooth integration of all MDI components, including the dose counter.

Our patented eDose Counter for MDIs is designed to be easy-to-use and reliable, and contributes to patient compliance.

> "Our unique sensing technology offers direct detection of the spray which eliminates risks of miscounting. The sensing technology is versatile and compatible with any metering valve design."

Our unique sensing technology offers direct detection of the spray which eliminates risks of miscounting. The sensing technology is versatile and compatible with any metering valve design. In addition, our eDose Counter for MDIs includes inhaler priming and medication reminders-to-use and end-of-product-life warnings (flashing digits) while remaining cost-effective.

For more information on Aptar Pharma's eDose Counter for MDIs, please come and see us at our table top at RDD Europe 2017 conference and/or visit our website: https://pharma.aptar.com/en-us/dispensing-solutions/edose-counter-mdis.html

ABOUT APTAR PHARMA

Aptar Pharma is part of the AptarGroup, Inc. family of companies, along with Aptar Beauty + Home and Aptar Food + Beverage. The company creates innovative drug delivery systems that meet the evolving needs of bio, healthcare and pharmaceutical companies around the world.

Aptar Pharma provides customers with a wide range of delivery technologies and analytical services backed by decades of proven expertise. AptarGroup is headquartered in Crystal Lake, IL, US, with manufacturing facilities in North America, Europe, Asia and South America.

ON drugDELIVERY

2017/18 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
May 2017	Injectable Drug Delivery: Devices Focus	DEADLINE PASSED
June 2017	Connected Drug Delivery Systems	April 17th
July 2017	Novel Oral Delivery Systems	May 22nd
Sept 2017	Wearable Injectors	July 24th
Oct 2017	Prefilled Syringes	Aug 21st
Nov 2017	Pulmonary & Nasal Drug Delivery	Sept 25th
Jan 2018	Opthalmic Drug Delivery	Nov 20th
Feb 2018	Prefilled Syringes	Dec 22nd
Mar 2018	Skin Drug Delivery: Dermol, Transdermal Microneedles	Jan 20th
April 2018	Pulmonery & Nasal Drug Delivery	Feb 19th

INTEGRATED DESIGN SPACE TO DEVELOP BETTER DPI FORMULATIONS

Here, Filipa Maia, PhD, and Maria Palha, MSc, both Scientists at Hovione, report a study whose objective was to establish relationships between blend rheology, product performance and capsule filling process efficiency that would allow for the definition of an integrated design space, capable of recognising, and exploring, the trade-offs between the development (product angle) and manufacturing (process angle) stages.

INTRODUCTION

Successful formulation development for a dry powder inhaler (DPI) is strongly influenced by the choice of excipient grades and ratios between them, since the rheological behaviour of the powder mixture will have a significant impact on several aspects of the final product, such as content uniformity and stability of the formulation, overall aerodynamic performance and also on the robustness and effectiveness of the capsule filling process. Theory indicates that higher percentages of fine excipient particles in mixtures benefit the aerodynamic performance (e.g. Fine Particle Fraction, $FPF_{(5\mu m/ED)}$). However, the same approach may not benefit several downstream process steps, like the blending itself, from the perspective of yield, or the capsule filling step, from a rejection rate (RR) perspective.

> "An integrated design space analysis was derived where we demonstrated that a compromise between different parameters of aerodynamic performance and downstream process performance needs to be carefully considered."

In the same way, device performance, from an emitted dose (ED) or emitted mass (EM) perspective, can also be hindered, which could not necessarily be a problem if the $FPF_{(5\mu m/ED)}$ is indeed improved, but would be unnerving for a patient who observes a significant portion of the product remaining in the capsule. For example, a high percentage of fine lactose in a formulation may have a beneficial impact on the $FPF_{(5\mu m/ED)}$, but a negative impact on the rheology of the formulation and consequently on the downstream processes, causing a high RR during the automatic capsule filling steps, and making the rejected product (with fill weight of the capsules out of the acceptable range) so significant that the process is not economically viable.

METHODS

Eighteen placebo blends with different coarse and fine lactose grades and with different percentages of fines (0, 4, 10 and 16%) were prepared. Coarse lactose grades used were Respitose SV003 and SV010 from DFE Pharma (Goch, Germany); fine lactose grades were Lactohale 300 and Respitose ML006 from DFE Pharma, and Sorbolac 400 from Meggle Pharma (Wasserburg, Germany).

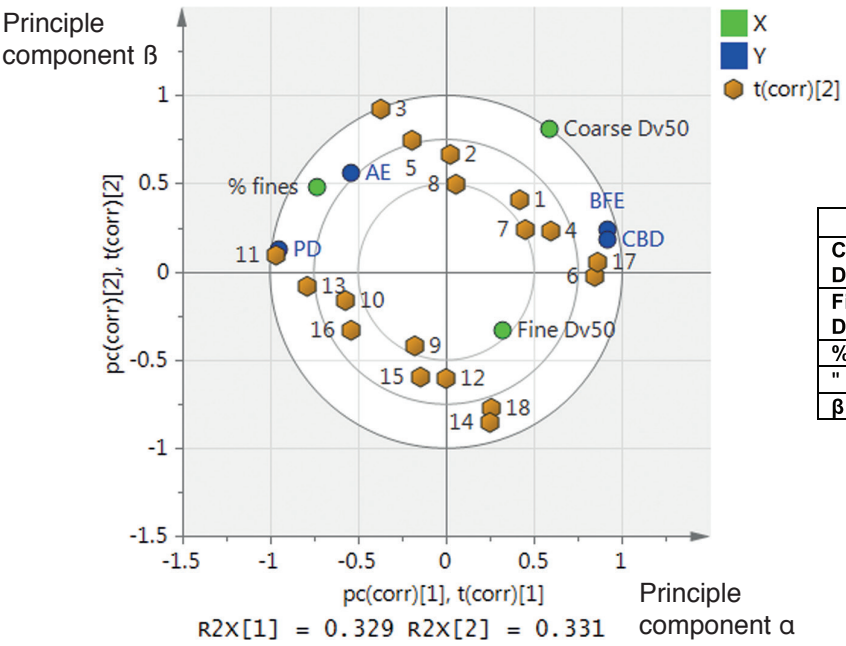
For each blend, both lactose grades (one coarse and one fine, total of 500 g) were screened through a 450 µm sieve and placed in a 2 L container. The mixture was then blended in a Turbula® T2F for 30 minutes at 46 rpm. The blends were left to rest for

Dr Filipa Maia
Scientist
T: +351 21982 9106
E: fmaia@hovione.com

Ms Maria Palha
Scientist
T: +351 21984 7559
E: mpalha@hovione.com

Hovione
Sete Casas
2674-506 Loures
Portugal

www.hovione.com



Blend	3	11	6	14
Coarse lactose Dv50 (! m)	105	60	105	60
Fine lactose Dv50 (! m)	5	5	17	17
% Fine lactose	16	16	4	4
"	-0.369	-0.968	0.846	0.247
β	0.925	0.0963	-0.0241	-0.853

Figure 1: Left: PLS regression biplot showing X variables, Y variables and observations for Model 1. Right: linking formulation composition with rheological properties (principal components α and β).

at least 24 hours to allow for relaxation of the powder. After that, all blends were analysed in an FT4 powder rheometer. Stability and variable flow rate, aeration and permeability standard tests were performed in triplicate. The obtained data were analysed using Umetrics SIMCA software (MKS Instruments, Malmö, Sweden).

Capsules were automatically filled using FlexaLab (MG2, Bologna, Italy) using two different dosators and targeting fill weights of 5 and 15 mg of powder, with acceptance limits of ±5% of the target fill weight. 1,000 capsules were filled for each set of conditions at a constant filling speed of 2,000 capsules per hour.

EM was determined using a DUSA with the equipment set to a pressure drop across the device equal to 4 kPa and an inspiratory volume of 4 L. The capsules filled with 5 mg and 15 mg were aerosolised using Hovione's proprietary inhaler PowdAir, with a flowrate of 39 L/min at 4 kPa. The gravimetric EM was calculated by considering the average of ten actuations, and the corresponding Relative Standard Deviation (RSD) was calculated. Multivariate statistical analysis of the data obtained was performed using SIMCA software.

Sixteen blends, with different coarse and fine lactose grades and with fine lactose amounts of 4%, 10% and 16%,

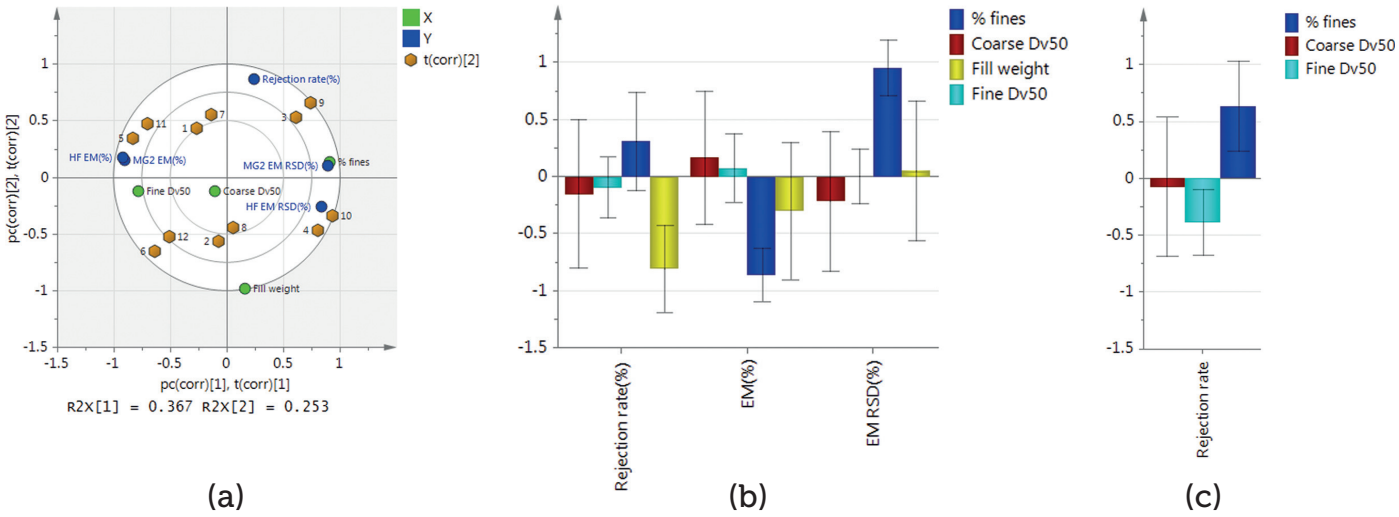


Figure 2: a) PLS results for the overall Model 2: biplot showing X variables, Y variables and observations, b) PLS results for the overall Model 2: co-efficients overview, showing the model coefficients and respective error for all the Y variables, and c) PLS model results: co-efficients overview for the rejection rate when the fill weight is not taken into account (Model 3).

were prepared. Each blend comprised a total amount of 200 g of two lactose grades, screened through a 450 µm sieve and placed in a 1 L container. The lactose mixtures were blended in a Turbula® T2F, followed by a four-step addition of the API that represented 1% w/w of the blend. Two different APIs were evaluated: fluticasone propionate (FP) and mometasone furoate (MF). The blends were left resting for at least 24 hours and afterwards evaluated for blend uniformity.

Capsules were hand filled with a target label claim of 125 µg of API with acceptance limits of ±5% of the target fill weight. The aerodynamic performance was assessed by Next Generation Impactor (NGI) (n=3 replicates) using PowdAir inhaler. The multivariate analysis was conducted, once again, using SIMCA software.

The creation of individual design spaces for rheology parameters *versus* ED, $FPF_{(5\mu m/ED)}$ and RR and of the combination of the three design spaces was performed using Mathematica 7 from Wolfram (Hanborough, UK).

RESULTS AND DISCUSSION

The three formulation parameters of particle size of the coarse lactose, particle size of the fine lactose and percentage of the fine lactose grade were correlated, using a partial least squares (PLS) regression with two principle components, with the rheological behaviour of the blends [Aeration Energy (AE), Basic Flowability Energy (BFE), Pressure Drop (PD) across the powder bed and Condensed Bulk Density (CBD)]. This is considered Model 1.

In Figure 1, the biplot with all X variables (inputs = formulation parameters), Y variables (outputs = rheology parameters) and observations is presented. The axes of the biplot represent the principal components. The points of the biplot represent the scores of the observations and variables on the principal components. The results for the global model demonstrate that the experimental data is well fitted, with an R^2 of 0.83 and a χ^2 of 0.75. From the regression performed, it is possible to capture the relationships between

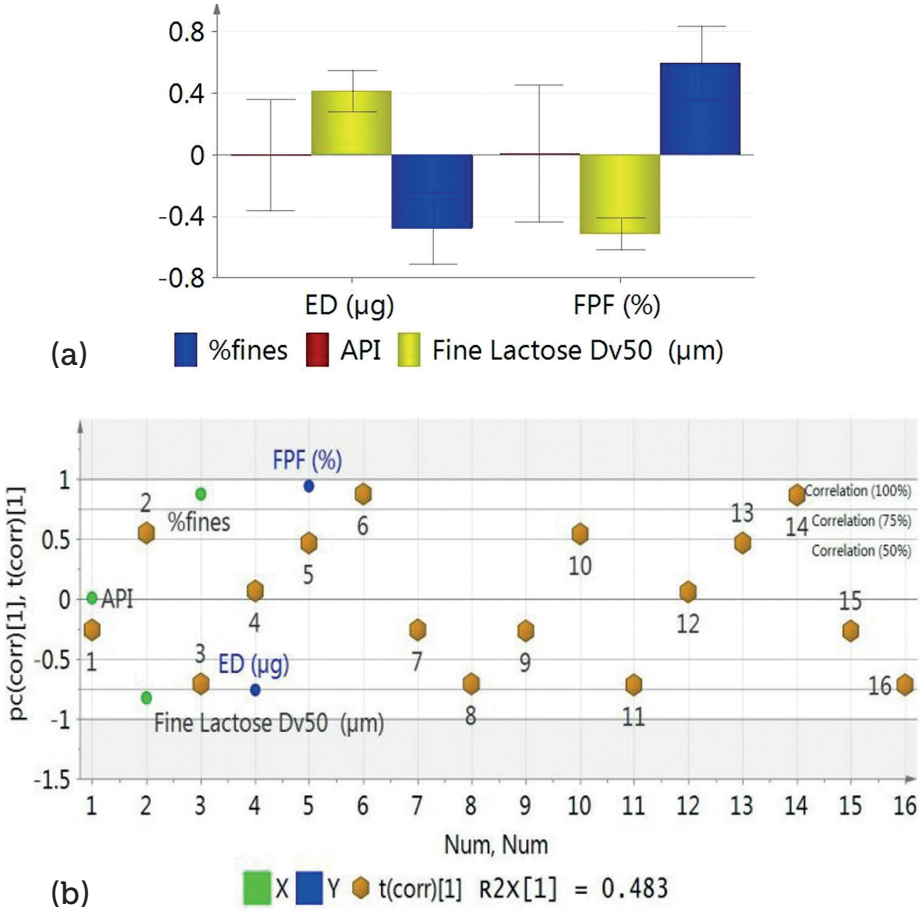


Figure 3: PLS results for Model 4: a) model co-efficients with corresponding error bars), and b) biplot showing X variables, Y variables and observations.

formulation parameters (blend composition) and rheology parameters (AE, BFE, PD, CBD) via two principal components (α and β), thus reduce the number of fundamental variables and facilitating subsequent mathematical treatment. The table presented in Figure 1 illustrates how these transformations work in practice for some representative blends, selected due to their distinctive nature.

A second model (Model 2) was developed considering the blends composition as input variables and both capsule filling rejection rate and gravimetric EM results as output variables. The results for the global model demonstrate that the entire set of experimental data is well fitted, with an R^2 of 0.82 and a χ^2 of 0.65. In terms of the individual output variables, all local models also showed good fits with R^2 values above 0.8 and χ^2 values above 0.5, thus validating the hypothesis that downstream processes (e.g. capsule filling) and inhaler performance correlate strongly to the nature of the carrier blends employed.

The biplot of the overall model is shown in Figure 2a, while Figure 2b shows the co-efficients, and corresponding error bars, for each of the individual output variables. In the biplot of the model, output variables perpendicular to input variables when considering the origin as a reference point show no correlation. On the other hand, output and input variables close to each other or in opposite locations of the plot are highly correlated. From the observation of these plots it is possible to conclude that the major contributor to capsule filling performance is the selected fill weight of the capsule: a high fill weight of 15 mg will reduce the rejection rate to practically zero, given its impact on the admissible (absolute) filling tolerance. Since with a 15 mg fill weight no relationship could be

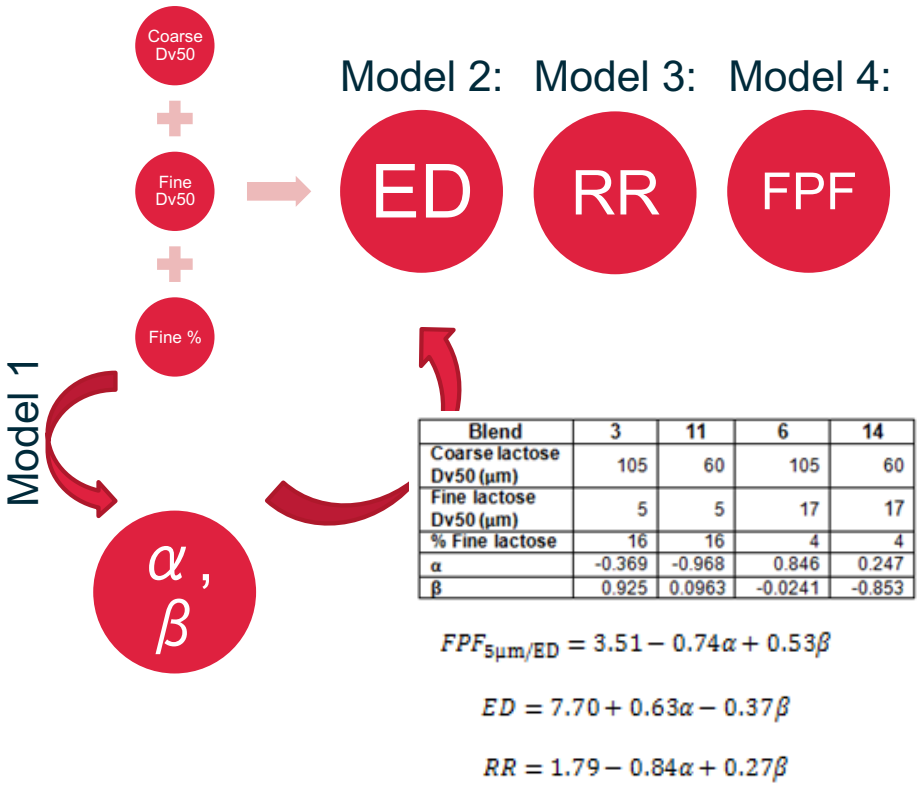


Figure 4: Schematic of the different statistical models applied to generate the design space and derived models for ED, $FPF_{(5\mu m/ED)}$ and RR as a function of α and β, via treatment of the experimental data.

observed between the rejection rate and the blends composition/rheology, a similar regression using only the 5 mg fill weight results was performed (Model 3); the results are depicted in Figure 2c where it can be observed that the percentage of fines and the particle size of the fine lactose grade are the major contributors to the rejection rate, while in opposing directions.

Finally, a statistical model was applied to the blends with both APIs (Model 4). This model presents a R^2 of 0.57 and χ^2 of 0.49 for the ED, and R^2 of 0.89 and χ^2 of 0.83 for the $FPF_{(5\mu m/ED)}$. These results indicate that this model has a high predictive power for the $FPF_{(5\mu m/ED)}$ but not as significantly for the ED. The model co-efficients and the biplot for both variables are presented in Figures 3a and 3b. It was observed that the API has no effect on either the ED or the $FPF_{(5\mu m/ED)}$. On the other hand, the Dv50 of the fine lactose has a positive contribution to the ED and a negative one to the $FPF_{(5\mu m/ED)}$. The percentage of fine lactose has the opposite effect on both variables. These results were expected since higher percentages and lower PSDs of fine lactose are associated with improved $FPF_{(5\mu m/ED)}$ but have a negative impact on the ED.

From the previous Models, as depicted in Figure 4, it was possible to derive a set of equations (presented in their scaled and centred version), which allow

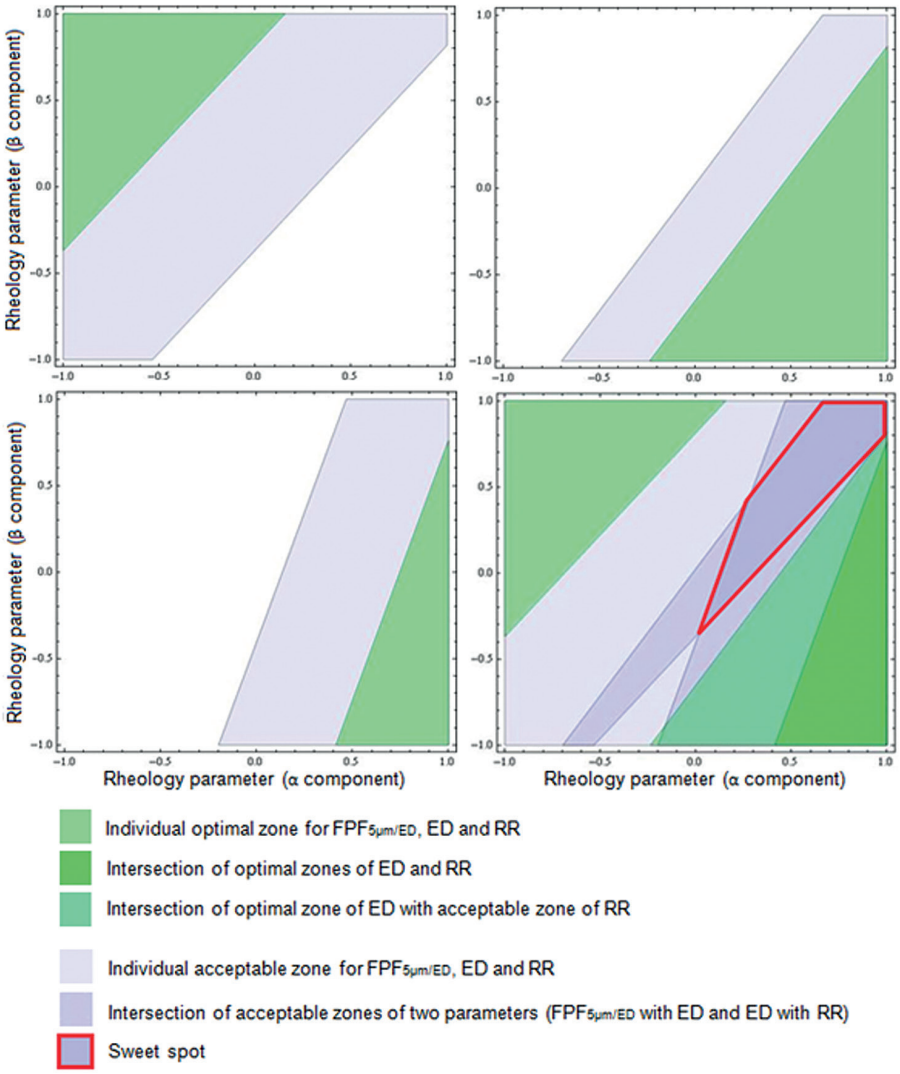


Figure 5: Design spaces regarding (a) $FPF_{(5\mu m/ED)}$, (b) ED, and (c) RR versus rheology parameters; and d) integrated design space.

the projection of the design spaces for $FPF_{(5\mu m/ED)}$, ED and RR, in function of α and β. The design spaces for each individual output variable are depicted in Figures 5a, b and c.

For the development of the design space regarding $FPF_{(5\mu m/ED)}$ *versus* rheology parameters, the optimal limit for $FPF_{(5\mu m/ED)}$ was ≥35% and the acceptable limit of $FPF_{(5\mu m/ED)}$ was ≥25%. For the development of the design space regarding ED versus rheology parameters, the optimal limit for ED was ≥80% (that corresponds to 100 µg of API) and the acceptable limit of ED was ≥75% (that corresponds to 94 µg of API), in order to comply with the US Pharmacopeia (USP) criteria for delivered dose uniformity, as defined in chapter <601>. For the development of the design space regarding RR *versus* rheology parameters, the optimal limit for RR was ≤10% and the acceptable limit of RR was ≤20%.

The integrated design space combining the three factors is presented in Figure 5d. Ideally, the sweet spot would be the area where the three optimal zones would intersect. However, from the figure presented above it can be observed that the optimal region for the $FPF_{(5\mu m/ED)}$ never intercepts the other two optimal/acceptable regions, and therefore the sweet spot obtained considers only the acceptable zones for all three parameters.

This result once again suggests that maximising the formulation's aerodynamic performance (i.e. by increasing the % of fine excipients) has a deleterious effect on both the capsule filling performance and also on the device performance (in an ED perspective). These two parameters are however correlated, as formulations that favour capsule filling performance also favour the ED.

CONCLUSION

Several conclusions can be drawn from the work performed including that, firstly, the rheology properties of lactose blends played an important role during the prediction of capsule filling and device performance, with high percentages of fine lactose and finer lactose grades yielding higher RR and lower EM. Secondly, the grade of fine lactose and the percentage of fine lactose also contribute to the aerodynamic performance of the formulations, since higher percentages and lower PSDs of fine lactose are typically associated with improved $FPF_{(5\mu m/ED)}$ and deleterious ED.

From these conclusions, an integrated design space analysis was derived where we demonstrated that a compromise between different parameters of aerodynamic performance and downstream process performance needs to be carefully considered, since formulations with maximum $FPF_{(5\mu m/ED)}$ may present poor ED results and higher rejection rates during capsule filling. Evaluating trade-offs is, therefore, of critical importance.

ABOUT THE AUTHORS

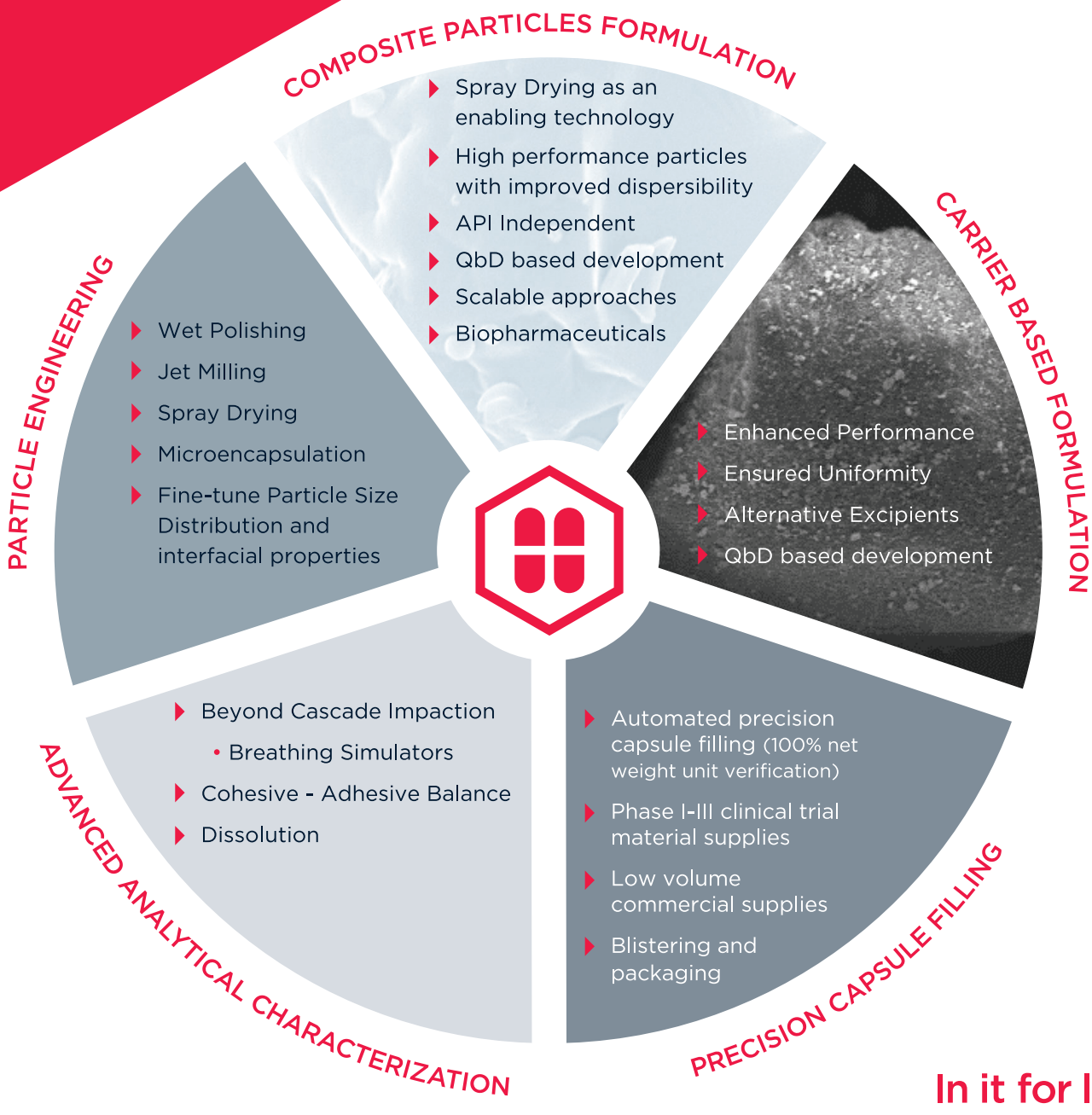
Filipa Maia holds a PhD in Chemical and Biological Engineering from the University of Porto. She joined the R&D Drug Product Development group at Hovione in 2013, where she has been working on particle design and formulation development projects, with particular focus on the area of Inhalation drug products. At Hovione, she is also scientific advisor for a PhD program focused on the development of *in vitro* dissolution techniques for evaluation of inhalation products.

Maria Palha has a degree in Pharmaceutical Sciences from the University of Porto. She has a strong expertise in development of particle design procedures and formulation development concerned with dry powder inhalers. Currently she works as a scientist at the Inhalation & Biopharmaceuticals group within R&D Drug Product Development at Hovione.

Hovione

Integrated Science for Inhalation

Full range of inhalation development and manufacturing services from pre-clinical to small commercial scales.



In it for life

INNOVATIVE NASAL APPLICATION REQUIRES INNOVATIVE FILLING TECHNOLOGY

By Karlheinz Seyfang, PhD

The majority of drugs administered nasally are used for the treatment of colds. Formulations such as drops, sprays, dosage sprays or ointments and gels contain locally active substances such as vasoconstrictors to reduce swelling of the nasal mucosa, or immunologically effective substances.

However, systemic resorption of active ingredients can also occur via the very well perfused nasal mucosa. In comparison to oral administration forms, this method, which has so far been little used, offers the same or even greater advantages for some molecules as do transdermal, pulmonary or parenteral applications: the first-pass metabolism during passage through the liver is avoided and the substances evade chemical or enzymatic degradation in the gastrointestinal tract.

Furthermore, it is a non-invasive treatment, which is now also used in emergency medicine due to its rapid onset of effect;[1] and is extremely advantageous for patients with a syringe phobia, and for children and the elderly. Many nasal applications are used as off-label systemic therapy. Examples of approved nasal applications are fentanyl (pain), desmopressin (enuresis nocturna), calcitonin (osteoporosis) and sumatriptan (migraine).

The nose, however, offers yet another highly interesting approach for the treatment of certain diseases, which can be categorised under the catchphrase "nose to brain delivery". Numerous animal models have shown that a variety of nasally applied molecules can pass directly into the brain, bypassing the blood-brain barrier (BBB). This alone is attractive because only about 2% of the drug molecules can overcome this barrier when delivered via systemic circulation.[2]

Targeted nasal administration of substances that are effective in the brain is the therapeutic area in which M&P Pharma (Emmetten, Switzerland) has been specialising in. As an example, M&P succeeded in getting dopamine directly into the brain with its nasal formulation, which allows a rapid and physiological replenishment of this substance to treat Parkinson's disease.[3]

GEL CARRIER & APPLCIATOR

As a carrier for active ingredients, M&P Pharma developed a locally well-tolerated thixotropic gel,[4] combining several positive properties: it adheres well to the nasal mucosa and is therefore not subject to immediate mucociliary self-cleaning, as is common with simple sprays and solutions. Due to its excellent spreading properties, the gel covers a large area after application and thus also reaches the areas of the nose which are important for resorption. The formulation is odourless and has proven itself as a carrier for numerous different active substances.

As with pulmonary therapy, the synergy between formulation and proper applicator (device) is also crucial for nasal application forms. The newly developed disposable applicator enables the discrete and precise administration of the formulation without risking the contamination of the drug or applicator tip, as is possible with multi-dose containers. For this reason, preservation of the formulation is not necessary. The chamber is shaped so that the gel can be dispensed reproducibly and almost completely. Neither a priming nor a particular inhalation technique is required, nor do patients have to position themselves a certain way. The applicator consists of an extrudable polymer. As with other plastics there is, of course, the risk that certain drugs would migrate into the plastic matrix or be adsorbed on the surface. Using the example of the steroid hormone testosterone, it could be shown that this effect does not occur when an inorganic additive in the form of titanium dioxide is added[5] to the plastic material (LDPE).

The first nasal oleogel product to be produced in this innovative dosage form consequently is a testosterone formulation for men. In a comparative study, M&P

Dr Karlheinz Seyfang
Principal Consultant,
Pharmaceutical Technology
E: karlheinz.seyfang@hoefliger.de

Harro Höfliger Verpackungsmaschinen GmbH
Helmholtzstr. 4,
71573 Allmersbach im Tal

www.hoefliger.de

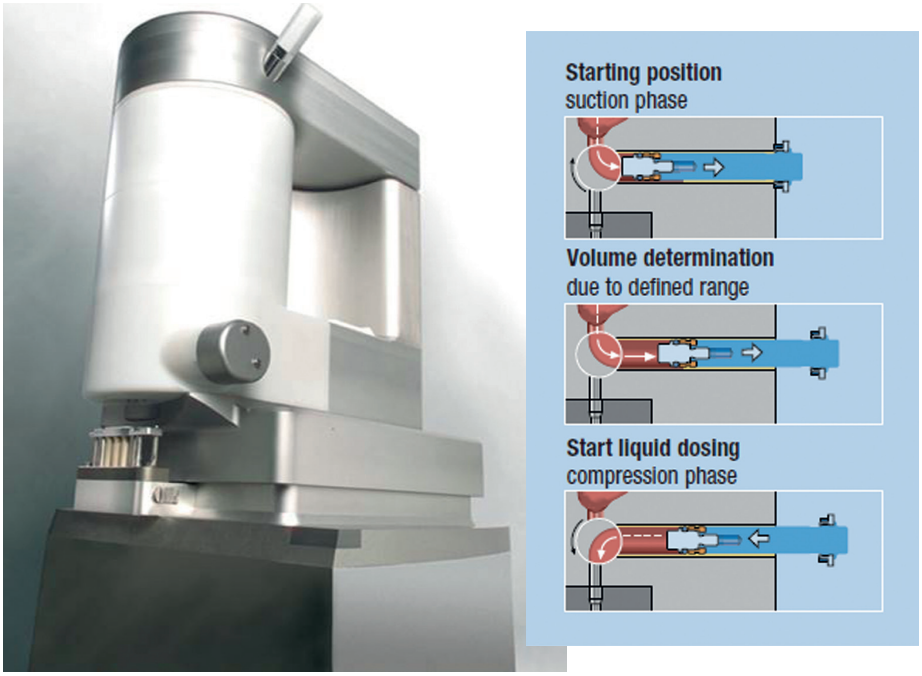


Figure 1: Structure and functional principle of rotary valve pump.

could show that nasally administered testosterone only has a bioavailability of 75% in serum compared with intravenous administration, however, it leads to a higher concentration of the active ingredient in the brain.[6] In the following, the project procedures will be described from initial filling tests to the concept and construction of a production machine.

THE DOSING METHOD

One of the first project tasks was to find a suitable dosing system for the thixotropic gel formulation. The viscosity range was defined as 3,000-10,000 cP, the dosing volumes being in the range of approximately 100-150 µL. Dosing accuracy of the individual doses during filling should correspond to a maximum relative standard deviation in mass of 3%. Since an increase in the processing temperature within the acceptable range does not reduce the gel's viscosity, filling took place at room temperature.

Several different dosing systems were available for integration into the filling system: time pressure dosing system (if necessary with a flow rate measuring device), peristaltic pumps, rotary piston pumps and rotary valve pumps for the liquid filling of hard capsules.

The decision was made in favour of the rotary valve pump (Figure 1) which combines several benefits: the dosing range required for hard capsules coincides with the fill quantities of the nasal applicator. The system has already been designed for highly viscous solutions and suspensions. It has a powerful adjustable agitator to reduce the viscosity of the thixotropic formulation during the filling operation. In order to minimise air gaps, filling of the material container is performed with an immersion tube below surface level. In addition, support pressure can be applied to the container in order to facilitate dosing and to improve dosing accuracy further. Furthermore, negative pressure can be applied at the beginning of the process in order to de-gas the products prior to filling.

The deciding factor for the final selection was the simple possibility to operate several fill points in parallel in a very small space, as is already the case with the capsule filling machines. There, 12 fill needles are used, spaced 15 mm apart. That way, scaling up of the system by multiplying the fill points can be easily accomplished.

MONODOSE NASAL APPLICATOR

The next task was to develop the design for the new applicators. Their form consists of a bottom part with a depression to accommodate the gel and the nozzle with tamper-evident closure, and a top part with the press point for squeezing out the gel. In the first version, both halves were connected like a butterfly using a hinge and had a mechanical pre-closure at the opposite side in order to compensate for the hinge's reset force during closing in the first step.

However, while testing the pilot machine, it turned out that the butterfly system was not suited for a fast-running production machine. In order to utilise the machine's optimal capacity, the butterfly device had to be changed into two individual parts. This is why the present applicator is manufactured separately in two parts, which are fed to the production machine from two stations (Figure 2). The pilot machine was fed manually whereas in the production machine, vibrating spiral conveyors are used.

THE SEALING PROCEDURE

Theoretically, the two low density polyethylene (LDPE) applicator halves can be closed or sealed in different ways. Two different methods, thermal sealing and ultrasonic welding, were examined in a preliminary study. The thermal sealing method turned out to be disadvantageous right from the beginning since the parts tended to stick to the sealing tool and generally a heating of the fill material should be avoided if at all possible. Better results were achieved by ultrasonic welding, where the heating effect was limited to the sealed seam and initial tests resulted in tight packages.

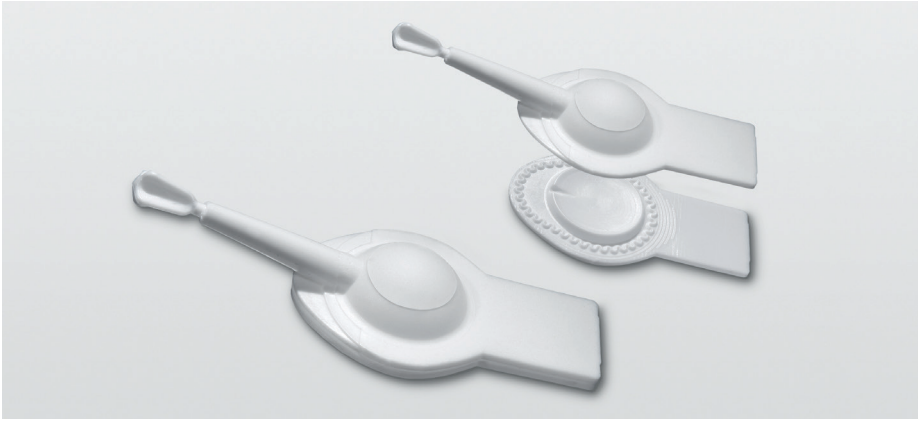


Figure 2: Nasal applicator in the final version .

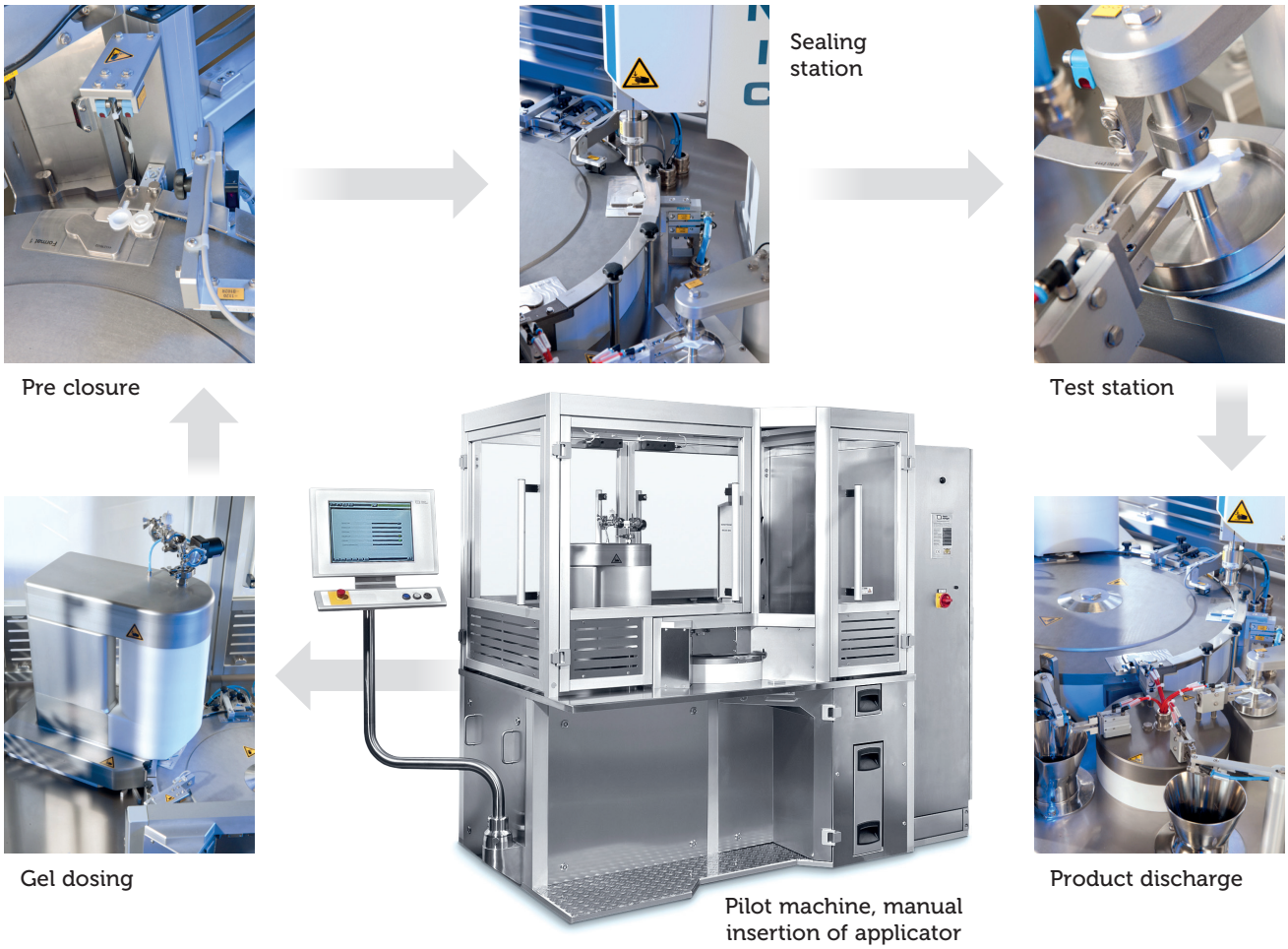


Figure 3: Pilot machine for the manufacture of 20 applicators / min.

For filling as well as closing the applicator, the exact positioning of the still open blank is required, but the application nozzle is in the way. During the subsequent closing operation, in which the top part is sealed onto the bottom part containing the nozzle, counter-pressure must be applied to the sealing edge of the bottom part over the entire sealing surface. Only then an overall hermetically tight sealing can be ensured.

Since part of the sealing edge is obscured by the application nozzle, it is impossible to apply counter-pressure in this particular area. This problem could be solved by equipping the sealing station with a swivelling support element.[7]

After finishing the initial tests, the concept for a pilot machine for the manufacture of clinical samples with an output of 20 parts/minute was adopted.

THE PILOT MACHINE

It was one of the central requirements of the concept that the core processes, including filling and sealing of the applicators, should be identical to those on a later production line. This is why we made sure that scaling-up of these stations was possible by simply

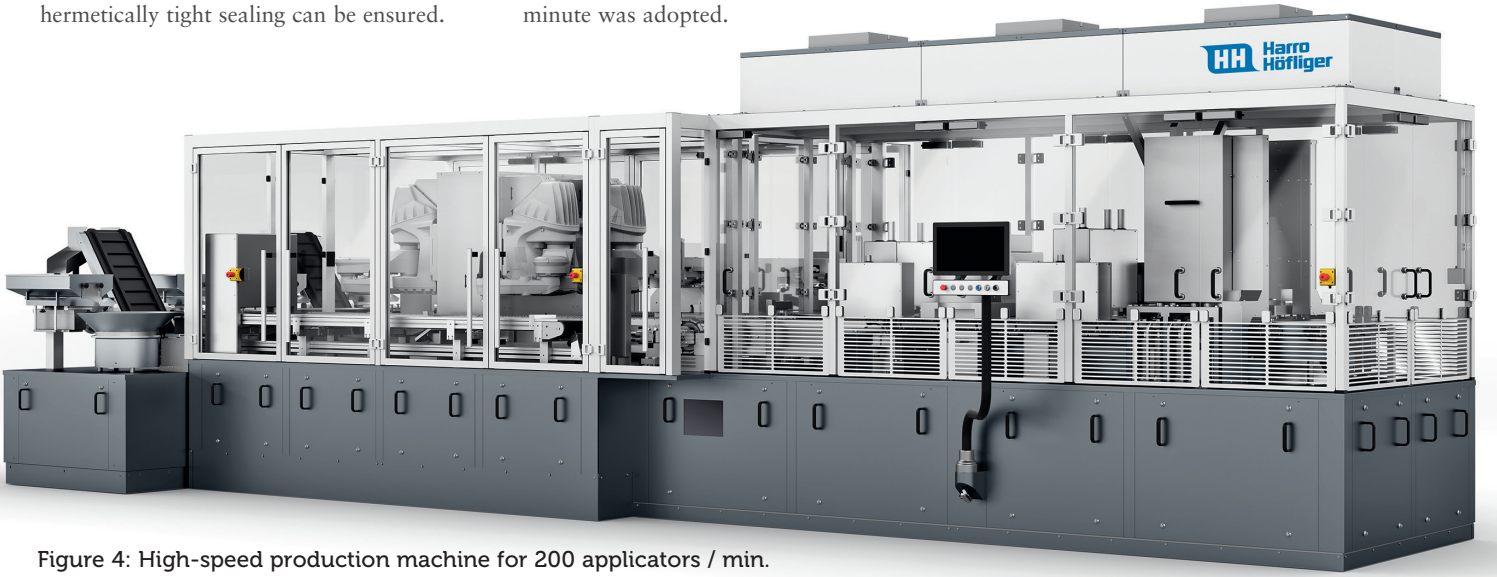


Figure 4: High-speed production machine for 200 applicators / min.

multiplying the elements. This resulted in the following design layout of the pilot machine (Figure 3).

The process starts with the manual insertion of the empty applicator into the receptacle of the rotary indexing table. The empty device then advances to the rotary valve pump where the gel is dosed and filled. In the subsequent pre-closing station, the top part is folded over onto the bottom part and fastened with the clip closure. The filled pre-closed applicators then advance to the ultrasonic welding station. A subsequent test station was planned to check the applicator for tightness before being ejected into the pass-part or fail-part channel at the last station.

From operating this pilot machine, valuable expertise about the production process could be gathered which was incorporated into the design of the production machine. The most important improvement was related to the welding process after filling of the applicator. Initially, a simple ridge was placed around the gel-filled depression in the area of the sealed seam, serving as a tight connection to the top part. In a series of tests, it was found that a change in design could focus ultrasonic energy and make sure that heating can only occur in the area of the sealed seam.

Another finding relates to the function of the test station. Originally it was planned to apply a defined normal force to the filled applicators, and to detect the possible lowering of the piston in any leaking packages by means of a displacement sensor. Unfortunately, this method was not suited for control purposes since the defects (pin holes) that were specifically created for test purposes, were obviously covered and closed by the gel mass and thus no measurable lowering occurred. In order to achieve correct positioning, the sonotrodes on the production machine are therefore guided on servo axes and their power consumption as well as the sealing time are monitored. The process window for tight sealing will be defined during process validation.

The pilot machine has a capacity of 20 parts/minute and has been used successfully for the manufacture of batches for stability tests and clinical trials. The fundamental production steps are identical to the production line, which was equipped with eight-fold tools.

THE PRODUCTION MACHINE

The centre of the production machine consists of an oval turret, which conveys the workpiece carriers with the applicators to the processing stations. In the infeed section, the narrow side of the oval turret adjoins the two conveyor belts for the separate infeed of the top and bottom parts. Ventilation of the machine is achieved via filter fan units (FFU) with H14 filters.

The parts are fed to the belts from two vibrating spiral conveyors with a capacity of 150 parts/minute each. One camera each detects the parts' positions on the belts and actuates two robots per belt, which take the parts, turn them into the correct position and deposit them again in a controlled manner with a capacity of 110 parts/minute. Mismatched parts are returned. This infeed section enables a production of 200 parts/minute.

After having been loaded with eight top and bottom parts, the workpiece carriers pass through the processing stations: first, the bottom parts are filled with gel at the dosing station. In the next station, the eight top parts are positioned in place. Then the applicators are welded together in two sealing stations. In order to keep the necessary minimum distance between the sonotrodes, this is done in two steps. After that, the completed good parts are transferred to the packaging line. Figure 4 shows the machine prior to dispatch to the customer.

OUTLOOK

In close co-operation between the pharmaceutical company and the machine manufacturer, an attractive comprehensive package consisting of formulation, applicator, process knowledge and production machines was created, which can be used for the manufacture of nasal dosage forms.

ACKNOWLEDGEMENT

I would like to thank Dr Claudia Mattern, M&P Pharma AG, and Mr Stefan Bernsau, Harro Höfliger, for their support in the compilation of this publication.

REFERENCES

1 *https://www.klinikum-nuernberg.de/DE/ueber_uns/Fachabteilungen_KN/kliniken/medizin1/fachinformationen/AZ_Ordner_versteckt/Intranasale_Applikation_VsJan2012.pdf (last accessed December 15, 2016)*

2 *Djupesland PG, Messina JC, Mahmoud RA, "The nasal approach to delivering treatment for brain diseases", Therapeutic Delivery, 2014, Vol 5(6), pp 709-733.*

3 *de Souza Silva MA, Topic B, Huston JP, Mattern C, "Intranasal dopamine application increases dopaminergic activity in the neostriatum and nucleus accumbens and enhances motor activity in the open field". Synapse, 2008, Mar, Vol 62(3), pp 176-84.*

4 *Mattern C, "Controlled release delivery system for nasal application of neurotransmitters." EP 2018825 (2011).*

5 *Mattern C, Use of container made of plastic material containing an inorganic additive, EP1674399, 2006.*

6 *Banks WA, Morley JE, Niehoff ML, Mattern C, "Delivery of testosterone to the brain by intranasal administration: comparison to intravenous testosterone". J Drug Target, 2009, Feb 17 (2), pp 91-7.*

7 *Joos T et al, "Filling and closing device and method for filling and closing an agent applicator". EP2626304 (2014).*

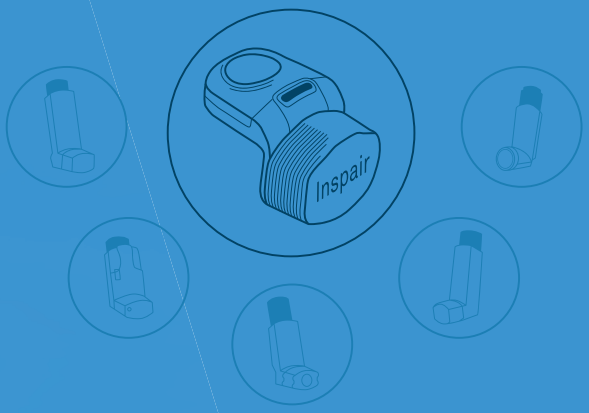
ABOUT THE AUTHOR

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

BIOCORP

Ready to boost your inhaler ?

Inspair, sensing technology compatible with inhalers



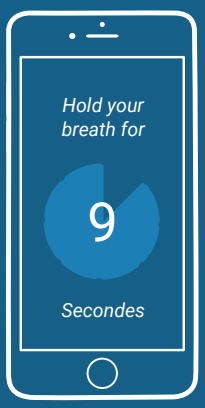
01 Sensing technology

Provides unique insights on inhaled therapies

- Hand-breath coordination
- Inhalation depth & speed
- Doses Inhaled

02 User friendly interface

Gives useful feed back to improve inhalation technique



03 Secured platform

Ensures health data storage and sharing with high protection standards

Patients Caregivers Physicians

info@biocorp.fr
biocorpsys.com