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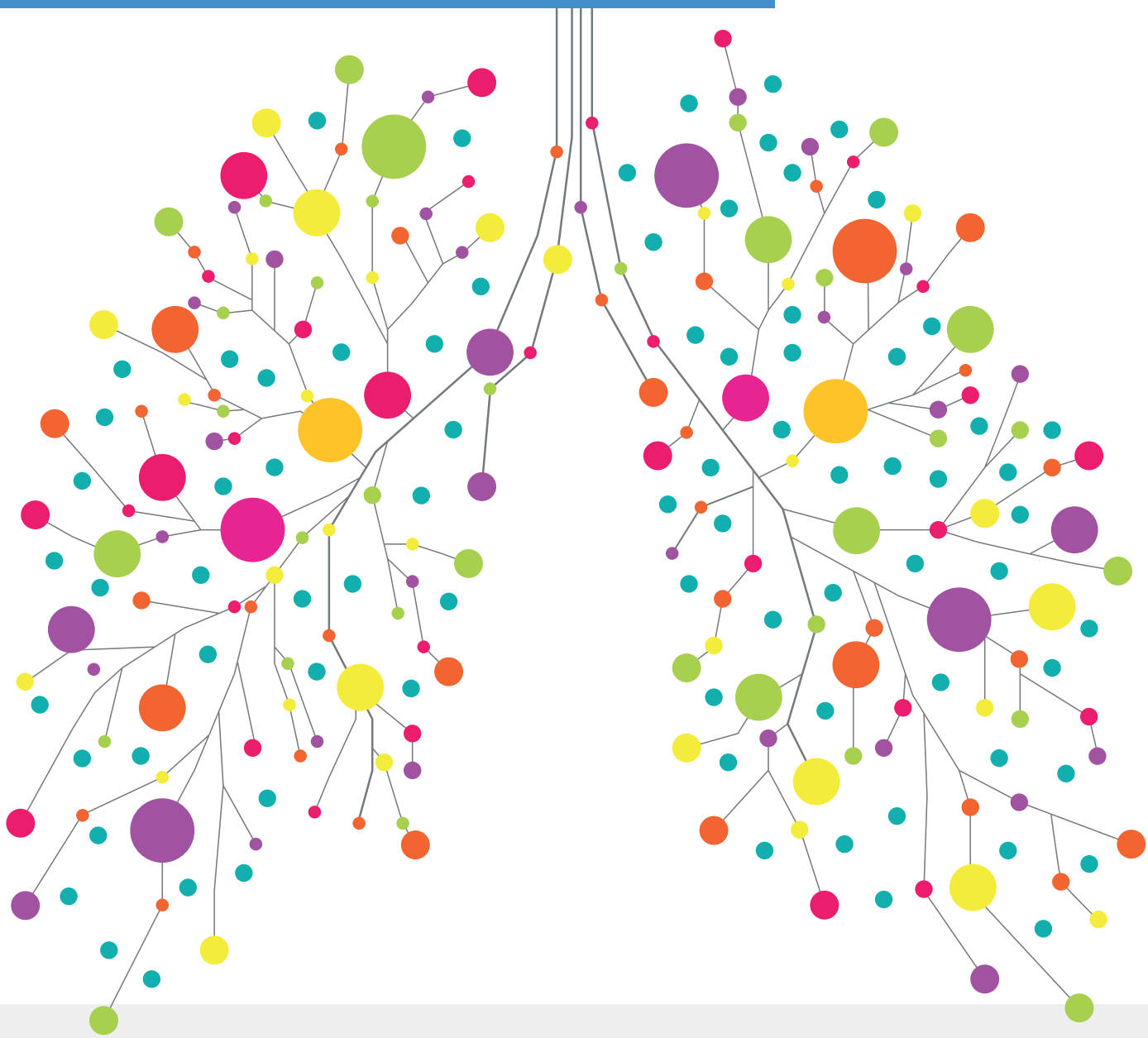

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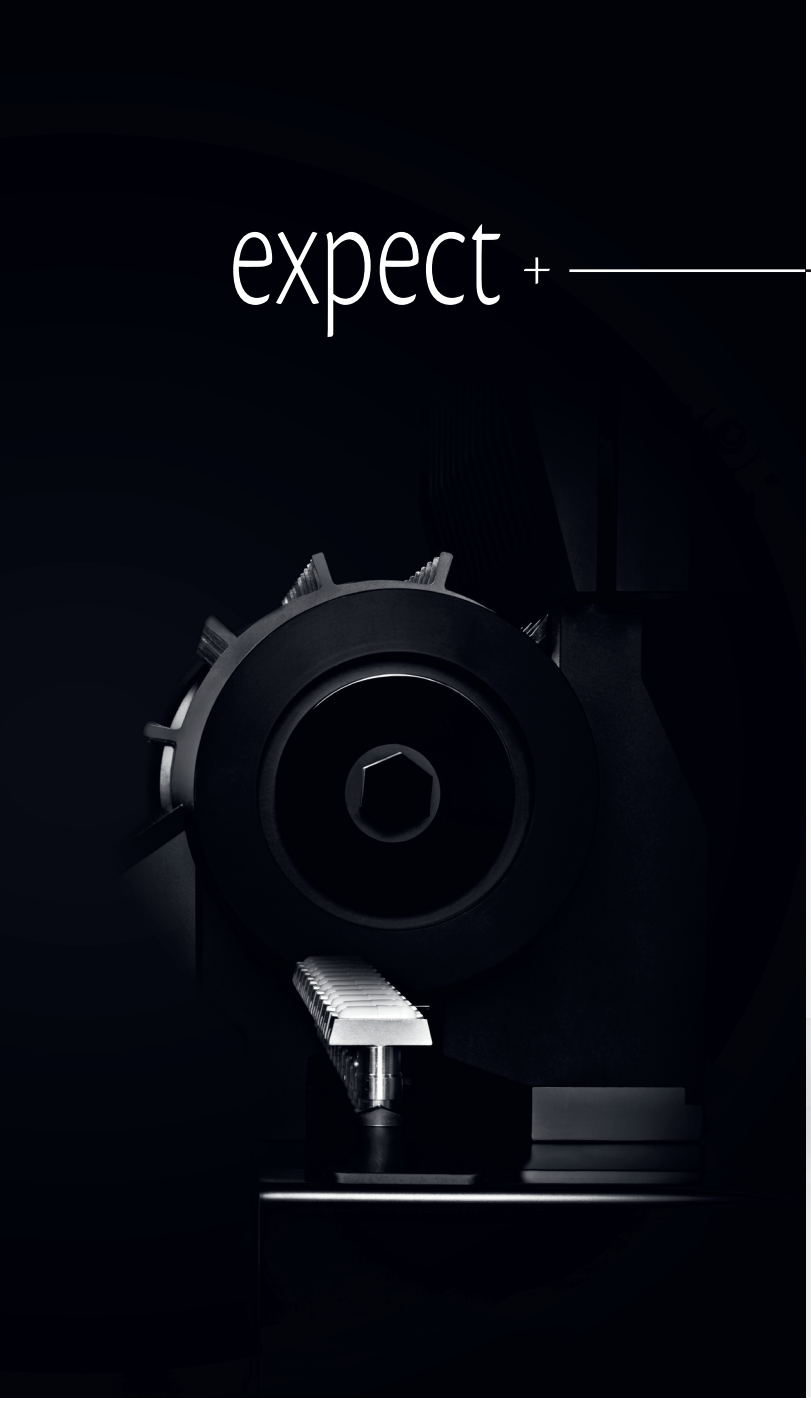

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PULMONARY & NASAL DELIVERY

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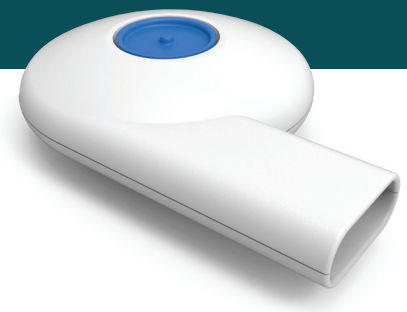

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IS THERE A FUTURE FOR THE RESPIRATORY DELIVERY OF BIOLOGICS?

In this article, Igor Gonda, PhD, Founder and Chief Executive Officer of Respidex, covers the field of nasal and pulmonary delivery of biologics, considers past failures and successes, and proposes answers to the challenges faced, from biological, biopharmaceutical and commercial standpoints.

The pulmonary and nasal delivery of biologics is intuitively attractive; it is an easy, non-invasive administration route with readily targetable portals – the mouth and the nostrils. On top of that, there is a lot of existing expertise in delivery of drugs both to the lung and to the nose for the treatment of diseases in those parts of the body, such as asthma, COPD, pulmonary arterial hypertension, cystic fibrosis, rhinitis and allergies. These types of therapies continue to attract investment and are growing in use (Figure 1).[1,2] However, current sales are almost entirely for small molecules. So why is it that there are so few biologics on the market delivered by these routes of administration, even for the treatment of respiratory diseases? How could it change?

> "After the heyday of pulmonary and nasal delivery of macromolecules in the 1990s, including proteins, peptides and gene therapies, it is quite remarkable how little progress has been made."

After the heyday of pulmonary and nasal delivery of macromolecules in the 1990s, including proteins, peptides and gene therapies,[3] it is quite remarkable how little progress has been made and how devastating the attrition rate has been for the vast majority of these products before and, in a few cases, after they reached the market.

This article will discuss some of the key factors contributing to the current lack of enthusiasm in this field and provide some thoughts as to what can be done to bring this very promising source of new

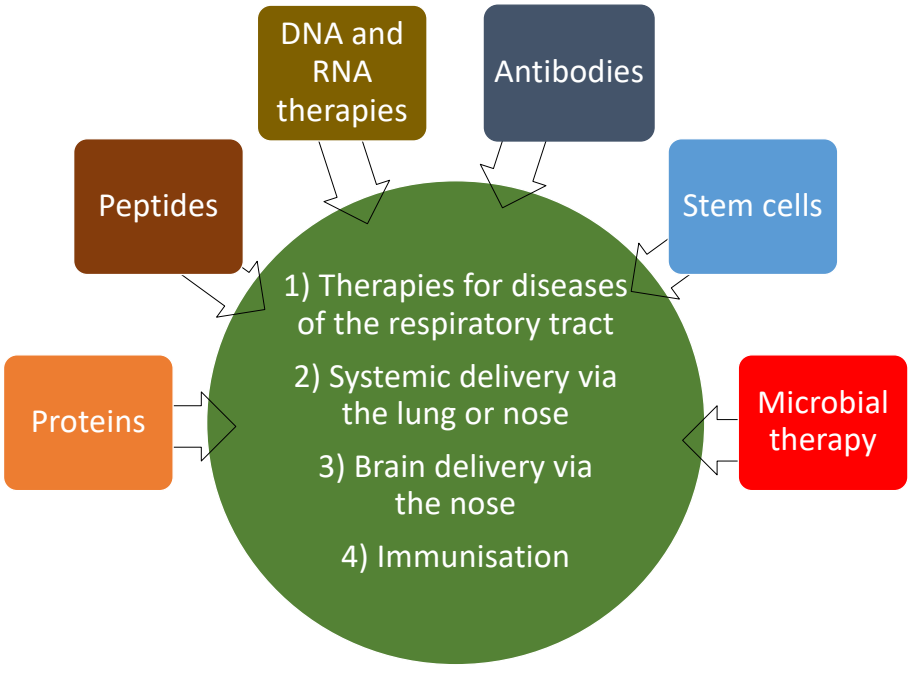

Figure 1: Potential for nasal and pulmonary delivery of biologics.

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therapeutics back on the stage to lead to attractive prophylaxis and treatment for a number of serious diseases.

BIOLOGICAL BARRIERS TO EFFECTIVE RESPIRATORY DELIVERY

The respiratory tract is the only part of the body which must be in continuous contact with the environment for us to survive. It is therefore not surprising that, in order for it to continue functioning over the course of many years, it has a multitude of protective mechanisms that act as barriers to entry of foreign materials, as well as other mechanisms that act to remove such materials should they penetrate beyond these barriers. Understanding the nature of these mechanisms and our ability to overcome them, or use them to our advantage, is therefore important.

Barriers Prior to Deposition

It goes almost without saying that orally or nasally inhaled substances cannot reach those parts of the respiratory tract that are not ventilated. This is particularly important to consider in the context of obstructions of the respiratory tract, be it "stuffy nose", or the presence of permanent or reversible airway obstructions in asthma and COPD. Combinations of drug, such as decongestants, bronchodilators, mucolytics, and non-drug therapies, such as physiotherapy, prior to biologic delivery, are examples of how some of these reversible obstacles can be overcome.

The human nasopharynx and oropharynx are especially efficient at filtering out large "non-respirable" particles. In the case of the nasopharynx, no matter whether the purpose is the delivery of drugs to the nose for local therapeutic treatment, or via the nose into the systemic circulation or the brain, this highly efficient filter is the desired "barrier" and the target for the therapy.

> "For bolus aerosols, placing of the bolus at the beginning of a slow inspiration and then chasing it with clean air provides the maximum probability of deposition in the distal airways and the alveoli."

Delivering large particles, or jets of fluid at high velocities, will maximise nasal deposition – and minimise the possibility of undesirable passage to the airways and beyond. However, the nose is anatomically complex and such a simplistic approach is far from able to achieve optimum targeting of various parts of the nose that may have different functions of therapeutic interest.[4]

A considerable number of studies have been done on preferential targeting to different parts of the nose.[5,6] For example, delivery of substances via the olfactory nerve into the brain requires delivery to the posterior upper nasal cavity.[7] Furthermore, it is not always clear what roles different parts of the nasal cavity have in terms of the desirable versus undesirable biological effects. Vaccination via the nose is likely to require targeting the dendritic cells, but their location appears to be mobile and also dependent on the disease and its treatment.[8]

Deposition of orally inhaled therapeutics in the mouth is invariably wasteful, except in relatively rare situations when the oral cavity is the therapeutic target. Because of the complex and dynamic anatomy of oropharynx, deposition there is also the most likely cause of intra- and inter-individual variability in lung delivery. Therefore, minimising deposition in the oropharynx is important for drugs where efficiency and precision of delivery matter. Depending on their aerodynamic properties, particles and droplets that penetrate these initial obstacles will deposit by impaction, interception (in the case of elongated particles), sedimentation and diffusion. If the residence time is insufficient for diffusion and sedimentation of the smallest particles to the walls of the respiratory tract, then they may be exhaled.

There has been extensive research on preferential targeting to different parts of respiratory tract. The key control parameters are the aerodynamic size distribution of the particles carrying the drug, the inspiratory flow rate and inspired volume. For bolus aerosols, placing of the bolus at the beginning of a slow inspiration and then chasing it with clean air provides the maximum probability of deposition in the distal airways and the alveoli. This very large absorptive surface area is ideal for systemic absorption of macromolecules, provided the carrier particles have small enough aerodynamic diameters (<3 µm) to escape inertial deposition in the oropharynx and large airways. Adequate time (approximately 10 s) is required for breath-holding to maximise the deposition of these particles by sedimentation and diffusion. Alternatively, hygroscopic growth of particles was proposed as a mechanism to inhale initially small particles that will then grow by absorbing moisture to maximise their deposition in distal parts of the respiratory tract.[9]

Post-deposition Mechanisms

The complexity of delivering therapeutics to the nose is due both to its anatomy and multiple mechanisms affecting the transport of drugs through it. Even the same anatomical region may handle particles deposited in adjacent places differently.[10]

In the anterior part of the nasal cavity, the material may drop out from the nose, it may be stationary for a prolonged period or it may be translocated into the posterior cavity and ultimately be swallowed. Depending on the properties of the therapeutic, parallel processes of absorption and metabolism may be taking place as well.[11] For large molecules, absorption from the nose is relatively slow while the aforementioned mechanisms are quite fast. Therefore, to maximise the therapeutic activity in the nose, or to achieve efficient absorption into the systemic circulation, the means to increase the residence time in the nose and to prevent unproductive elimination needs to be proactively sought. Most efforts in this area have involved the use of bio-adhesive drug carriers.[10,12]

The nasal cavity has extensive intra- and extra-cellular enzymatic activity, containing both peptidases and proteases. Studies with peptides showed that, by using peptide inhibitors, it is possible to enhance nasal absorption. Indeed, to improve the bioavailability of nasally delivered therapeutics of this nature, enzyme inhibitors paired together with formulations that increase the residence time in the nose may be necessary. Otherwise, even for relatively small peptides, the systemic bioavailability is of the order of approximately 1%.[12] Biologics that are resistant to enzymatic degradation in the nose are an alternative to the use of enzyme inhibitors.

Deposition Of Biologics in the Airways and Alveoli

Once particles deposit on conducting airways, mucociliary clearance will start translocating them upwards and they may ultimately get swallowed. Macrophages, and possibly other phagocytotic cells, can

"Protection against metabolic activity can be achieved by encapsulation in carriers. Liposomes have the advantage of resembling the natural components of the lung and have been extensively tested in large late-stage clinical trials with small molecules."

also ingest such particles which can be used to our advantage if they are the therapeutic target.

The lung has relatively low metabolic activity compared with the gastro-intestinal tract. The presence of protease activity is generally associated with lung diseases, such as alpha-1 antitrypsin (A1AT) deficiency with absence or abnormally low levels of the natural protease neutraliser A1AT, or in cystic fibrosis, where high levels of proteases are the result of chronic inflammation and infection.

There is evidence from animal studies that peptidase inhibitors increase the bioavailability of inhaled peptides such as insulin and calcitonin delivered to the lung.[13,14] Mucociliary clearance is absent from alveoli but alveolar macrophages can phagocytose particles there.

These removal mechanisms compete against the biologics' intended therapeutic activities, be it binding to receptors within the respiratory tract, or absorption. Protection against metabolic activity can be achieved by encapsulation in carriers. Liposomes have the advantage of resembling the natural components of the lung and have been extensively tested in large late-stage clinical trials with small molecules.[15,16]

MARKET BARRIERS TO DELIVERY OF BIOLOGICS

Cost

Most biologics are much more expensive to manufacture than small molecules. The low systemic bioavailability of the nasal and pulmonary routes requires much higher doses than injections, which for costly biologics may render these administration modes less attractive.

In contrast, delivering biologics directly to the sites of therapeutic action in the respiratory tract makes these routes very attractive not just from the cost-of-goods perspective but also to reduce the potential for systemic side effects. An example of such a product is recombinant human DNase for the treatment of cystic fibrosis – one of the few approved inhaled biologics to have achieved sustained success.

Safety

There have been relatively few studies published on the results of long-term animal and human safety of biologics delivered by inhalation. The concern about carcinogenicity of inhaled insulin expressed by Pfizer with respect to their inhaled product Exubera®, which they dropped and returned to Nektar Therapeutics (San Francisco, CA, US),[17] undoubtedly adversely affected not only other inhaled insulin products, but also the whole field of delivery of biologics by inhalation. Although the number of lung cancer cases associated with the use of Exubera (all in smokers) and MannKind's Afrezza® (smokers and non-smokers) has been low, it remains a concern.[18,19] To the best of my knowledge, no other biologics have reported carcinogenicity findings during their development or post-approval. The most extensive published animal and human safety studies appear to be for recombinant human DNase.[20] Studies with inhaled proteins suggest generally good safety.[21]

Lacklustre Performance of Marketed Inhaled Insulin Products

Unfortunately, the widespread exuberance about the market potential for Exubera, the first approved inhaled insulin product, followed by failure to achieve even a small fraction of the sales forecasts had a massive negative impact on the whole field of inhaled delivery of biologics. And, in more recent times Afrezza, the second approved inhaled product, which overcame several of the weaknesses of Exubera (e.g. large inhaler, complicated instructions for use and maintenance) also fell far short of expectations.

There is no single explanation for the commercial disappointments with these products.[18] The common factors for both Afrezza and Exubera were:

- **Fast-acting insulin only.** Since many diabetics need to use both short- and long-acting insulins, neither of these products provided a full solution for patients. Future products of this kind need to look more holistically to solve the patients' needs.
- **The lack of experience.** Patients and their caregivers, as well as the sales and marketing forces behind the products, lacked experience with inhaled products, including the requirements for regular respiratory safety testing and future efforts in this area will require better education of all key stakeholders. First and foremost, the development scientists have to design the new product such that it meets the patients' needs and is more attractive compared with existing therapies, reducing rather than increasing the burden on the patient and the provider.
- **Significant improvement of injectors.** During the development of Exubera and Afrezza insulin, injection device technology saw notable advancement. This is a tough area to deal with, but anticipation of evolutionary improvements in existing products, such as smaller gauge needles, that could then become highly competitive against a revolutionary product, in this case inhaled insulin, before and during development and marketing the product could save a lot of later disappointment.
- **Both products were dry powders, with evidence for respiratory side-effects.** Patients with asthma and COPD were excluded from the labels of both Exubera and Afrezza. Yet, apart from hypoglycaemia, the most common side-effects were cough and throat pain or irritation. Using formulations and devices that minimise upper and central airway deposition, with compositions that have a low probability of airway irritation, may overcome these issues and possibly improve the uptake of such products.
  An example of such development was AERx iDMS that used an aqueous formulation of insulin delivered with a highly efficient inhaler (Aradigm Corporation, Hayward, CA, US) targeting alveoli with small, nearly monodisperse droplets delivered as a bolus at the beginning of a slow inhalation. These formulations were well tolerated even in patients with asthma and COPD. Whether such attributes will significantly improve market penetration through better tolerability and ability to include patients with such common co-morbidities remains to be seen.

Slow Entry of Biosimilars

One of the commercial drivers for research into the delivery of biologics via pulmonary and nasal delivery was the anticipation of rapid introduction of biosimilar copies of approved biologics. It was expected that, as with small molecules, changes in the route of administration from injections to more convenient, non-invasive methods would provide patient-attractive competitive advantages to the company introducing such a product, as well as the possibility of significant extension of exclusivity through delivery-related patents.

However, the path to biosimilar approvals turned out to be much more complex than for small molecules. In the US, identical copies of existing drug products, i.e. generics, can be approved on the basis of a very much abbreviated approval process, the US FDA's ANDA. Innovative improvements of already approved small-molecule drugs, such as changing the route of administration from injections to oral or nasal inhalation, can be pursued via the 505(b2) regulatory path that can utilise the existing public information about the drug's safety and efficacy. Such products are often patent-protected and may also gain regulatory exclusivity via other means, such as via an orphan drug designation.

Because of the much increased complexity of biologics, the regulatory rules for biosimilars have taken a long time to evolve and implement. These factors have contributed to a relatively slow entry of such products, especially into the US market. Consequently, neither the originators of the products nor the new entrants have embraced alternative means of delivery, including nasal and pulmonary, to make more competitive "bio-betters". Considering the risk and cost involved with the development of new therapies based on new molecules, and especially on new mechanisms of action, it is possible that bio-betters based on more attractive delivery methods will be pursued now.[22]

There is already much concern about the relative cost/benefit of the recent market entries of biologics for the treatment of asthma.[23] This is an obvious area where inhalation products using the same, or similar molecules, delivered directly to the site of action in the respiratory tract, are likely to improve the therapeutic ratio (efficacy/safety) and potentially reduce the cost of raw materials.

Fear of the Unknown

Development of new products and technologies using pulmonary and nasal routes for biologics is not mainstream pharmaceutical and biotech activity, as the default option remains injectables. Only when it is recognised that locally administered treatment is practically inevitable, as in the case of recombinant human DNase and gene therapies for cystic fibrosis, will these routes be taken to be the first option.

I have a very vivid memory from sitting on a panel of experts on delivery of biologics in the early 2000s at an investors' conference; a senior executive from a large biotech company seriously claimed that pulmonary delivery of biologics was "impossible". Yet, by that time recombinant human DNase was already approved and successful results with inhaled biologics in humans were published in reputable journals. I would not be surprised if that is still a widespread perception outside the close-knit community of respiratory delivery aficionados.

This is not helped by the fact that the causes for some of the very disappointing failures in late stage clinical trials with inhaled biologics were never explained, such as the inhaled gene therapies and Alpha-1 Antitrypsin,[24] or lung surfactant therapies.[25] On the other hand, the low efficacy of recombinant human DNase outside cystic fibrosis is quite well understood and using improved molecules and better prospectively identified patients may make modified recombinant human DNase viable in indications such as COPD.[26]

"Development of new products and technologies using pulmonary and nasal routes for biologics is not mainstream pharmaceutical and biotech activity, as the default option remains injectables. Only when it is recognised that locally administered treatment is practically inevitable, will these routes be taken to be the first option."

"Maximising efficiency through the improved delivery of biologic agents to the desired sites and their protection against unproductive elimination is desirable, and there is both extensive expertise and availability of much improved devices and formulations now to help achieve these goals."

CONCLUSION

Delivery of several types of biologics via the pulmonary and nasal routes is clearly feasible and may lead to very valuable products for patients whose needs are not met today, or only currently met with a high treatment burden. Maximising efficiency through the improved delivery of biologic agents to the desired sites and their protection against unproductive elimination is desirable, and there is both extensive expertise and availability of much improved devices and formulations now to help achieve these goals.

Previous approvals of injected biologics, taken together with experience with approval processes of current pulmonary and nasal products, will certainly assist in shaping the regulatory paths for these new products. Since it is likely that the control groups in clinical trials will be patients using the existing approved route of administration for the same biologic, enrolment for clinical trials as well as choice of endpoints should be much easier and the risk much lower than for placebo-controlled trials of new drugs or biologics.

But technical optimisation and abbreviated regulatory paths alone will not be a guarantee for success. The development teams working on the next generation of inhaled biologics, especially for those to be used outside respiratory medicine, should learn from

history; inhaled products should be designed, developed and marketed through close collaboration with the patients and their healthcare providers to be attractive for all key stakeholders. Collecting information during development to support the socio-economic benefits of these new products is important, beyond the need to prove efficacy and safety.

ABOUT THE COMPANY

Respidex is a consultancy helping pharmaceutical companies in their R&D activities, regulatory strategy, financing and commercialisation of products for prevention, diagnosis and treatment of diseases. Respidex clients include small early preclinical companies as well as enterprises in late stage clinical development.

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ABOUT THE AUTHOR

Igor Gonda, PhD, is the Founder of Respidex, a San Francisco-based consulting company. Dr Gonda has held a variety of executive positions in US and Australian private and public pharmaceutical and biotech companies. His research focus was primarily in the area of drugs and biologics administered to the lung and nose conducted in industry and, prior to that, in universities in England, Australia and the US. Dr Gonda's current interests additionally include the involvement of patient advocacy groups in pharmaceutical R&D, venture philanthropy and the regulatory process to accelerate availability of cures for their diseases, and in opportunities for making individualised precision medicines faster and cheaper.

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GUILLAUME BROUET, APTAR PHARMA

Guillaume Brouet is Vice-President, Analytical, Regulatory and Scientific Affairs for Aptar Pharma. He has 24 years of experience in the development and qualification of drug delivery systems as well as analytical and formulation development. He has spoken previously at multiple respiratory and nasal drug delivery conferences. Mr Brouet graduated from Ecole Supérieure de Chimie Organique et Minérale (ESCOM, Paris, France) and earned an MSc in Physical Chemistry, which he obtained at the University of Houston, TX, US.

In this interview with *ONdrugDelivery Magazine*, Mr Brouet discusses how Aptar Pharma uses its device development expertise and infrastructure to provide its pharmaceutical company customers a comprehensive services offering around device development, global regulatory approval and commercialisation. He discusses the range of services available, especially for respiratory devices.

Q Please tell us about your role and your responsibilities at Aptar Pharma?

A I entered the Analytical, Regulatory and Scientific Affairs role about two years ago to further develop the expertise of Aptar Pharma in these three areas. I am also responsible for developing the services offered by Aptar, around the device technology we offer to our customers, so that in addition to the device they receive a complete solution.

My responsibility is to manage the teams that look after analytical science, regulatory science and, from an operational standpoint, to develop this expertise and make sure it can be leveraged in the best way we can to help our customers get their products onto the market as quickly and as safely as possible.

My team consists of around 90 people, mainly located in Europe but also globally. One team, located in the US, is Aptar Pharma's speciality inhalables testing company, Next Breath (Baltimore, MD, US). Aptar Pharma acquired this company in 2008.

Q Aptar Pharma offers a range of services for drug development. Can you tell us more about these services?

A We have a solid leadership position in the market for devices used for respiratory, including nasal delivery. The range of services accompanies our device offering to share and leverage our expertise and know-how wherever it is useful to our customers to help them accelerate development, and minimise regulatory risks.

> "Pharma's expertise is in the molecule itself but Aptar's is in how you develop the device, how you industrialise the device and ensure that it does not begin to cause problems when you begin to manufacture at scale."

Aptar Pharma's range of services includes extractables and leachables testing, for example. We manufacture these devices, we select the raw materials and define the bill of materials, so we're actually in the best possible position to establish the extractables and leachables profile as a service to our customers.

Our regulatory experience is very important. As a device supplier we are exposed to multiple product applications and thus multiple opportunities to interact with the different regulatory bodies around the world – primarily this is the FDA in the US, but elsewhere too, in Latin America and China for example. This expertise can be leveraged to facilitate the registration process for our pharma partners from the finished drug product, and answer any questions related to the device itself, the way it was developed and so on.

Our service offering also includes manufacturing support. We understand how the manufacturing lines at our customers' facilities will accommodate the device technology we supply, so we can make sure these lines run smoothly when an Aptar Pharma product is introduced. We ensure that these manufacturing lines are appropriately designed for the right manipulation and handling of Aptar technology.

Our range of services (see Box 1) helps our customers from early development all the way to commercialisation and beyond, with routine supply and support after a product has reached the market.

We work with big pharma all the time and a large pharma company will have a sizeable device group, but this device group may not have the range and diversity of exposure to the multiple device programmes that we have. Their experience would, by definition, largely be limited to the sorts of devices that are used by the company they are part of.

Moreover, we now increasingly work with organisations that don't have any device technology expertise, that don't have a device development group. In these cases,

BOX 1: SUMMARY OF APTAR PHARMA SERVICES

R&D TO PHASE I

- Aptar Pharma QuickStart™ kits
- Device design and rapid prototyping
- Filling and assembly support (animal adapters and filling kit)
- *In vitro* feasibility assessments and comparability
- Actuation system, actuation profile
- Container closure integrity
- Nasal cast deposition evaluation
- Biocompatibility testing
- Ready-to-submit IND package

CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

- Test methods to support batch release
- ICH Stability Program
- Impurities and degradation control
- Spray characterisation
- Structural equivalence (gel structure, deposition, spreading, dissolution, and absorption)
- Chemical specific particle sizing
- Finished product specification
- Temperature cycling and ageing studies

EXTRACTABLES AND LEACHABLES (E&L)

- Established extractables and related DMF file
- Ready-to-submit extractables report
- Routine testing and C of A
- Validation of extractable methods
- E&L reports
- Leachables studies performed on stability

CUSTOMISATION

- Fully integrated design house with rapid prototyping
- Quality-by-design customisation with complete design history file
- Customisation of branding and aesthetics
- Human factors (HF)-driven customisations
- Formulation, indication and patient-specific device optimisation

IN VITRO BIOEQUIVALENCE (IVBE)

- Method development and validation (Test and Reference Listed Drug – RLD)
- Feasibility assessment and comparability evaluation
- Dose performance testing
- Filling and assembly support
- Drug product and spray characterisation
- Priming and re-priming
- Labelling, randomisation and blinding for IVBE
- Statistical analysis (population bioequivalence)
- Ready-to-submit IVBE report

CLINICAL STUDIES SUPPORT

- Establishment of CMC acceptance criteria
- Drug product clinical release
- Device trainers for patient onboarding
- Formative HF studies
- Ready-to-submit HF strategy
- Threshold comparative analysis report

DIGITAL HEALTH

- Clinical trial optimisation
- Patient onboarding
- Fully integrated connected platform delivery systems in nasal, respiratory, ophthalmic, dermal and injectables, amongst others

REGULATORY SUBMISSION AND POST-LAUNCH SUPPORT

- Design history file
- Risk evaluation and mitigation strategy
- Release specs for individual device constituent parts
- Reliability
- FDA/PAI audit support
- Investigation management
- Change control management
- Data trending for critical quality attributes (CQAs)
- Device trainer kits for commercial sales support
- Annual product review

anything we can bring with respect to the registration of the device – in support of a US combination product approval for instance – will be extremely useful.

Pharma's expertise is in the molecule itself but Aptar's is in how you develop the device, how you industrialise the device and ensure that it does not begin to cause problems when you begin to manufacture at scale, once the product has reached the market. We're able to foresee and avoid problems that they might not be aware of, because of our extensive experience.

And beyond avoiding problems, it makes development easier, quicker, and safer if we can leverage the expertise we have built over many years within Aptar.

Q Aptar Pharma is a leader in respiratory. Can you tell us more about this particular expertise?

A Aptar Pharma is a leader in supplying metering valves for metered-dose inhalers and has also developed at least two dry-power inhaler devices, one of which was brought to the market in China and India. We have a lot of exposure to respiratory drugs related to device development.

Respiratory products are complex. Obviously, the device is a critical part of the overall finished product and needs to be very precisely designed, manufactured and controlled, otherwise the efficiency and potentially also the safety of the drug product can be compromised. Our expertise is not only in understanding the mechanical engineering part of the device technology but moreover making sure that this device technology meets the requirements of regulators, making sure the specifications meet the safety requirements. This includes things like extractables and leachables in MDIs and evaluating the bioequivalence criteria for nasal sprays.

Our scientists, from analytical scientists to formulation scientists to regulatory experts, have progressed with the company over the years, or acquired significant experience working for leading players in the industry.

We are also investigating opportunities in connected devices, specifically connected inhalers. Two specific partnership were made public, one of which is with Propeller Health (Madison, WI, US). This gives us the opportunity to develop expertise in the interaction of the drug product, and in particular the device part of the product, with the patient directly. We will expand and continue to grow this expertise in multiple fields wherever it brings value to our customers and their patients.

Q How do Aptar Pharma's respiratory services fit within the broader context of Aptar Pharma's services offering?

A Having been associated with the development of multiple respiratory drug products, respiratory is where we have naturally first built our service offering expertise. The complicated nature of respiratory drug development meant that it made sense to offer this expertise as a service. However, Aptar Pharma has a much broader offering, looking at other delivery routes.

Injectables and ophthalmics, for example, are complex combination products that also require solid device expertise when bringing a product to market, so it makes sense to expand our services offering into these areas as well.

We're probably not as advanced as we are in respiratory at this point, but the same principles certainly apply. For example, extractables and leachables testing is equally applicable to an ophthalmic drug product. It is important to avoid harmful extractables being introduced into the eye in the same way as it is important to avoid it in the lungs.

Q In addition to the services you mentioned earlier what other services does Aptar Pharma offer for respiratory drug development?

A We have built significant expertise over the years in the area of pharmaceutical testing and this is something we can really leverage to help our customers develop their programmes. For example, when we develop a dry-powder inhaler (DPI), we never claim that this inhaler will be suitable for every drug product. But we need to be able to make sure there's a good fit between the device technology and the drug it is required to deliver.

> "All of this knowledge is documented so that we can make it available to our customers alongside the development programme. What we can offer as a service package has become more comprehensive and now encompasses many dimensions of device development throughout the entire drug development process."

We have developed analytical methods to measure the pharmaceutical performance of DPIs with multiple drugs. We have developed analytical methods to test our own devices very specifically and we would conduct early feasibility studies to at least cover the initial development steps. We can also offer guidance as to how the drug could be formulated if it is to be used jointly with our device technology. So we have expanded into formulation and pharmaceutical testing as it relates to the development of products using our device technologies.

We can also customise the device itself for drugs that require specific adjustments in our technology. Examples of this include customisation for a specific patient population, or because of specific requirements based on the profile of the drug whether it's because it's a very high dose, a very low dose, highly moisture sensitive or highly potent. This capability to customise can clearly be very useful in developing respiratory drugs, so this is something we can leverage for the benefit of our partners.

Combination product regulatory compliance requires a lot in terms of how you document the device, including all the design controls that are associated with the development programme. We can provide a lot of documentation to our partners and package it so that it's a hassle-free exercise for them to document the device, the way it was developed and the way it functions, in accordance with the requirements from the user and from the profile of their particular drug.

Q Aptar Pharma has been involved in many combination product approvals. Can you tell us more about these and how you can help customers in their regulatory filings?

A We have been involved with numerous combination product approvals both before and since the regulation specific to combination products was introduced. Previously, the device present in a combination product was certainly important but not looked at with the same level of scrutiny by the agencies as it is now. Therefore, like the entire industry, we have had to upgrade our documentation not only internally but also in the files that are supplied to our customers and to the regulatory agencies directly.

We can help our customers with packaging this information. For each project we can make sure there is a documentation package that can be submitted to our customer and to all of the regulators and we can customise the split – what goes to regulators, what goes to customers, what is available for consultation on-site in case, for example, a facility is inspected for design control. We have all this pre-assembled, pre-packaged so that customers can quickly, and with no risk of delay, move safely through their development and on to the registration process.

Q Aptar Pharma obviously has expertise with regulatory filings and the regulatory agencies in the major markets, but what about emerging markets?

A Pharma companies want to introduce many of their products on a global level. This means not only in the US and Europe, but also having the same product introduced, in say, China and Brazil – both of which, like the US and Europe, have become very demanding regulatory bodies.

Aptar Pharma has a regulatory team in China, where we have had products registered for many years. We have had a presence at the forums organised by the CFDA and have had regular direct dealings with the agency. The same applies for Anvisa in Brazil. Next Breath is actually the only non-Brazilian laboratory registered to conduct nasal spray testing in Brazil and has a direct relationship with Anvisa.

We know how to format the documentation and select how much we need to document device technology in the context of a registration in different countries. That puts us in a position to support our customers on a truly global basis.

Q Aptar Pharma can customise the services offered to each development challenge. How does this work in respiratory?

A The primary expertise of the pharma company itself is more in drug development and formulation science, whereas for us it is the device. So we're proposing a new model whereby during development we undertake, as part of our service offering, *anything* related to the device that is useful for our customers. This might be developing analytical methods using the device, or developing customised lab-scale filling equipment, or larger equipment used for the final assembly of the drug product. We also conduct *in vitro* testing and package it all.

We can be present from the beginning of development all the way through commercialisation, and take on a share of the development activities for anything related to the device. This puts us in the best position to document this appropriately to regulators, reducing the risk compared with leaving these activities to another service provider with no background in device technology.

This model can also include utilising our in-depth understanding of human factors, which stems from having been exposed to multiple programmes and having devices that have been used in the context of multiple drug products. We have gathered extensive knowledge of how our patients interact with our device technology.

Take something as simple as actuation force. We need an understanding of how patients use a nasal spray and how much force they would be able to exert on a device to use it successfully. We have this knowledge. Through our medical director and partners, we have been conducting specific user trials.

All of this knowledge is documented so that we can make it available to our customers alongside the development programme. What we can offer as a service package has become more comprehensive and now encompasses many dimensions of device development throughout the entire drug development process.

Q How does Aptar Pharma's services offering help its clients deliver more patient-centric products?

A Aptar Pharma hired a Medical Director a few years ago and since then, we started systematically, for all new product developments, to conduct human factors research. We wanted to understand everything about the way the patient interacts with the device itself and perform design control risk analysis based on patients' needs and patient-related risks, from the very beginning. This means that when we are involved in the development, all this background documentation is in place and is available to our customers.

Of course, human factors testing also needs to be done in the context of the final product's intended patient population and in the context of the profile of the particular drug. It is very difficult to run a specific manufacturer study that is drug and disease agnostic without knowing what the finished product will be. But in the initial steps, the general background around how patients can use the device is built and then what we do jointly with customers is expand from that to complete the final studies directly related to the drug product itself and the intended patient population.

Patient-centricity feeds into connectivity. We've built expertise in the development of electronic devices from a technology standpoint. For example, in the area of connected inhalers, we have started working with Propeller Health. Connectivity gives us even more patient insights so that we can understand even better how patients interact with devices. Undertaking development using connected inhalers also teaches us what connectivity brings to the patient so that we can move forward with developing technology that is useful for patients.

Q Why do you think your customers like working with Aptar Pharma Services?

A Our respiratory expertise, experience and track-record are very important factors. We're continuously building this expertise, building teams over time so our customers can benefit from the experience of people who have had exposure to multiple situations, multiple device programmes, multiple drugs, multiple developments that are very valuable on the route to commercialisation.

Aptar Pharma has a great development team, people who are responsible for developing prototypes, and who are familiar with the constraints of manufacturing devices in the millions, and who know that these constraints must be considered from day one. This is a key part of Aptar Pharma's core device expertise, and we approach our services offering in the same way.

From day one, having this target of bringing the product to the market as quickly and as safely as possible is very important, and I think it's well-recognised by our customers. The fact that we bring the patient on board and are increasingly considering the needs and requirements of the patient is also appreciated.

> "The fact that we are truly global – both in terms of our presence and our experience – is crucial. It costs around a billion dollars to develop a new drug product today and a company making that investment wouldn't then want to restrict their market to one or two territories."

The fact that we are truly global – both in terms of our presence and our experience – is crucial. It costs around a billion dollars to develop a new drug product today and a company making that investment wouldn't then want to restrict their market to one or two territories. Being able to get support from Aptar Pharma in several parts of the world is something that our customers value.

Finally, customer orientation has always been very important in Aptar Pharma's culture. It sounds simple and obvious, but this has genuinely always been a very important dimension of how we organise ourselves, how we develop the culture of the organisation. Whatever we have established for our device technology offering flows through to the services offering we bring, the same customer focus and same customer orientation. It is something that we know our customers recognise and appreciate.

ABOUT THE COMPANY

Aptar Pharma provides innovative drug delivery systems, components and active packaging solutions to pharmaceutical, consumer healthcare and biotech customers worldwide, spanning a wide range of routes of administration, including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma's portfolio of stage-specific service offerings are designed to address regulatory needs proactively and accelerate approval. With a strong focus on innovation, Aptar Pharma is leading the way in developing connected devices to deliver digital medicines. With a global manufacturing footprint of 12 GMP sites, Aptar Pharma provides security of supply and local support to customers. Aptar Pharma is part of AptarGroup, Inc (NYSE:ATR).

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Together, we can tackle patient adherence. Let's connect.

Aptar Pharma – delivering connected, intuitive devices to improve patient health outcomes

As the leader in respiratory drug delivery systems, Aptar Pharma is focused on supporting customers and patients to effectively treat respiratory diseases including asthma & COPD.

Today, 60% of patients fail to comply with their medication regimen. At Aptar Pharma, we strongly believe that patient behavior can be changed through connected and intuitive, user-friendly devices. This can significantly increase dose adherence and improve patient health outcomes. That's why we are partnering with digital health solution providers to develop a portfolio of connected devices such as MDIs and DPIs.

To find out more about how we can help you deliver better patient health outcomes via connectivity, call **Sai Shankar**, Director, Business Development – Connected Devices, at Aptar Pharma on **+1 847-800-6058** or email **sai.shankar@aptar.com**

Delivering solutions, shaping the future.

Aptar pharma

THE CHALLENGES OF DELIVERING QBD IN NOVEL RESPIRATORY DEVELOPMENT – KNOWLEDGE- AND RISK-BASED APPROACHES

In this article, David Belton, Founder and Director of Quentis, discusses the meaning of quality by design in novel respiratory drug delivery device development. He covers how, with more novel devices, prior knowledge may be insufficient for a standard FMEA-style risk analysis, and alternate science-based methods, such as functional mapping and knowledge scoring, can help in achieving QbD.

INTRODUCTION

There is currently significant development activity within the respiratory device arena, driven both by new drug development and the opportunity to launch generic equivalents. With new products, there is frequently a commercial business driver to develop a distinctive delivery mechanism. And for generics, because the patents on the drug expire before those on a device, there are opportunities to develop novel, non-infringing drug delivery systems to gain a competitive advantage. We have also seen the challenges of gaining regulatory approval for clone-type devices where a significant amount of knowledge needs to be gained to create a robust product.

Considering this drive towards highly novel devices and the accelerated launch of clone devices, this article covers specific challenges in achieving Quality by Design (QbD) of novel mechanisms. In particular it focuses on the relationship between risk-based and knowledge-based approaches in showing understanding and control of the device design.

> "In fact, while the acronym QbD is often recited without much thought, it is actually a fairly profound statement. A clearer way to state it is 'Quality. By Design'."

QUALITY. BY DESIGN

To fully consider the challenges of developing modern respiratory drug delivery systems it is worth looking again at the core QbD guidance, ICH Q8. In fact, while the acronym QbD is often recited without much thought, it is actually a fairly profound statement. A clearer way to state it is "Quality. By Design". This begins to convey the intent of QbD, which is that the quality characteristics are designed-in and well understood. For a drug product or device this naturally leads to the key concepts of design understanding, design robustness, manufacturing understanding and manufacturing robustness.

When we look at ICH Q8 for drug delivery systems, they are mentioned only fleetingly, described as "important to demonstrate that a reproducible and accurate dose of the product is delivered under testing conditions… which simulate the use of the product". Reading on though we come across terms that should be familiar to anyone working in device design and development, including design space, design of experiments, process analytical technology (PAT) (now very much a part of Industry 4.0), process robustness and, of course, quality.

With respect to pharmaceutical development, the guidance identifies four examples of QbD's systematic approach:

- Incorporation of prior knowledge
- Design of experiments
- Quality risk management
- Knowledge management.

The guidance also notes that the level of knowledge gained for science-based and risk-based submissions is key rather than the volume of data. It's an interesting point that, in my experience around device development, I have heard the term "risk-based approach" probably ten times more than I have ever heard the terms "science-based", "knowledge-based" or "data-

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"The particular challenge here is that the more novel a design is, the less prior knowledge exists and the more those in the review, even experts, have to lean into making educated guesses and hunches."

based" approach. If you find this familiar as well, then I believe a more balanced approach to risk- and science-based knowledge is important, and is particularly important with novel drug delivery devices to achieve Quality. By Design.

RISK AND PRIOR KNOWLEDGE

So why do I believe that a more balanced approach is required for development and risk management? And why is this particularly important to novel devices? It is generally agreed that the quality of a risk assessment is often dependent on the range of required skill sets and experience in the room when the risk assessment is carried out.

In the early stages of device development, prior knowledge and expertise are heavily relied upon to support risk assessments, as there will likely only be limited information available, such as sketches and rapid-prototyped working models. The particular challenge here is that the more novel a design is, the less prior knowledge exists and the more those in the review, even experts, have to lean into making educated guesses and hunches. This leaves open the risk of both gaps (unknown unknowns) and over-analysis of known, or "safe", areas occurs.

"In taking a balanced approach to novel device development, it becomes more important to gain knowledge through science-based approaches to avoid the potential for gaps in risk assessment."

There is then the potential for these early risk assessments to be used as the basis for later reviews, causing the gaps to remain unnoticed until late in a programme, by which point there are generally much higher costs associated with managing issues. Therefore, in taking a balanced approach to novel device development, it becomes more important to gain knowledge through science-based approaches to avoid the potential for gaps in risk assessment.

FUNCTIONAL REQUIREMENTS

There are a number of existing techniques to gain knowledge and define the functional requirements of a product. These come through documents such as user requirement specifications (URS), engineering design specifications, user event trees, fault tree analysis and mapping through use of trace matrices.

These documents are extremely effective at defining the functional requirements of a device, but do not specifically define how the device achieves those requirements. It is not uncommon for these functional requirements to be directly risk assessed. Where the functional mechanism is fundamentally understood this is not an issue.

When it comes to novel devices, it is more akin to asking: "Show me the device works by proving it doesn't fail in all possibilities". One way to visualise this is by trying to define the shape of a dartboard through risk-assessing all the ways the darts could miss.

To expand on this analogy, it is important to have the risk assessment to understand the consequences of not hitting the dartboard, but directly defining the shape and function of the dartboard seems to be a simpler, direct approach. Considering this in a devices context, a more straightforward, and QbD aligned, approach is to ask the question: "Show me the device works by showing me you understand how the device works".

MECHANISMS FOR KNOWLEDGE DEVELOPMENT

There are two main approaches for knowledge development:

- Predictive modelling
- Physical testing.

Predictive Modelling

Predictive modelling covers a wide range of tools. This includes complex analysis, such as finite element analysis (FEA), computational fluid dynamics (CFD) and tolerance models, through to understanding spring rates, frictional movement and similar activities. These methodologies have proven to be very powerful in performing rapid design iterations early in design and in being used to support understanding throughout the development lifecycle of a device.

Physical Testing

Modelling of parts through various rapid prototyping methods is becoming the norm in development. As these, and later more industrially representative samples, are tested in development, they can provide physical validation (or sometimes otherwise) of theoretical models. The two approaches are highly complementary and allow for real life issues to be found and models to be refined to predict results in many more scenarios than can usually be manufactured.

At a basic level these types of models and tests are made on core functions of a device – for example, steps of preparation, dosing, delivery and counting. With complex respiratory devices, there are usually multiple components and interfaces working to deliver a core function. Often, these components contribute to more than one function within the device. The next layer of understanding is being able to understand the performance characteristics of these individual interfaces. If they can be optimised, understood and controlled, that moves us significantly towards having a well understood design that is robust and can achieve high quality levels.

STRUCTURED FUNCTIONAL RELATIONSHIPS

So far, I have discussed the risks in risk-assessing a novel device where unknown unknowns may exist, and also covered the ever-improving standard approaches in defining functional requirements and functional knowledge. The way these are often managed is by then using this functional information to (returning to my earlier dartboard analogy) define all the "missed darts" and not the dartboard itself via a risk assessment.

Personally, this led me to consider why we do this. There are the obvious answers, such as: "These are what the policies/guidances/regulators tell us to do",

"... the process of creating a functional map in a broad-based team encourages improved understanding of the design and allows the participants to think about a device from a different viewpoint than they might normally otherwise."

"We need to understand the risks" and the like. One other reason is that a risk assessment, particularly failure mode and effects analysis (FMEA) which is most commonly used, is an excellent way to structure the information. There is a clear distinction between a failure mode, potential causes and effects which connects a requirement not being met (the effect), and the source of the problem (the cause). This then leads to another question – why do we need to flip these functional modes into failure modes in order to describe this, or put another way, "What is the opposite of an FMEA?" Would it be easier and more thorough to have a process that described structured functional relationships rather than failure modes?

FUNCTIONAL MAPPING

The solution to this "opposite FMEA" is a functional map. The basic concept behind this is that rather than describe all the things that can go wrong with a device, it is used to describe all the things that need to go right to achieve a function. This can be a powerful tool as, by definition, this is a finite list. By using a mapping process, similar in many ways to quality functional deployment (QFD), top level functions can be connected effectively with ever more fundamental design features.

For example, starting from a top level function, you can go to a contributing interface, a component, a surface and a dimension. By looking at specific device functions, a functional map also allows for identification of where a feature may be performing more than one role. Typically, this happens where a feature is performing both a primary and secondary function. A risk analysis will often focus on the primary relationship to the detriment of the second, which may have different control requirements or design space.

An effective functional map also acts as a thorough guide to connecting functional requirements in a URS through to support FMEAs. There is also a more general benefit, which is that the process of creating a functional map in a broad-based team encourages improved understanding of the design and allows the participants to think about a device from a different viewpoint than they might normally otherwise.

KNOWLEDGE SCORING

A further benefit of functional mapping is that is provides a structure to perform a knowledge assessment across the device, and can be used to identify gaps in knowledge. Similar to the functional map utilising the same cause and effect approach as a FMEA, one approach for a knowledge assessment is to look the FMEA scoring methodology, such as severity and occurrence. There is a less direct link in this comparison, but there is benefit to defining metrics that can be scored, and have similar action limits set as in an FMEA. When looking at knowledge scoring, the two requirements identified were:

- Knowledge level
- Strength of relationship.

Knowledge Level

The knowledge level can be scored based upon the precision and level of understanding of a relationship. The scoring should be based on data. At the highest end is having a fully predictive model which closely aligns with observed physical models. Also in this category are functions that can be based on fundamental physical properties. Lower knowledge levels would be partially predictive models, empirical data from a limited design space and, at the bottom, no data at all.

Strength of Relationship

Whilst the knowledge level score is completely data-driven, the strength of the relationship can be a mix of evidential data and expert judgement. It is likely that not every aspect of a device and every potential contributing factor can be fully investigated, and focus is needed on key relationships. In essence, this scoring allows for a sense-check of "Does it matter?" In much the same way that you might separate control, noise and experimental factors in a design of experiments, this score looks to categorise the likely strength of the relationship from all factors described in the "What needs to go right?" set.

Via this knowledge assessment, core functional gaps in understanding where there is believed to be a strong relationship with limited data can be identified and closed as early as possible in development. This complements an FMEA in defining where more knowledge is required, as well as where assessed risks need to be proven correct or not.

SUMMARY

In some devices there lies the risk that the more novel the mechanism, the less prior experience is of value in FMEAs, which can potentially lead to the risk assessment containing gaps that present their own risk to development. Existing knowledge processes, such as theoretical and physical modelling, remain good practice to both define and understand the functionality of a device. However, there is an opportunity to enhance this through the application of data-based functional maps and knowledge scoring alongside more classic FMEA-style risk-based approaches. This can support improved, faster design processes and deliver the robust QbD products that the market demands.

ABOUT THE AUTHOR

David Belton is Founder and Director of Quentis, a medical device engineering consultancy specialising in providing design assurance and industrialisation know-how throughout the product lifecycle. Mr Belton has a degree in mechanical engineering from Loughborough University (Loughborough, UK) and has spent 20 years in both the electronics and drug delivery industries, bringing new products to market ranging right from the world's first 3G phone network to world-class dry powder inhalers.

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AUTOMATING UNDER UNCERTAINTY – GOOD PRACTICES

In this article, Simon Drexler, Director, Linear Motion Technologies, ATS Automation, discusses lessons learned and good practices when dealing with uncertainty at the various stages of automation development for drug delivery device manufacturing.

Making decisions whilst dealing with uncertainty is a challenge we all face every day in both our personal and professional lives. Such decisions can be even more taxing when capital expenditure is involved, which is often the case when driving growth initiatives and is nearly always the case when investing in automation.

One could make the argument that we deal in more uncertainty today than we have ever before. Information travels instantly, therefore our local area of influence is impacted by events that occur around the world. The ongoing trade dispute between the US and China impacts two of the world's largest economies, creating uncertainty around the world. The EU is working through its own uncertainty with the ongoing Brexit negotiations. While these events are occurring, mainstream news organisations are consistently speculating on which event will pull the world economy into its next recession.

The challenge then is that, even in these uncertain conditions, business leaders cannot be content with the status quo. They must continue to strive for growth and drive towards what is best for their stakeholders and shareholders. Therefore, they are tasked with finding opportunities to strengthen and grow business. The main difficulty is to ensure that the uncertainty present in the marketplace does not drive them to make a wrong turn.

> "The end vision for automation is especially important as it affects the foundational technologies chosen and processes developed."

"By definition there are no longer any 'best practices' that can guarantee success for an organisation; there are only good practices that we can stumble upon through experimentation." This excerpt from Alison Randle's article "Three Proven Ways To Navigate Uncertainty" effectively frames the fact that there is no silver bullet to solve a problem, only hard-earned lessons that can be applied from those that have experienced similar situations before.

Uncertainty in automation, as seen in Figure 1, is driven from one of three sources:

- **Product:** Largely due to the changes and revisions that occur through the design lifecycle. For instance, a dry powdered inhaler design may still be evolving in response to user feedback to design concepts or subcomponent manufacturing capabilities.

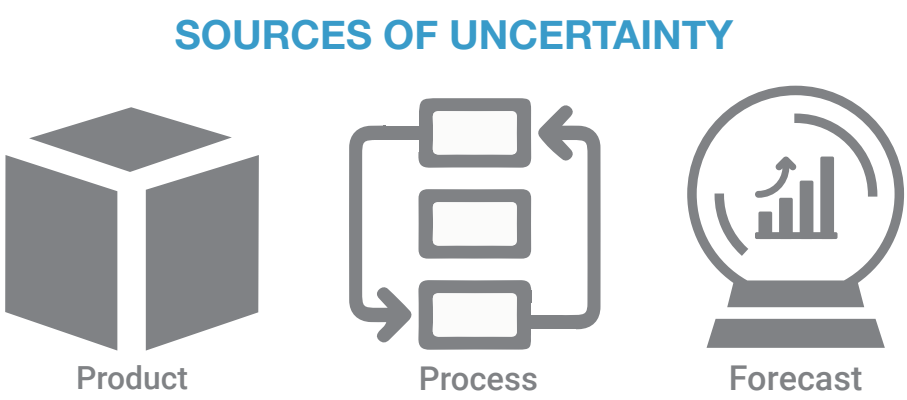

Figure 1: Uncertainty in automation is derived from product, process or forecast.

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- **Process:** Evolving how production occurs at different volumes, with each stage bringing unique challenges. For instance, at different production volumes of an inhaler, a semi-automated or fully automated process could be justified over a manual process step, but each may have a different process verification step.
- **Forecast:** The difficulty in predicting the market conditions for the product you are producing. For instance, there is uncertainty around how closely the actual production launch volumes of a new respiratory device will match the marketing team's projections.

There are several good practices to apply when determining a path to automation while in uncertain conditions. Each of them sounds simple on paper but each is difficult to apply in practice – easy to say, hard to do.

AUTOMATING UNDER UNCERTAINTY: GOOD PRACTICES

Good Practice 1 – Focus on the Finish Line

In the development phase it is critical to understand the end vision, or finish line, in order to make good decisions in the short term. This also happens to be one of Steven Covey's "*7 Habits of Highly Effective People*" from his bestselling book. He says: "Begin with the End in Mind means to begin each day, task, or project with a clear vision of your desired direction and destination, and then continue by flexing your proactive muscles to make things happen."

> "Each of the good practices outlined work in conjunction with each other, similar to the project management triangle."

The end vision for automation is especially important as it affects the foundational technologies chosen and processes developed. The challenge here is that it is often hard to see the forest for the trees when you are working towards a launch or next deadline. You may not be thinking of the ultimate end, but only about a successful next step – a common mistake.

Good Practice 2 – A Stable Foundation

Borrowing wisdom from the construction industry, the foundation is the most important selection you can make. The biggest reason for this is that any mistakes you make in the foundation will only get worse as you go up, known as compounding defects. In practice, selecting a foundation that adapts to the ever-changing needs of the business is in the best interests of all parties, even if at the beginning it seems to be more than is required.

Good Practice 3 – Re-align the Wheel

"Don't reinvent the wheel, just re-align it" is a quote from Anthony D'Angelo. In the manufacturing and automation world, you should try to not re-invent something if you don't have to, as doing so takes capacity away from things that are core to your process and adds additional risk. The "re-alignment" part of the quote is very important – often you only need a tweak to an existing design rather than a fundamentally novel approach. It is often worth taking an impact to expected performance to use an off-the-shelf (OTS) piece of equipment. In all cases, you'll get to where you are going faster if you can use proven components.

It is a common misapplication to look at each good practice in isolation. However, each of the practices outlined work in conjunction with each other, similar to the project management triangle. Knowing the finish line helps when choosing the right technologies, and knowing the right technologies helps to define the finish line and select the right foundation.

APPLYING GOOD PRACTICES

Development Phase

The product development phase is the most challenging phase for automation because uncertainty is high in all three of product, process and forecast. Typically, something is being attempted for the first time whether it be a new product, process or market:

- **Product** is in development, waiting for information from various groups to complete the first market-ready revision. Sourcing, manufacturing, product testing, design or all of the above are making decisions before the product is complete as the team is trying to move fast to take advantage of the opportunity identified.

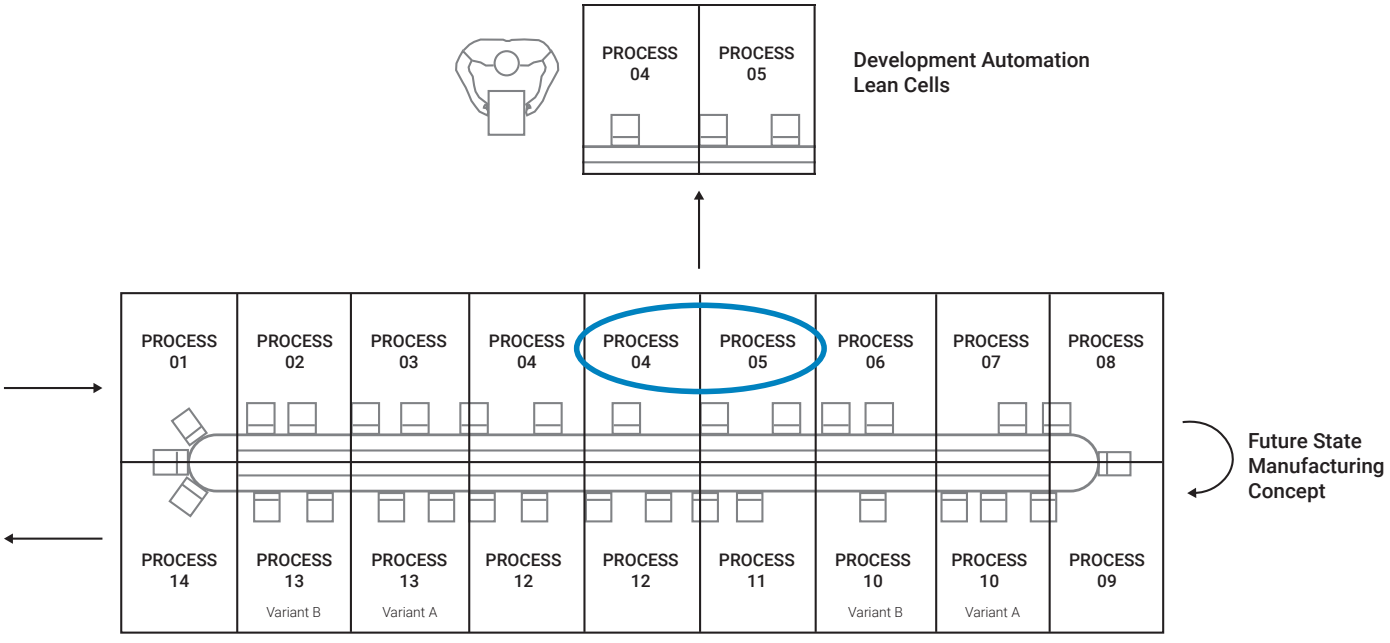

Figure 2: With the finish line in mind, select appropriate technologies and automation early to assist with the development phase.

- **Process** is uncertain because no products have been made in volume for market. The lack of definition on the product itself leaves a number of questions about the process of putting it together.
- **Forecast** is relatively unknown because, without response and adoption from the end user, it is difficult to pinpoint your production levels.

Starting with the end in mind, choose technology that you can grow from development quantities to high volume. Any lessons learned, intellectual property (IP) generated or skills fostered in the workforce can now be applied later in the production process. As shown in Figure 2, a component of a high-volume concept can be used for product and process development – in this case, to build process knowledge on the equipment for the future.

Flexibility in foundational technologies is the most important decision you can make in the development phase. Uncertainty is high; therefore, make choices that give you room to adapt as the picture becomes clearer. Stability is equally important in development so that time and effort is not wasted on troubleshooting, keeping the focus squarely on building your IP. While development is underway, it is helpful to mix manual and automated processes, as shown in Figure 3. An appropriate balance minimises capital investment, promotes discovery, provides control of critical processes, and facilitates quick responses to product and process changes.

There is a bias towards developing custom systems out of the gate. However, even if the OTS component is performance limited, it is better to work with it in the development phase. The reason is the uncertainty level is high so even if you build something custom-made it may not be the right thing. Using OTS components helps you to learn more about product and process, as well as giving time for forecasting.

It is best to select platforms and technologies that interface well with standard automation components and practices. This allows you to build up your expertise by focusing on the parts of the process that are underdeveloped while relying on proven technologies where possible. Note that OTS technologies may drive some design decisions for you as you work through the production process.

In the development stage it is critical to have an end vision in mind, so select flexible and stable foundational technologies and avoid developing custom process technology while so much uncertainty remains present. The aim is to dedicate all efforts to product and process development to remove uncertainty, using automation to execute common steps and processes that cannot be done manually. The goal is to work with the same technologies now that are planned for use in later phases. This will save time and money.

Commercialisation Phase

Time is very important as we shift into the commercialisation stage, where it is all about speed. Uncertainty begins to decline, while market traction and knowledge increases. The most important thing to know as you scale-up is that you may need to make adjustments to your plan. Regardless of the amount of preparation, the reality is that the physical interaction of product and equipment might not go as expected as speed and volumes increase. The positive thing to note about this phase is that some of the risk will start to subside:

- **Product** is now in a mature form as we prepare for launch.
- **Process** for manufacturing is defined but higher-volume manufacturing may dictate changes.
- **Forecast** is the highest source of uncertainty, as lessons for market adoption have not yet been learned in volume.

For the finish line, it is most important to define the long-term manufacturing strategy. Centralised manufacturing will drive different decisions than a decentralised local-for-local approach. This decision will have the most significant impact on the scale-up of an automation system. Volumes change significantly between the two options, which drives component selection and process development decisions.

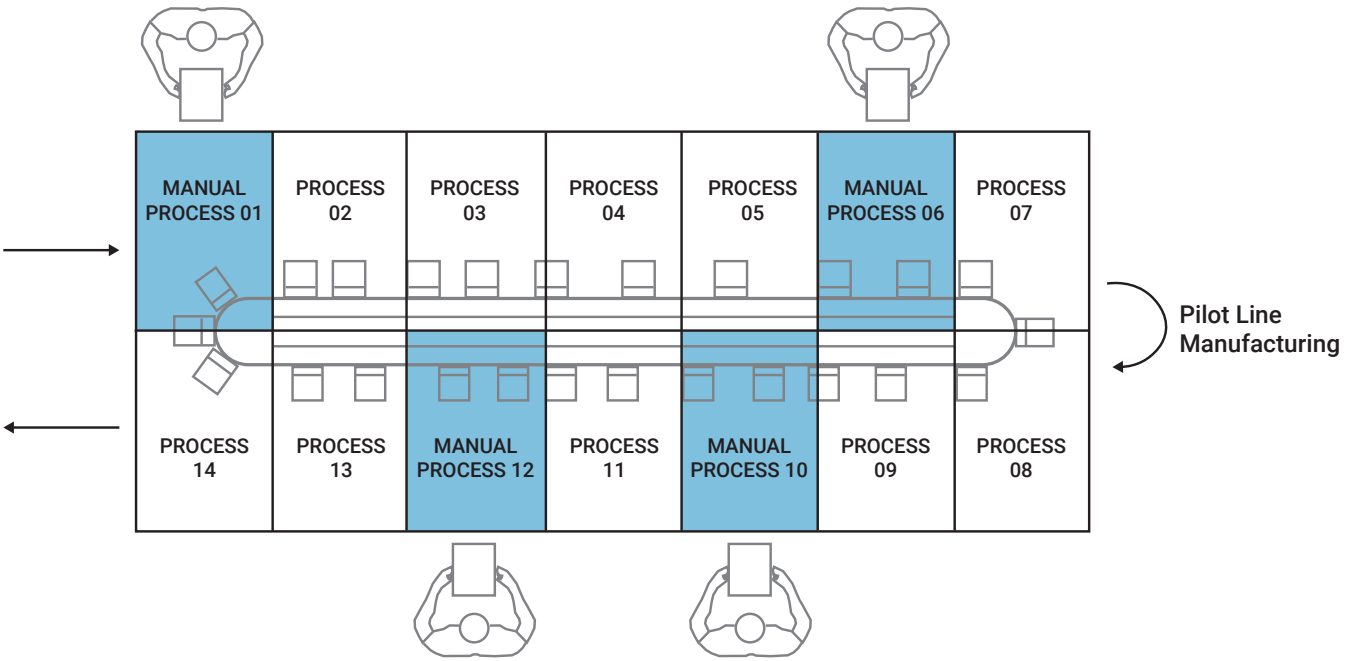

Figure 3: Combining manual and automated processes will minimise capital investment but promote development of a manufacturing platform that will be representative of the final commercial solution.

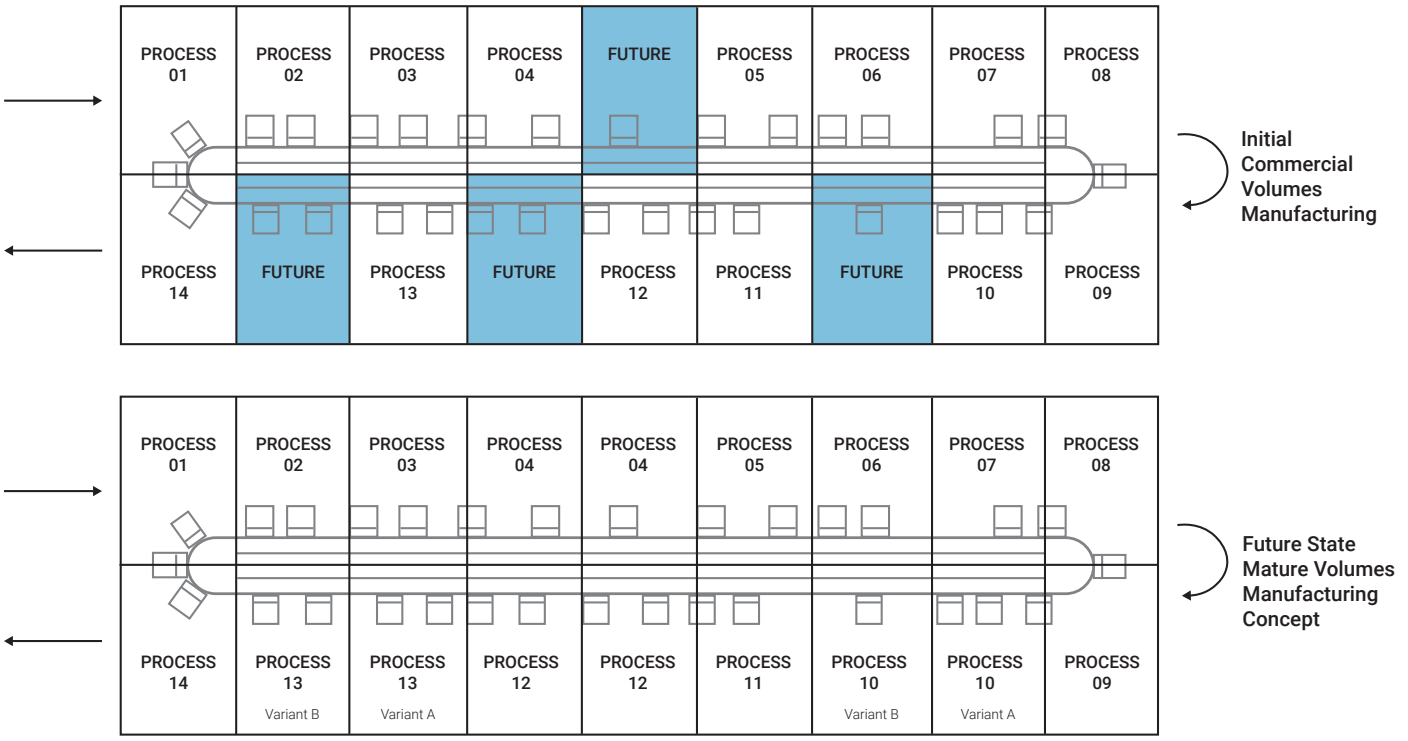

Figure 4: Flexible technology that allows processes to be re-ordered, combined, replicated, adjusted, or swapped-out, anticipates volume increases, product changes or variants, and efficiency improvements.

Maintaining flexibility is a key consideration. You have uncertainty in process design, you need to leave room for iteration. This is where the major advantage of a flexible foundation benefits machine builders and their partners. Understanding that things are unlikely to go exactly as planned, technology that allows processes to be re-ordered, replicated, adjusted or swapped out leaves room for product demand increases, product changes or variant introductions, efficiency improvements, etc, as shown in Figure 4. Technologies that are future proofed in this way are extremely advantageous.

In scaling up production we want to avoid re-aligning the wheel where possible, but on the other hand there is more scope to do so. As volumes increase, the case for custom process technologies increases, but duplicating OTS equipment or re-aligning components may still be a viable approach. A manufacturing platform that can accommodate various process technologies in both process control and accuracy is important for keeping options open.

Throughout commercialisation, speed is the critical driving factor. A clear understanding of the overall manufacturing strategy will drive the correct decisions to reach the finish line faster. Flexibility in the chosen technologies remains critical because volume drives new assembly interactions that are unlikely to unfold as expected. Continued use, and even replication, of the OTS technologies used in development shares lessons where possible, progresses automation development faster and, most importantly, allows focus to be on production.

Mature Phase

The greener pastures of decision making under uncertainty is the high-volume phase. We've gone through the difficulties of product and process developments and are now benefitting from the smart decisions made in earlier stages. It is time to grow volume in less uncertain conditions:

- **Product** is proven in market; iterations are fewer and further between.
- **Process** is known from commercialisation efforts.
- **Forecast** is largely known but susceptible to uncertainty from external factors.

When applying good practices, the focus shifts from development to lifecycle management. Stability and easy-to-use technologies become more important as

"Moving through the stages of development, the benefits of focussing on the finish line, choosing flexible and stable foundational technologies, and re-aligning not re-inventing the wheel are realised in both time and resources expended."

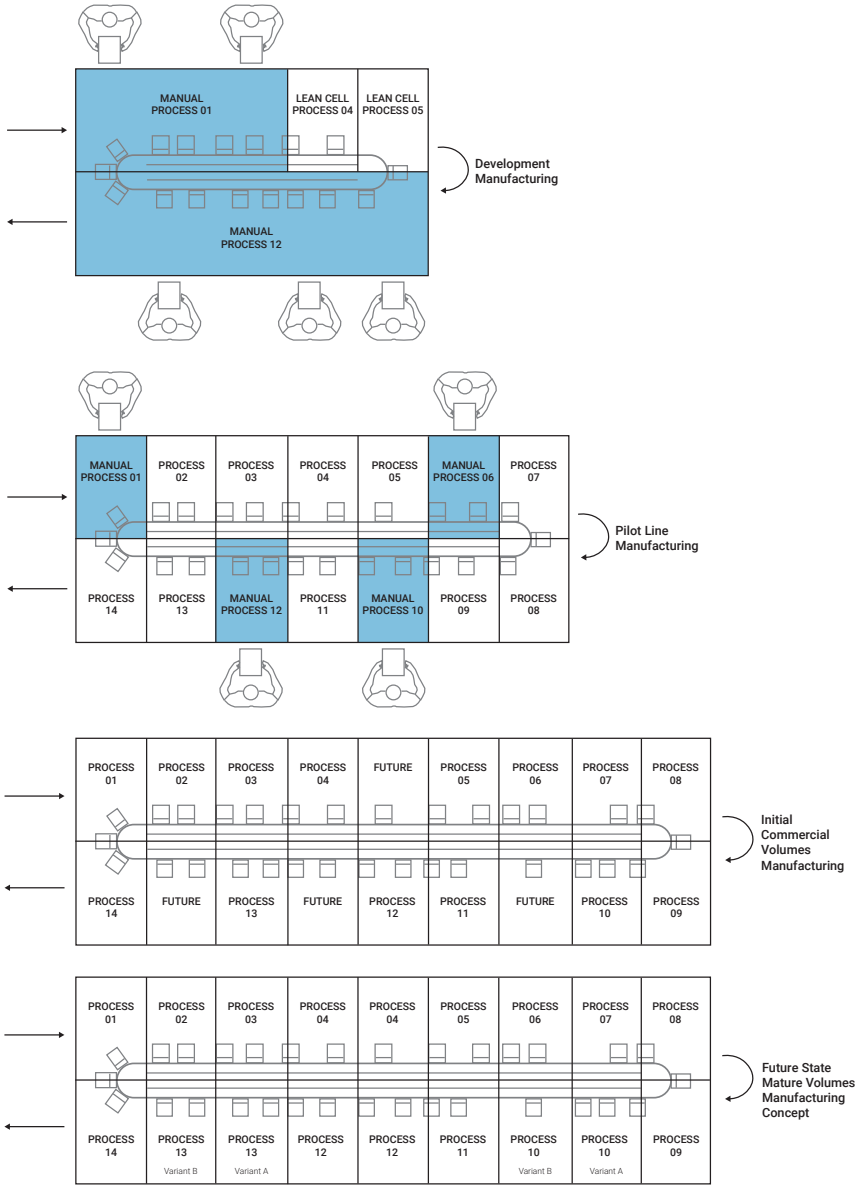

Figure 5: Start with the end in mind – automation progression from development through to mature manufacturing.

the process experts are re-deployed to other areas of the business. Manufacturers require flexibility in capacity only as they seek to balance a level loaded production volume with surge capacity. Custom processes now bear fruit due to volume and the lack of uncertainty in other areas.

CONCLUSION

The ideal automation progression from development through high volume is shown in Figure 5. The process begins with a development cell that is a component of the concept for high-volume automation. The move from low-volume to high-volume occurs using foundational design standards and building blocks to efficiently build the automation cell. Figure 5 illustrates the main advantage of starting with the end in mind.

Selecting the right foundation allows you to travel down either the centralised or decentralised path. Modular foundations enable growing a centralised foundation, whether it be by physically growing it or investing in incrementally larger systems while re-deploying the smaller systems to other products. A decentralised manufacturing strategy requires that the platform aligns with the skillset of the support network where the system will be deployed, whether that be the control system or other components. Asynchronous foundations allow for straightforward replication of technology within a larger cell, but custom development is not discouraged in mature volume stages. There is no need to make performance concessions here as the level of uncertainty is low.

Moving through the stages of development, the benefits of focussing on the finish line, choosing flexible and stable foundational technologies, and re-aligning not re-inventing the wheel are realised in both time and resources expended. To reach our end goal as quickly as possible and begin realising the full benefit of automation, we must focus on making incremental progress towards the finish line every step of the way.

We all have an incredible opportunity in front of us with the advancements in automation technology – do not let a little uncertainty get in the way.

ABOUT THE COMPANY

ATS Automation provides innovative, custom designed, built and installed manufacturing solutions. Founded in 1978, ATS uses its industry-leading knowledge and global capabilities to serve the sophisticated automation systems' needs of multinational customers in industries such as life sciences, medical devices, computer/electronics, energy, transportation and consumer products.

ATS also leverages its many years of experience and skills to fulfil the specialised automation product manufacturing requirements of customers. ATS employs approximately 4,300 people at 23 manufacturing facilities and >50 offices in North America, Europe, southeast Asia and China. ATS shares are traded on the Toronto Stock Exchange under the symbol ATA.

ABOUT THE AUTHOR

Simon Drexler is the leader of the Linear Motion Technologies (LMT) group within ATS' Innovation Center. Initially joining ATS as an Application Engineer he moved into several progressive roles, which led to helping local startup companies and accelerators in Waterloo, Ontario. At Clearpath Robotics he led the evolution of the OTTO industrial product line, overseeing market strategy, product development roadmap and programme execution. He was named *Supply & Demand Chain Executive Magazine*'s "Pro to Know" as well as one of *Plant Magazine*'s "Top 40 Engineering Leaders Under 40" in 2016. As well as leading the LMT group today, Mr Drexler also sits on the Board of Advisors for Canadian Manufacturers and Exporters.

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BEST PRACTICES AND CONSIDERATIONS IN DEVELOPING EFFECTIVE TRAINING DEVICES FOR THE PULMONARY HEALTHCARE MARKET

In this article, Joe Reynolds, Research Manager at Noble, discusses the current state of pulmonary drug delivery device trainers, including their value to patients, the complexities of modern design and the stringent requirements on ensuring their quality.

Over the years, many industry stakeholders and pharmaceutical manufacturers have come to realise the importance of patient training and the role it has on promoting healthy outcomes and effective disease management. Many studies suggest that without proper training during the onboarding process (the first 30 to 90 days of treatment) patients are more likely to drop off from their prescribed therapy or incorrectly use drug delivery devices, including metered dose inhalers (MDIs), dry powder inhalers (DPIs), nebulisers and other forms of self-administration.

Designed primarily for at-home use, pulmonary drug delivery is an effective route of administration for localised and systemic uptake of pharmaceutical products. As a result, pulmonary administration is often a viable alternative to more invasive routes, with future growth potential across new therapeutic areas. These products are frequently marketed as combination therapies, consisting of API and a drug delivery device. When properly used by patients, these devices are effective in delivering a prescribed dose to the lungs. However, user errors can result in injuries, partial delivery and suboptimal therapeutic outcomes for patients.

> "93% of patients prescribed an MDI failed to use their devices properly, with more than half missing three or more of the required use steps."

According to a study conducted by the University of Texas Medical Branch at Galveston (UTMB),[1] 93% of patients prescribed an MDI failed to use their devices properly, with more than half missing three or more of the required use steps (Table 1). The most common mistakes were failure to prime, exhaling and co-ordinating actuation with the necessary timing, force and duration of inhalation.

As an addition to standard instructions for use (IFU) and package inserts, healthcare providers are often expected to onboard patients and provide access to training and education. While these training strategies can be very effective, research suggests that there is often a great deal of variability and inconsistency in the effectiveness of such training and in patients' ability to retain the information and apply it to the successful use of their delivery system.

Further research has shown that many patients are looking for increased access to education and support for self-administration. A study conducted by Noble surveyed patients and examined the impact that device training solutions had on patients using an MDI. The study examined

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Step	Description	Risk of Error
1	Prepare device	Low
2	Remove mouthpiece	Low
3	Inspect the mouth piece for obstructions	High
4	Prepare dose	Medium
5	Exhale, away from the device	High
6	Place device in mouth	Medium
7	Actuate dose	High
8	Inhale with the appropriate force, duration & sequence	High
9	Hold breath (as specified in IFU)	Medium
10	Repeat dose as prescribed	Medium
11	Clean and store device as prescribed	Medium

Table 1: Required use steps for MDIs and risk of error.

"82% of users said they would feel most confident with a training device that detects errors. Additionally, 76% of users prefer some form of error detection to aid in overcoming anxiety about administering treatment."

five different training solutions, ranging from standard IFU to smart error correcting training, in an effort to better understand how training technology can reduce device errors. 82% of users said they would feel most confident with a training device that detects errors. Additionally, 76% of users said they would prefer some form of error detection to aid in overcoming anxiety about administering treatment. For example, one device that was tested included IFU and would whistle if used incorrectly.

To address the common gaps in patient onboarding, training devices are often used to create consistent experiences for patients through the use of novel technologies and mechanisms that fully simulate the mechanical aspects of the drug delivery experience. While these devices appear to be fairly simple at first glance, numerous design and engineering challenges must be addressed in order to successfully develop authentic training devices and other onboarding solutions.

INTERNAL DESIGN AND TECHNOLOGY OF TRAINING DEVICES

Engineering training devices for manufacturability and repeatability is a delicate balance. Fully understanding device development and mechanical design is one of the first steps in engineering robust training device solutions. The exterior of the device should emulate the real drug delivery device as closely as possible, so that patients become familiar with key features and physical characteristics, such as the look, feel and weight of their commercial delivery devices. The interior design of training devices also need to be meticulously engineered in order to provide a proper training experience. To accomplish this, human factors must be taken into consideration throughout the design process to ensure that training devices align with the physical, cognitive and emotional needs of users.

In addition to understanding user needs, Noble has analysed a variety of on-market delivery systems to understand their handling requirements and critical functions. Though in some cases mechanisms similar to commercial devices are used, ground-up mechanical design is usually employed to integrate all necessary functions into a resettable and reusable training device. This means that the training device will look the same as the real thing on the outside, however, it will be vastly different internally. Once human and environmental factors have been taken into consideration, design inputs can be documented and prioritised to mitigate user errors and maximise the value to pulmonary drug delivery device training.

When looking at the case for pulmonary smart training devices, they are designed to monitor patient behaviours and provide corrective feedback during the early stages of the learning process. While there are many variables that influence the deposition of pulmonary therapeutics, including timing, force, volume and muscle memory, trainers should be developed to support patients in establishing motor and muscle skills, along with the appropriate level of force required to use their inhaler effectively. How the patient interfaces with the delivery

"One of the most seemingly simple design requirements is to make the device look like the real product externally, which presents its own set of challenges."

"Critical functions, such as activation forces and the auditory feedback of calibrated whistles, are tested at several points during design, development and manufacturing."

device plays an important role in drug deposition and achieving full absorption. When designing a device it's important to understand the sequence of steps patients go through and the risk of error associated with each (Table 1).

EXTERNAL DESIGN OF THE TRAINING DEVICE

As mentioned previously, external details are also crucial to the design and engineering process. Characteristics of the inhaler, such as the overall shape, mouthpiece, dose indicators and size and shape of the canister, are all accurately matched to the real device so that patients are able to familiarise themselves with its look and feel. However, this is a complex task, due to the fact that the interior of a training device contains additional mechanisms which allow the device to be used multiple times.

One of the most seemingly simple design requirements is to make the device look like the real product externally, which presents its own set of challenges. For example, if the trainer looks exactly like the real device one may mistakenly use a trainer in an emergency or vice-versa. This is typically addressed with optimised packaging, labelling and graphical training instructions. Trainers usually have large labels which read "Trainer, This Device Contains No Drug". In every other regard, the trainer appears exactly the same, in terms of size, shape, textures and Pantone-matched colour schemes (or complimentary colours to denote that it is a trainer).

Other considerations that must be prioritised include ancillary training features like augmented auditory and/or video-based training instructions. Many of the trainers currently in development include some form of collateral training, such as talking packaging, sensor-based error-correction, smart device application or a combination of these features.

QUALITY CONTROL PROCESS

Quality design standards are paramount when designing training devices, in order to ensure that every patient has a consistent and accurate training experience. Noble conducts rigorous device testing, taking into consideration each brand's specified requirements. One of the keys to success is utilising optimised standard operating procedures (SOPs) and standard inspection procedures (SIPs) in the assembly process at the factory. Many manual and semi-automated tests and inspections are integrated throughout the process to verify that targets will be met on the final assembly stage, reducing scrap rate and ensuring a high quality product.

Critical functions, such as activation forces and the auditory feedback of calibrated whistles, are tested at several points during design, development and manufacturing. During pilot runs, many other tests are also performed to evaluate that the device functions as intended and conforms to specifications and other design inputs. Some of these include environmental, accelerated ageing/life, shipping, drop-testing and materials compliance. Though not a formally regulated device category, Noble treats the design and manufacturing of trainers much like a regulated product to ensure the highest final quality product.

CONCLUSION

As training technology becomes more prevalent in the pharmaceutical industry, the engineering and capabilities of these devices will continue to advance, creating a more complex and intricate engineering process. These advancements are necessary, as they will allow patients to become more confident in their treatments, overcome treatment barriers and ultimately lead healthier lives.

In order for training devices to work efficiently, it is necessary that devices are tested with stringent standards. Patients need to familiarise themselves with the device in order to learn and anticipate the steps necessary for proper drug administration. This requires training devices to replicate the ergonomics, interaction and injection time of the actual device accurately.

In today's market, a growing number of patients are being prescribed self-administered treatments. Pharmaceutical companies that prioritise the patient experience, using training technology to help these patients properly onboard to therapy will continue to benefit through competitive advantages and the value they create within the industry.

ABOUT THE COMPANY

Founded in 1994, Noble® is a leader in medical device training solutions, patient onboarding strategies and multisensory product development for the world's top pharmaceutical brands and biotechnology companies. Focused on driving innovation, Noble works closely with brand, device and commercialisation teams to develop turnkey solutions that improve onboarding and adherence, bringing value to clients and patients alike.

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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, pharmaceutical and biopharmaceutical manufacturers. Mr Reynolds earned his Bachelor of Science in Business Administration from the University of Central Florida, a Master of Science in Marketing from the University of South Florida, and a Master of Science in Pharmacy and Master Certificate in Drug Regulatory Affairs from the University of Florida.

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RDD ASIA 2018 CONFERENCE REVIEW AND UPCOMING RDD EVENT PREVIEWS

The Respiratory Drug Delivery (RDD®) conference series has become a must-attend event for researchers, product developers and vendors concerned with all aspects of nasal and inhaled pharmaceuticals. Participation brings attendees into frequent contact with colleagues, clients and customers located around the world, especially now that RDD conferences are established on three continents.

All three conferences - RDD (the North American event), RDD Europe and RDD Asia - are biennial, alternating between North America and Asia events in even numbered years, and a Europe event in odd numbered years.

A session at RDD Europe 2017

RDD ASIA 2018 Respiratory Drug Delivery

The most recent RDD event was RDD Asia 2018, co-organised by RDD Online and Aptar Pharma. It was held at the Grand Hyatt Kochi in Kerala, India, on November 14–16, 2018. The venue was a business friendly, western-style waterfront hotel located on Bolgatty Island, about 32 km from the Kochi International Airport, ensuring easy access from the US, Europe and Asia. The meeting attracted about 200 attendees from 16 countries. The majority of participants were from India, augmented by 23% from Europe, 11% from the rest of Asia and 8% from the US. The pharmaceutical industry sent the most delegates (31%), but there were strong showings by instrument (10%) and service companies (27%), and a smaller contingent of government and academic scientists (7%).

Few conferences allow English-speaking Asian scientists and managers to access high-quality, peer-reviewed science directly pertaining to inhaled product development without the necessity of securing a visa and flying long distances. RDD Asia 2018 provided such an opportunity by bringing western experts to India to present alongside local specialists with expertise in Asia-centric issues.

All delegates were warmly welcomed by the conference chairman, Richard Dalby (University of Maryland, MD, US), before enjoying a plenary lecture from Rob Price (University of Bath, UK) speaking on "Challenging the Bioequivalence Hurdles for OINDPs: Achieving Q3 Structural Equivalence". Additional presentations were offered in sessions addressing "Advancing Regulatory Science of Inhaled and Nasal Products", "Predictive Models to Support Inhalation Science", and "Satisfying Patient Needs in the Global Marketplace". The response to the talks presented by Indian and international speakers was enthusiastic, as was made apparent by delegate feedback and the high level of audience engagement during podium sessions.

RDD Asia 2018 underscored India's emergence as a global power in inhaled and nasal pharmaceutical development and patient care. The poster session, technology exhibition and workshops each created opportunities for exchanging ideas and discussion, with connected devices generating a lot of buzz. There were 26 exhibiting companies and six workshop presentations, providing ample networking opportunities to attendees, including first-timers and RDD regulars.

The workshop sessions, with their small group, hands-on demonstrations and/or case study format, were particularly suited to exchange of detailed ideas and quick acquisition of relevant new knowledge directly applicable to pulmonary and nasal drug delivery. Workshops have proven to be an excellent tool for connecting scientists and business professionals to their suppliers, service providers and regulators in a relaxed atmosphere that fosters open communication. Exhibitors were available throughout both conference days to answer questions about their products and services and some reported barely having time to eat as a result.

The spectacular views at the welcome reception on the rooftop terrace of the Grand Hyatt Hotel got the networking started and, on the Thursday evening, the gala fiesta dinner on the palm lawns of the hotel provided attendees with ample opportunity to unite with old friends and form new partnerships.

Peer-reviewed speaker papers and poster abstracts were made available in print to all delegates, with access also available on mobile devices via RDD's conference website.

RDD EUROPE 2019 Respiratory Drug Delivery

Respiratory Drug Delivery Europe 2019, which takes place on May 7-10, 2019, in Lisbon, Portugal, is designed for emerging and high-level scientists, academics, clinicians and industrial and regulatory specialists. It is a must-attend conference for companies involved in researching, developing, testing or marketing of medicines, devices and services associated with pulmonary or nasal pharmaceutical products. The conference is jointly organised by RDD Online and Aptar Pharma.

The programme features all new scientific content, including expert presentations during themed sessions titled:

- "New Approaches to Treating Old Diseases"
- "Pipes, Particles and Predictions: New Insights into Deposition"
- "Re-inventing Inhalers for the Digital Age"
- "Take a Deep Breath: Brexit and Environmental Sustainability"
- "New Approaches to Inhalation Product Development and Production".

The table-top technology exhibition and scientific poster session will be co-located close to meal and refreshment stations to ensure maximum interaction between delegates and academics, excipient, device and equipment designers, and component and service suppliers. Workshop sessions will feature practical and interactive demonstrations of innovative technologies, products and services tailored to individual interests, such as connected health, excipient and device selection or product evaluation.

Recognising the importance and contributions of emerging scientists, all accepted poster abstracts from graduate students are automatically eligible for the VCU RDD Peter R Byron Graduate Student Award, which covers the winning student's registration fee, travel expenses and accommodation up to a maximum of US$2,000 (£1,500). Graduate student work will also feature in the poster session and presentations. The schedule will allow ample time to reflect on and discuss the ideas presented at the conference, while meeting new collaborators and business partners in a range of formal and informal settings.

Registration for RDD Europe 2019 is currently open. Students and employees of academic and government agencies receive a substantial discount.

RDD 2020 CALIFORNIA
Respiratory Drug Delivery

The programme for RDD Europe 2019 is full, but RDD is welcoming submission of talk titles and speaker nominations for the next North American meeting until August 1, 2019. Potential speakers with novel data and insights are invited to submit a 200-word summary of their purpose and major findings to the Organising Committee. Each summary will be reviewed for originality, merit and programme fit before invitations are issued.

Respiratory Drug Delivery 2020, organised by RDD Online with cooperation from Virginia Commonwealth University (Richmond, VA, US), will be held at JW Marriott Desert Springs, Palm Desert, California on April 26-30, 2020.

The poster abstract submission deadline for this meeting is January 13, 2020. Companies are also invited to participate in the technology exhibition at which components, excipients, hardware or services may be displayed on a table. Details and sign-up for tables will become available in late 2019 on RDD Online's website, which will also outline sponsorship opportunities to maximise the value of participation.

For more information on RDD Europe 2019 and RDD 2020, please visit www.rddonline.com or contact info@rddonline.com

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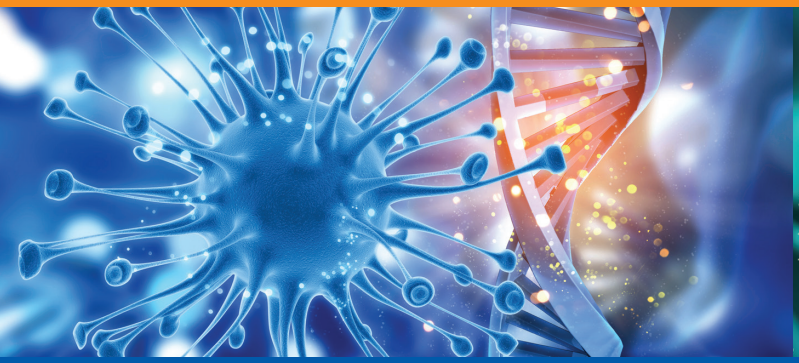

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PAUL ALLSOP, MILES KOTTMAN, HANNAH PRIESTLY & JON REED, CONSORT MEDICAL

Paul Allsop is a Senior Development Engineer for Consort Medical's Product Engineering team. He has 22 years' experience innovating drug delivery devices, for which he has a number of patents to his name. He joined Consort in 1997 and has held roles of increasing responsibility within the R&D function. During his time with Consort Medical he has primarily been involved in the design and development of pMDI valves and actuators, including dose counters. Mr Allsop also designed the Unidose Xtra spring powered nasal device with its unique patented trigger mechanism.

Miles Kottman, Alliance Manager at Consort Medical, has more than 25 years' experience in the development and industrialisation of medical devices. His career began in *in vitro* diagnostics. As a programme manager, he led multiple inhalation device programmes from early-stage product development through to high-volume production. Then, as Head of Programme Management at the Bespak division, he was responsible for the programme portfolio and its new-product-introduction process. Now operating in a commercial role, he manages commercial partnerships for existing and new products and opportunities. He is responsible for commercially supporting customers with the Unidose Xtra nasal delivery device.

Hannah Priestley is Graduate Commercial Manager at Consort Medical having joined the company's Graduate Scheme in September 2018 after graduating from The University of Warwick (UK) with an MSc in Medical Biotechnology and Business Management. Her role involves learning all aspects of the commercial function, including analysis of key market segments including nasal, injectable and respiratory.

Jon Reed, Business Development Director at Consort Medical, has more than 15 years' experience, in both healthcare and pharma, including managing complex solutions into the pharma industry. Mr Reed has an MBA specialising in business strategy and is responsible for commercially supporting customers with Consort Medical's Unidose Xtra nasal delivery device.

In this interview with *ONdrugDelivery Magazine*, this group of colleagues from Consort Medical discuss the company's integrated formulation and device offering, and focus on its simple, low-cost, single unit-dose, spring powered nasal device, Unidose Xtra.

"Consort's full value proposition to customers … means that we not only have the device itself, but we can formulate API to go into that device, we can manufacture, assemble and package the device, and supply that to the end-customer, streamlining the supply chain."

Q Could you give an overview of Consort Medical's broad offering and business structure, in particular in light of the rebranding last year?

MK Consort Medical is a developer and manufacturer of drugs and premium drug delivery devices. Globally, we employ around 2,000 staff and we're committed to investing in patient- clinical- and customer-driven innovations to create new treatments. We offer customers a single source for drug and device development, formulation, manufacture, fill and finished form, with two integrated operational divisions – Bespak and Aesica.

We partner with pharma companies with our core business providing innovative, life-improving treatments to patients across the world through two integrated activities. One is the design, development, and manufacturing of high-performance drug delivery devices such as, injectables, nasal, and ocular delivery systems as well as point-of-care diagnostics. The other integrated activity is the development, formulation, and manufacture of active pharmaceutical ingredients (APIs) and finished-dose drugs to the highest quality standards.

In summary, Consort Medical offers a one-stop service to streamline the development of pharmaceuticals, and their route to market.

The Bespak division was founded in 1959 so we have more than 50 years' experience in drug delivery. We work with customers across a full spectrum from the pharma and biotech industries, that are developing specialist drugs through to branded generics.

Today, we make in excess of half-a-billion devices annually, mainly through our King's Lynn (Norfolk, UK) site. We make over two-and-a-half billion moulded components annually, so we specialise in high-volume, high-complexity injection moulding and complex device assembly. We've also got capabilities for prototyping, and low-volume to high-volume automated production.

> "The nasal route is particularly suitable for delivering drugs that require rapid onset of action."

JR Turning to the Aesica division, Aesica is a full-service developer and manufacturer (CDMO) of active pharmaceutical ingredients (APIs) and finished dosage forms. We partner with customers to provide a flexible, efficient and dependable service that leverages our innovative approach and more than 30 years' experience. We continuously invest in the latest technologies and develop our people to stay at the forefront of the industry. As part of the Consort Medical Group, we work together with our drug delivery device experts to accelerate the route to market of drug-device combinations, through streamlined supply, for our customers at any stage of the development cycle.

We have a number of large pharmaceutical company partners and manufacturing sites across Europe, mainly in Germany, Italy and the UK. Our Queenborough site on the Isle of Sheppey (Kent, UK) is one of our largest.

Aesica's core competency, combined with that of Bespak, enables Consort to offer a unique end-to-end service to its customers. For example, with the Unidose Xtra, single unit-dose, spring powered nasal delivery device (see Figure 1), this combined offering means that we not only have the device itself, but we can formulate API to go into that device, we can assemble and package the device, and supply that to the end-customer, streamlining the supply chain.

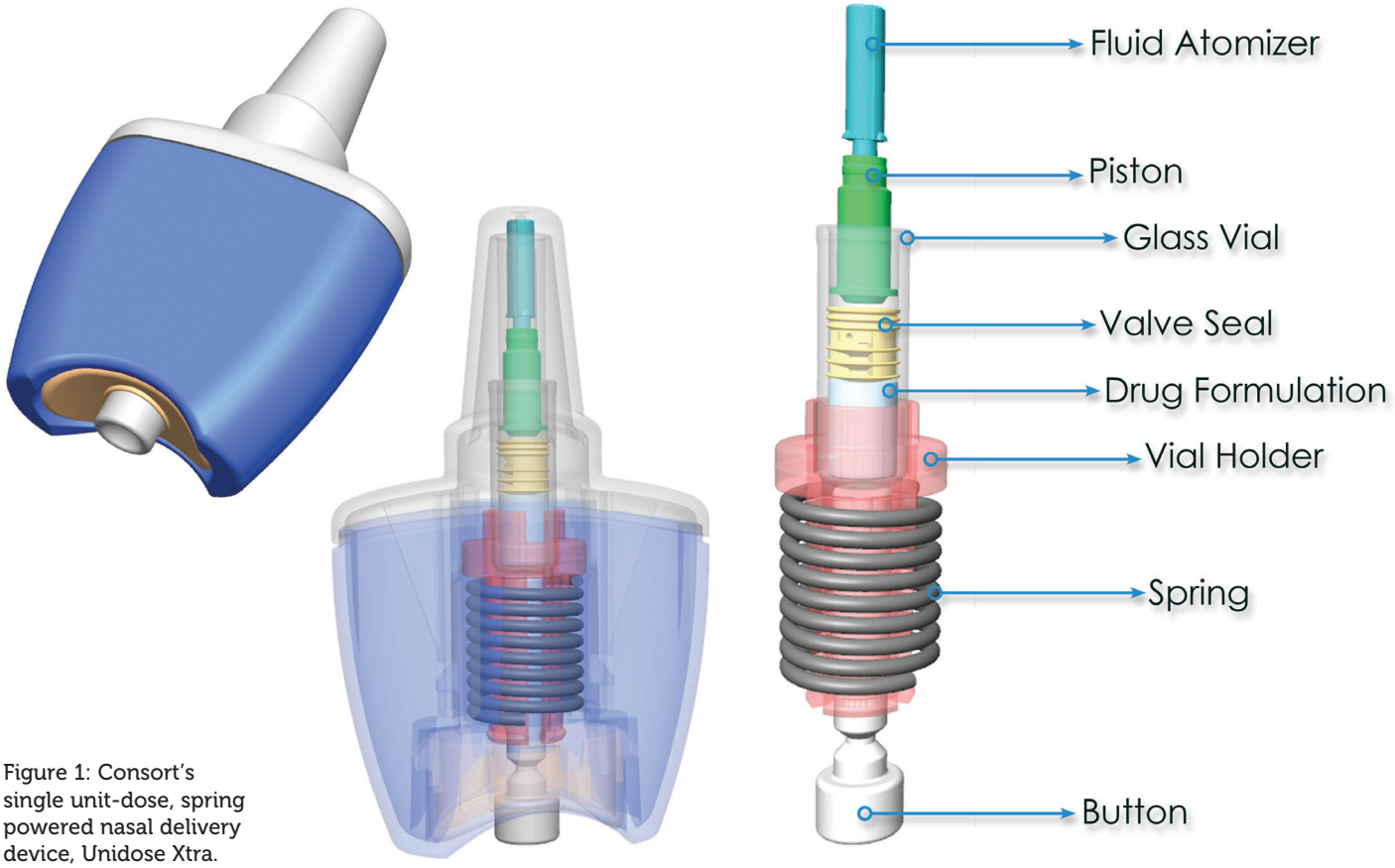

Figure 1: Consort's single unit-dose, spring powered nasal delivery device, Unidose Xtra.

The major advantage is that we are able to offer a single-supply-chain solution to customers wanting combination products.

Q Let's focus on nasal delivery now. From the point of view of the demands and requirements of today's market, what can nasal delivery offer?

MK There is a well-established nasal delivery market across a wide range of therapies. The two types of delivery devices (for aqueous formulations) are multi-dose, pump-like products, and unit dose-type products. The interesting area for us, where we're observing market growth and recent product approvals, is with unit-dose products. In particular, we're seeing the repurposing of treatments that have traditionally been administered by injection. Examples of these include therapies for pain management, and emergency lifesaving treatments. New formulations, and reformulations, are emerging and with the inclusion of drug absorption enhancers it is allowing smaller delivered volumes and lower dosages, which is ideal for administration through the nasal cavity. Together with lower cost and simpler devices, these developments can offer many benefits over and above autoinjectors, for pharma companies and the end user.

HP The nasal route is particularly suitable for delivering drugs that require rapid onset of action. It has advantages over both the oral and parenteral routes. Nasal delivery is non-invasive yet fast-acting, reaching the systemic circulation quickly. It avoids first-pass metabolism and there's potential for direct delivery to the brain. This makes nasal delivery suitable in the treatment of anaphylaxis, pain, migraine and, in particular, opioid overdose. Focusing on opioid overdose, according to the US Centers for Disease Control and Prevention, in the US 47,000 people died in 2017, and currently 130 people a day die, from opioid overdose.

In the treatment of anaphylaxis and opioid overdose, it's important to remember that it may not actually be the recipient of the drug that's delivering it. Treatment often requires third-party intervention and the nasal cavity gives good access for quick delivery for a relatively unskilled, untrained individual. So to place a device into somebody's nostril is relatively simple, especially in an emergency situation.

> "We recognise and generate the necessary performance data on our products, which is made available to share with partners for regulatory submissions, significantly reducing their risk burden."

Q What are the most important patient needs, and how can a nasal delivery system meet these needs?

PA Patients need intuitive, simple devices for any type of application, including nasal. A unit-dose nasal system offers an ideal, simple, one-handed device solution, which is easy to use and small enough to carry around everywhere. This all helps to promote patient compliance. In some cases devices also need to be used by a third-party to administer the drug to a patient without the need for any skill or training.

Users of the device also need flexibility. They don't want a device where their own interaction interferes with successful delivery. If they have to perform a set of tasks in a very specific way to achieve optimum delivery, that's not ideal because everybody will do things differently. It is key to have a device that anybody can use, and it doesn't really matter too much how they use it, they still achieve the same end result, successful drug delivery.

For example, in a standard pump-based nasal device, variability in actuation speed can lead to a difference in spray performance, whereas ideally this should not be influenced by the user. Also, force to actuate is key to achieving optimum delivery. Therefore we have developed a device with a low actuation force and the utilisation of a spring takes care of the required force and velocity element for us. Having a low actuation force makes a device more user-friendly and attractive to a wider variety of users.

In a Laboratory environment where a machine is used to activate these types of devices, variability can be low due to the parameters being used. What we've aimed for with our Unidose Xtra device is to provide Laboratory performance in the patients' hands, so that any variability between users has minimal influence. That probably can't be said for some other devices in the marketplace where they require a fixed group of parameters to be used to achieve optimum delivery. Designing this influence of patient variability out of the device's performance I think is key.

JR Portability is another factor. In anaphylactic shock, for example, some of the key benefits for patients with epinephrine (adrenaline) administered through a nasal spray rather than through a parenteral autoinjector centre around how compact and portable the device is. People who could suffer from anaphylactic shock typically need to carry around an autoinjector wherever they go. Unit dose nasal devices, like the Unidose Xtra, are actually very compact, very portable – they can fit into your pocket.

Q What do you see are the pharma industry's needs when it comes to selecting the best delivery solutions partner? How can a nasal delivery system meet those needs?

JR When developing a product to serve a customer need, there are so many factors that must be considered and I think one of the big advantages that Consort has is that we understand the device as well as actually developing a formulation to go in that device. Pharmaceutical companies are looking for a path to move a project all the way to a finished product, developing the formulation and device performance in unison with technical and regulatory input for their submission.

A key part of our value proposition is that we can undertake the formulation

> "Submissions can be time-consuming, expensive, and risky. Pharma companies are looking for technology that is proven across a number of potential populations, therapies and drugs, with supporting data around robustness and reliability."

"Beyond designing, developing and supporting regulatory approval we have a manufacturing platform behind us to be able to manufacture in line with market demands."

work in our actual devices, or device work in formulations we've also developed. This reduces the number of companies involved in bringing a product to market. Increasingly, pharmaceutical companies are looking to streamline the approach in this way, decreasing time to market.

With its integrated offering, Consort can truly determine the best path forward. We're offering both formulation- and device-based solutions and so there's no vested interest in recommending one or the other. It's a genuine decision as to what's truly the best approach to guarantee the best outcomes for the project, based on expertise and capabilities across both device and formulation aspects, and a knowledge of the whole project.

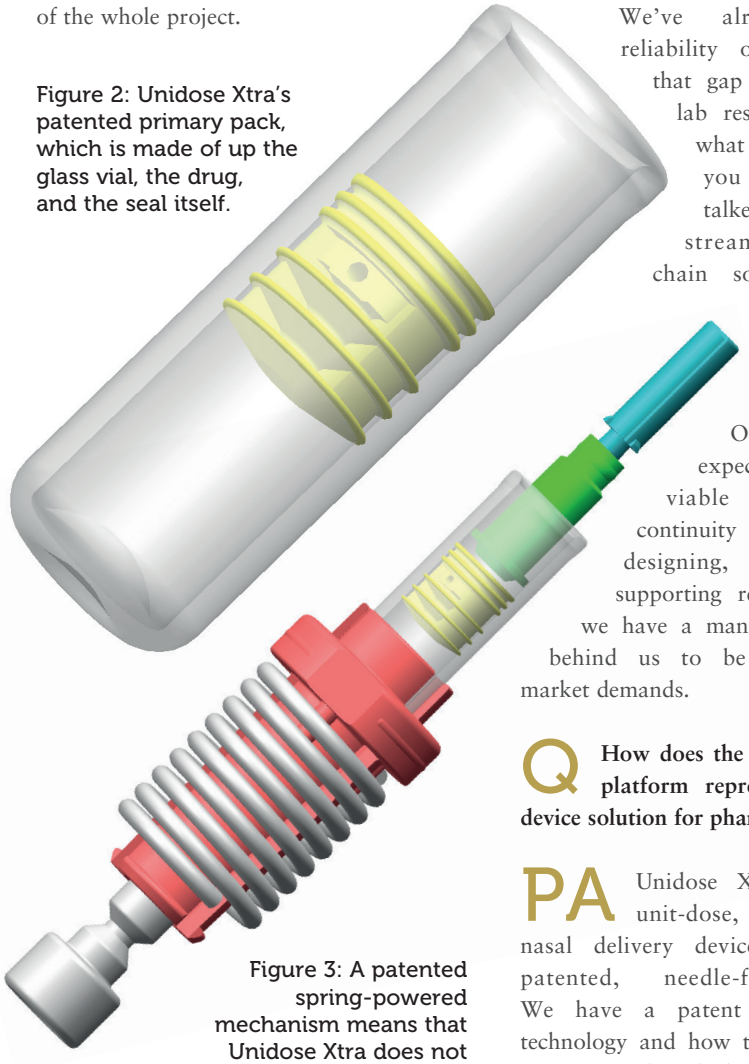

Figure 2: Unidose Xtra's patented primary pack, which is made of up the glass vial, the drug, and the seal itself.

Figure 3: A patented spring-powered mechanism means that Unidose Xtra does not rely on the actuation force or speed provided by the patient or user.

MK From a partner such as Consort Medical, pharma and biotech companies are looking for the lowest-risk approach for their product and their submission. Device development and drug development submissions can be time-consuming, expensive, and risky. Pharma companies are looking for technology that is proven across a number of potential populations, therapies and drugs, with supporting data around robustness and reliability. We recognise and generate the necessary performance data on our products, which is made available to share with partners for regulatory submissions, significantly reducing their risk burden.

We've already mentioned reliability of dosing, closing that gap between what the lab results give you and what actual performance you get, and we've talked about a robust, streamlined supply chain solution with fast speed to market. All of these factors feed into reducing risk. Our partners can expect a commercially viable product with continuity of supply. Beyond designing, developing and supporting regulatory approval, we have a manufacturing platform behind us to be able to support market demands.

Q How does the Unidose Xtra nasal platform represent an attractive device solution for pharma partners?

PA Unidose Xtra is our single unit-dose, spring powered nasal delivery device. It incorporates patented, needle-free technology. We have a patent around the seal technology and how that operates in the primary pack, which is made of up the glass vial, the drug, and the seal itself (Figure 2). As we have a patented spring-powered mechanism (Figure 3), Unidose Xtra does not rely on the actuation force or speed being provided by the end user.

Being spring-driven like an autoinjector takes away user variability, so Unidose Xtra delivery is completely, 100% controlled by the device itself. The user simply triggers the device by pressing a button and the device does the rest. In addition to simple, low-force, push-button operation, there's minimal button travel as well. This is all key and means it is suitable for a variety of users. Whether a child is using it or an elderly patient, or even an untrained third party, they'll all be able to easily trigger the device so that the mechanism can take over and deliver the same dosage at the same rate, irrespective of the user.

Unidose Xtra has an ambidextrous profile. It's not orientation-dependent, which would be important in an opioid-overdose situation if somebody is horizontal as opposed to somebody standing up or sitting down. So it can be used in any orientation without any impact on performance.

The Unidose Xtra activation button also serves as a use indicator. It moves as you depress it of course, but then as the device triggers and takes over, the button actually moves inside the device, offering a clear indication that it has been used. Therefore having no button visible makes it very obvious to a user that a device has already been used. Obviously, no cleaning or priming is required because it's single-use.

We have developed a platform device that's fully adjustable. For example, the spray pattern can be tailored. Pharma companies are looking to differentiate their products, so we can customise the styling, colours, etc. The optimised delivery for the device is set at 100 µL, so it's targeted around the standard volume that's typical for these types of nasal devices. Regarding materials selection, we can verify extractables profiles for specific parts and, as with all devices, we use regulatory compliant materials where necessary.

MK With our customer-focussed service, we represent a true partner, with the shared objective of delivering the end-solution. From a product development and industrialisation perspective teamed with a robust New Product Introduction process, we offer an end-to-end service for Unidose Xtra.

From formulation development, all the way through to device manufacture, filling, packaging and release.

ABOUT THE COMPANY

Consort Medical is a global CDMO, providing advanced delivery technologies, formulation and manufacturing solutions for drugs. Its customers include many of the largest pharmaceutical companies.

Optimising world-class drug delivery device development and manufacture, together with drug API and finished dose formulation and manufacture, within the same group streamlines and accelerates Consort's pharma customers' drug route to market.

The Consort group is at the leading edge of innovation and is committed to investing in patient and customer driven innovation, with the potential to create new treatments, new markets and new opportunities. It also continues to diversify into adjacent complementary markets and technologies which leverage our core competencies in drug formulation, manufacturing and delivery.

The company's King's Lynn, UK facility produces around 600 million devices per annum. It comprises 35,047 m² of manufacturing space, 21,409 m² of which is clean room. It has 30 fully automated assembly suites and 137 injection moulding machines. Around four billion components are assembled annually and 3.3 billion plastic components moulded annually. This output maintains six sigma quality (less than 3.4 defects/million). The Milton Keynes, UK, facility comprises 6,000 m² of manufacturing space of which 2,000 m² is clean room.

Consort group comprises two integrated operating divisions:

Bespak Drug Delivery Devices — a global market leader in the development and manufacture of drug delivery devices, providing pharma companies with inhaler and autoinjector technologies and development and manufacturing services.

Aesica Development & Manufacture API & Finished Dose — a leading pharmaceutical CDMO serving pharmaceutical companies with API and finished dose formulation development and manufacturing services.

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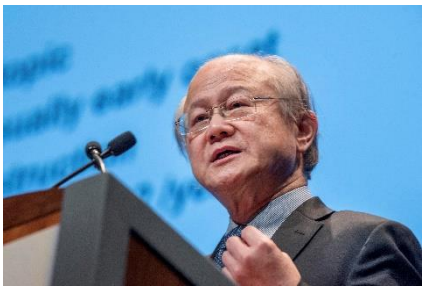

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DEPOSITION IN THREE NASAL CAST MODELS USING RETRONOSE CONCEPT

In this article, Laurent Vecellio, PhD, Research Engineer, CEPR, INSERM U1100, University of Tours, and Scientific Director, Nemera; Déborah Le Pennec, Research Technician, CEPR, INSERM U1100, University of Tours; Guillaume Grevin, Senior Design Engineer, Nemera; and Alain Regard, Technology Product Manager, Nemera; discuss a study conducted to test particle deposition characteristics of the RetroNose device prototype for nasal drug delivery.

INTRODUCTION

Nasal drug delivery is linked with interest in three fields of pharmaceutical targeting:

- Topical
- Systemic
- Central nervous system.

The clinical efficacy of a nasal treatment depends on how it is deposited in the nose, because the pharmaceutical target (local, systemic, brain) is directly related to a specific nasal anatomical site. A recent study on chronic rhinosinusitis (CRS) patients has shown how the deposition distribution of corticosteroids in the nasal cavities can have an impact on clinical outcomes.[1] This study has demonstrated the importance of homogenous deposition in the different target regions of the nasal cavity for treating CRS. The turbinates, the maxillary sinuses and the ethmoid regions have been identified as important drug delivery target

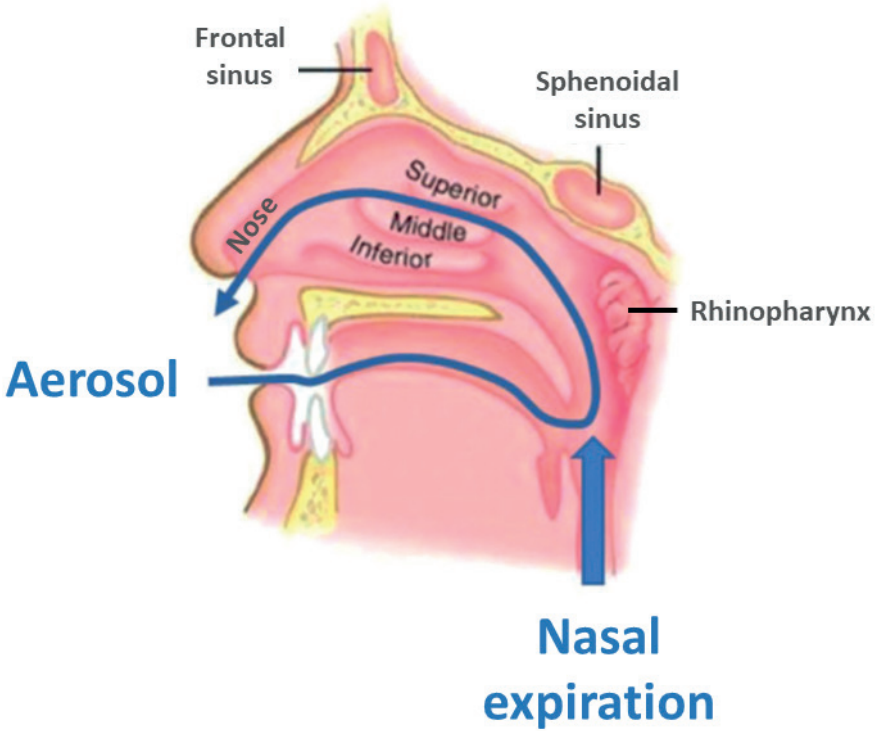

Figure 1: The RetroNose concept: drug delivery through the buccal cavity during the nasal expiratory phase, causes drug particles to enter the nasal cavities through the rhinopharynx.

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"This new device, RetroNose, uses a pMDI to administer the drug through the buccal cavity during the nasal expiratory phase."

Figure 2: RetroNose prototype device examples.

sites for local treatment of inflammation and infection in rhinological pathologies.[2] Systemic delivery is enhanced by exposing the drug to the middle and inferior turbinates and the septum which have a high vascularisation and large surface area (around 150 cm^2).

An alternate nasal delivery device concept, RetroNose, has been developed to achieve better drug deposition in the different regions of the nose (Figure 1).[3-4] RetroNose (Figure 2) uses a pressurised metered dose inhaler (pMDI) to administer the drug through the buccal cavity during the nasal expiratory phase. Drug particles enter the nasal cavities through the rhinopharynx, which has a significant impact on drug deposition profile. A recent study has already presented data from five asthmatic patients with rhinosinusitis treated with an aerosol therapy exhaled through the nose[5-6] using a similar concept.

The evaluation of nasal drug delivery device performance is traditionally done via regulatory *in vitro* tests:

- The dose delivery is measured and gives information about the consistency of dose delivered to the patient.
- The droplet size informs about the particle size distribution and potential lung penetration.
- Spray plume and spray pattern give information about the geometry of the spray.

Although these measurements are relevant for describing the *in vitro* characteristics produced by a nasal sprays pump, they are not adapted for the RetroNose device, as the medication is administered orally. Instead, anatomical models such as cadaver heads,[7] nasal cavity replicas[8] or nasal casts[9] are used to measure drug deposition across anatomical regions. Nasal casts are consequently more adapted for performance evaluation of the RetroNose device.

The main objective of the study discussed hereafter was to compare the deposition obtained by the RetroNose prototype with a nasal spray pump using three different nasal casts.

MATERIAL AND METHODS

The RetroNose prototype device was a pMDI (Inhalia®, Nemera, France) filled with HFA 134a gas (no surfactant) and a 12 µm active compound (API-1) particle size, resulting in a 14.8 ±0.4 µm mass median aerodynamic diameter measured by cascade impactor. A standard nasal pump (Flixonase®, France, GSK) was filled with API-1 solution, resulting in a 48 ±2 µm volume mean diameter measured by laser diffraction (n=3).

API-1 deposition in the nasal casts was studied using three different anatomical models, one developed by the Virginia Commonwealth University (VCU, Richmond, VA, US),[10] and two 3D-printed models recently obtained from females (FANI 1 & FANI 2, CEPR, INSERM U1100, University of Tours, Tours, France).

"A high variability in deposition was observed for the nasal spray compared with the RetroNose prototype device for the different regions of nasal cavities, except for in the middle part."

Nasal casts were connected to a mouth and a lung model, including a filter to measure potential drug penetration in the lungs.

Different regions of interest were defined in the nasal casts:

- Mouth
- Nose
- Upper part of the nasal cavity
- Middle part of the nasal cavity
- Lower part of the nasal cavity
- Rhinopharynx.

Three additional regions of interests were added for the FANI 1 & 2 nasal casts (maxillary sinuses, frontal sinuses, sphenoids). The different regions were washed with different volumes of sodium hydroxide using syringes. API-1 was assayed by a spectrophotometric method.

An additional experiment was performed using a second active product (API-2). A Flixotide® (125 µg fluticasone, GSK, France) pMDI was used in the RetroNose prototype and was radiolabelled with Tc99m, as previously described by Chand *et al.*[11] Nasal administration was performed on the VCU model. Deposition was imaged using a gamma camera and was fused with a nasal cast scan.

RESULTS

Results from the experiments demonstrated the following:

- No active compound was detected in the lung model for nasal spray and RetroNose.
- About 50% of the drug was deposited in the nose for the nasal spray.
- About 50% of the drug was deposited into the mouth using the RetroNose prototype.
- Less than 5% of the delivered dose was exhaled in ambient air using the RetroNose device.
- Results showed a major deposition in the middle part of the nasal cavity using the RetroNose device, in contrast to the nasal spray which emphasised deposition in the front of the nose.
- Greater depositions in maxillary sinuses, sphenoides and frontal sinuses were detected when using the RetroNose device compared with the nasal spray.

A high variability in deposition was observed for the nasal spray compared with the RetroNose prototype device for the

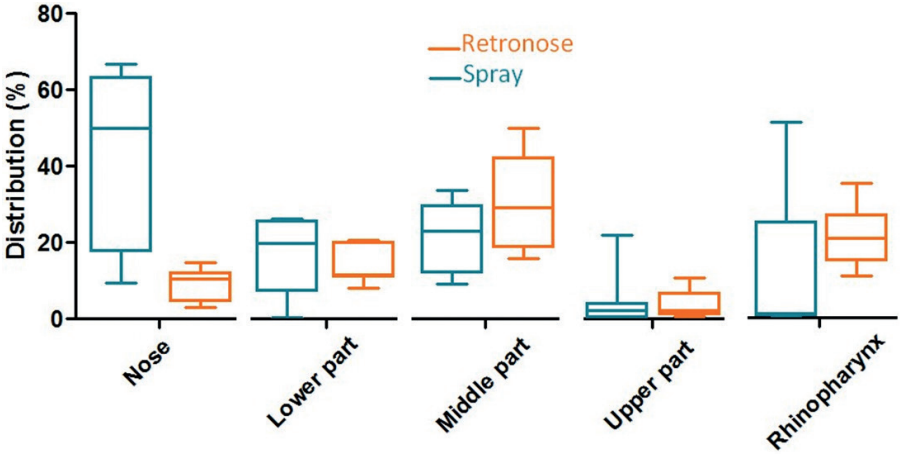

Figure 3: Drug deposition in the different regions of the nasal cavities (upper airway model) using three different nasal cast models for a standard nasal spray (A) and RetroNose (B). (Results expressed in terms of deposited fraction in nasal cavity, n=3 for each nasal cast.)

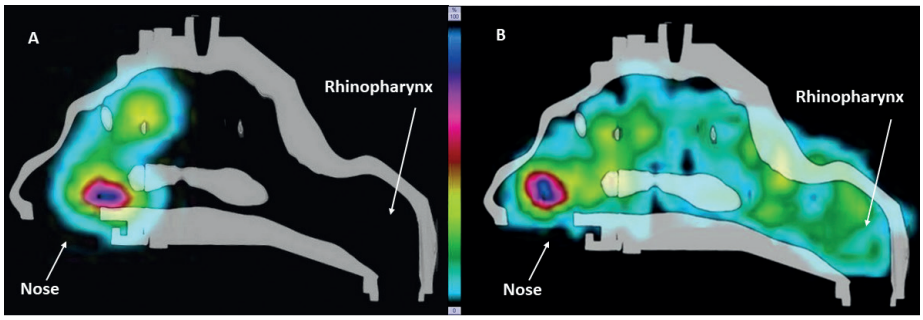

Figure 4: Radioactive deposition of fluticasone in the VCU model with Flixonase® nasal spray (A), and Flixotide® RetroNose prototype device (B).

different regions of nasal cavities, except for in the middle part (Figure 3). This variability should be more important for a nasal spray where the angle and penetration is not controlled during spray administration. For a nasal spray, drug particles are not likely to reach the rhinopharynx region, whereas a significant deposition rate is consistently observed when using the RetroNose device.

Deposition images show a more distal and homogeneous deposition in the VCU nasal model when using the RetroNose device compared with a nasal spray (Figure 4).

> "The homogenous deposition obtained with the RetroNose prototype device demonstrates its ability to administer the corticosteroid directly into the different anatomical regions of interest, including the sinuses."

DISCUSSION

The deposition differences between a nasal spray and the RetroNose device can be explained by the particle size and the route of administration. The particle size generated by the RetroNose device is smaller (12 µm) than the nasal spray (47 µm) and therefore the kinetics of the particles in the nasal cavities is different, resulting in different deposition between the two. Administration through the mouth also induces a difference in air humidity compared with nasal administration, which can increase the size of the particles. Particle intake from the oropharynx instead of the nose can also explain the difference in terms of penetration and deposition in the different regions of the nasal cavities. Depositions in the mouth and oropharynx using the RetroNose device can be explained by the particle velocity generated by the pMDI. Similar deposition has been reported when using commercialised pMDIs for inhalation.

The homogenous deposition (Figure 3) obtained with the RetroNose prototype device demonstrates its ability to administer the corticosteroid directly into the different anatomical regions of interest, including the sinuses. This deposition pattern is very different to that of the nasal spray, where the drug is deposited in the first centimetres of the nose. Similar homogenous depositions have been reported using a nebuliser, and have demonstrated increased drug retention in the nasal cavities and higher clinical efficacy than a nasal spray.[1] In this study, the RetroNose device used a pMDI as an aerosol generator and can be defined as a portable, multidose device for nasal delivery without lung deposition.

CONCLUSION

This study has shown promising results with regard to a new method of nasal drug administration for producing a more homogenous deposition distribution than a standard nasal spray. The RetroNose device demonstrated potential to be of interest for local, vaccine and systemic nasal drug delivery.

ACKNOWLEDGEMENT

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CounterAct

130 A DAY AND GROWING: ANSWERING THE US OPIOID OVERDOSE EPIDEMIC

In this article, Todd Pizitz, PhD, and Donald Mealing, both Co-Founders of CounterAct, discuss the ongoing opioid crisis in the US and the current use of the opioid reversal medication naxalone, and introduce the CounterAct device for naxalone home use.

In the US in 2017, over 47,000 deaths were attributable to opioid-based substances.[1] The average number of deaths per day from opioid overdoses, currently around 130, continues to rise. In fact, some researchers project that opioid overdose deaths are estimated to increase annually by 147%, approaching 81,700 by 2025.[2] Due to this upward trend in the number of deaths, recent estimates have determined that one is more likely to die from an accidental opioid overdose than from a motor vehicle accident.[3]

> "According to the US Centers for Disease Control and Prevention (CDC), the administration of naloxone from the years 1996 to 2014 assisted in reversing the effects of opioid overdoses in an estimated 26,000 cases.[4]"

As with any epidemic, researchers, scientists, legislators and interventionists are endeavouring to slow or cure the progression of the life-ending situations and circumstances. Similar efforts occurred in 1981 when the first cases of auto-immune deficiency syndrome (AIDS) began to emerge; the disease was identified and studied, and interventions were created to reduce death rates and treat AIDS and associated syndromes. The opioid epidemic, too, has been identified and studied, but the interventions or requisite changes have not moved swiftly enough yet to see the death rate drop.

One such intervention aimed at reducing the opioid overdose death rate is increasing the availability of naloxone, which is an opioid reversal medication, approved for public use by the US FDA in 1971. Beginning in 1996, naloxone was more widely marketed, distributed and made available to people who are not medically trained. Naloxone is marketed as a generic and brand names such as Narcan® (ADAPT Pharma, Radnor, PA, US) and Evzio® (kaléo, Richmond, VA, US) have emerged as FDA-approved naloxone products to counter the effects of an opioid overdose.

Evzio, a hand-held autoinjector that delivers naloxone IM, was approved in the US in 2014. Narcan, an intranasal naloxone product, was approved in 2015. According to the US Centers for Disease Control and Prevention (CDC), the administration of naloxone from the years 1996 to 2014 assisted in reversing the effects of opioid overdoses in an estimated 26,000 cases.[4]

Even with these two FDA-approved formulations of naloxone available for public use, the death rate from opioid overdoses has not declined. Recent efforts through legislation, such as the

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Figure 1: The CounterAct naloxone device fits on top of a standard US prescription pill bottle.

co-prescription bills in states such as California and the US Surgeon General recommending that the public carry naloxone, have not made a significant impact in reducing the deaths associated with opioids.

CounterAct is a small technology start-up dedicated to tackling the opioid crisis and reducing the overdose death rate. Its founders have personal experience with the effects of the crisis. The company was founded to realise an idea the founders had in 2017 whilst discussing an FDA innovation challenge on reducing opioid deaths.

At the core of the idea was how best to improve speed of access to and provide wider availability of life-saving naloxone. Following its FDA approval, Narcan saw rapid adoption by emergency medical response agencies as a must-have opioid overdose resource. Narcan's simple nasal spray route of administration, combined with its single unit-dose applicator, provided law enforcement and medical first responders with an extremely compact, efficient and effective intervention tool. Narcan has demonstrated noteworthy success in reversing the effects of an opioid overdose and has commonly been administered by emergency medical responders.

"One key way to improve public access to naloxone is to improve its proximity to opioid patients. CounterAct's device aligns with this priority by placing a unit-dose of life-saving naloxone on top of the container holding an opioid patient's prescription pills."

Part of the opioid epidemic is the prescription opioid landscape. Accidental ingestion of opioid medication resulting in an overdose accounts for an estimated 40% of all of the opioid overdose deaths.[5] In other words, an estimated 46 people a day have been dying from prescription opioid overdoses. In 2017, the CDC reported that 191,218,272 prescriptions were written for opioid medications in the US. Narcan has, as mentioned previously, been adopted by emergency medical responders, but has not crossed into widespread public use, even with almost 200 million opioid prescriptions written annually.

But how then could naloxone's public availability and time to access be improved over emergency response? CounterAct conceived of an idea to expand upon Narcan's utility by designing a unique device suited for opioid patient home use.

One key way to improve public access to naloxone is to improve its proximity to opioid patients. CounterAct's device aligns with this priority by placing a unit-dose of life-saving naloxone on top of the container holding an opioid patient's prescription pills (Figure 1). In a suspected overdose emergency, a patient's family members, friends or associates can instantly administer the naloxone spray after calling the emergency services, thus saving precious time. Additionally, the cautionary effect of having the two medications paired together may prove to increase patient medication compliance to prescriber's recommendations, offering a reminder that misuse of opioid medication can result in death.

"Having a naloxone nasal spray in the home is akin to having a fire extinguisher in case of fire."

Specific features the CounterAct device were incorporated for non-emergency, non-medical trained personnel suited for home use. Having a naloxone nasal spray in the home is akin to having a fire extinguisher in case of fire. In fact, The National Association of Fire Equipment Distributors (NAFED) reported that out of the 13,221 fire incidents reported, fire extinguishers successfully extinguished 12,505 fires, lending strong support for having a fire extinguisher in your residence or place of work.[6] Therefore, having immediate access to life-saving medication such as naloxone will likely increase the probability of surviving the effects of an opioid overdose if administered in a timely manner.

From an economic perspective, a recent summary authored by the Council of Economic Advisers revealed the economic burden of the opioid crisis in 2015 was US$504 billion (£384 billion), with the mortality costs consisting of over $428 billion.[7] Widespread dissemination of naloxone will reduce the healthcare costs associated with the opioid epidemic.

The CounterAct device provides a practical home-based solution to combat opioid overdose rates. The legislative efforts underway to mandate prescribers to co-prescribe naloxone with opioid medications, such as the aforementioned legislation passed in California in September 2018, will hopefully spur more accessibility of this lifesaving medication, and begin the process of ending the opioid epidemic.

ABOUT THE COMPANY

CounterAct is comprised of Co-Fouders Todd Pizitz, PhD, and Donald Mealing. The company has completed its pre-IND meeting with FDA and has a developmental 505(B)(2) regulatory path as a drug-device combination product. CounterAct has filed both national and international non-provisional patents. The company anticipates collaborating with major drug and device manufacturers to expedite its approvals and time to market.

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ABOUT THE AUTHORS

Todd Pizitz, PhD, is a licensed clinical and forensic psychologist in private practice in Vista (CA, US). As a forensic psychologist, Dr Pizitz works with those afflicted with various types of addiction. For the past 16 years, he has worked closely with private and public defence attorneys, family court services, the District Attorney's office, county adult and juvenile probation, and federal probation.

Don Mealing is a business entrepreneur with more than 25 years' experience as a chief executive officer over a variety of successful businesses. He was founder and CEO of American Corrective Counseling Services (San Clemente, CA, US), one of the largest private counseling diversion companies servicing courts and prosecutors across the US criminal justice system. Mr Mealing has served on numerous boards, including 14 years on the Board of Regents, Harris Manchester College, Oxford University, UK. He has lost three close relatives to opioid overdose.

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2019 ISAM CONGRESS PREVIEW

Montreux, Switzerland, May 25–29, 2019

By Prof Dr Barbara Rothen-Rutishauser, Co-Chair BioNanomaterials, Adolphe Merkle Institute, University Fribourg, Switzerland and Conference Chair ISAM 2019.

The 22nd Congress of the International Society for Aerosols in Medicine (ISAM) will be held in Montreux, Switzerland, from May 25-29, 2019. The congress will bring together about 400 international attendees at one of the largest pulmonary drug delivery and respiratory health conferences. The attendees will include clinicians, respiratory healthcare professionals, aerosol engineers, formulation scientists and regulatory representatives. The scientific organising committee includes Barbara Rothen-Rutishauser, Fabian Blank, Stephan Ehrmann, Otmar Schmid and Jessica Oakes. This group is supported by the ISAM organisation, Swiss Foundation for Research in Microtechnology (FSRM) (Neuchâtel, Switzerland) and CyCOM (Frankenberg, Germany).

SCIENTIFIC SESSIONS

ISAM 2019 will focus on the following topics:

- New devices and emerging therapies
- Bridging the gap between *in vitro*, *in silico* and clinical data
- Novel strategies for pulmonary immune-modulation in respiratory disease
- Paediatric and cystic fibrosis disease focus: pulmonary hypertension, predictive lung (disease) models for aerosolisation therapy
- Developing novel uses for old drugs
- ERS/ISAM session: inhalation therapy for chronic lung disease
- A hot topic debate about digitalisation and perspectives for inhaled therapy.

Sessions will utilise various formats and experts will engage in discussions with the audience.

SELECT ORAL PRESENTATIONS

The organising committee is particularly focused on the presentation of current, unique and state-of-the-art data. While all accepted abstracts will be presented as posters, the committee will also be selecting abstracts for 15-minute oral presentations. All abstracts will be indexed in the official ISAM *Journal of Aerosol Medicine and Pulmonary Drug Delivery* and published online for access after the congress. Abstract submission is available via the congress website.

PRE-CONGRESS WORKSHOPS

Preceding the congress, on May 25, interactive workshops will be held on the following topics:

- The basics of aerosol technology for respiratory drug delivery

Figure 1: The Montreux Music & Convention Centre (2m2c) in Montreux, Switzerland. Copyright © Lionel Flusin.

- Digital Health in Inhaled Drug Delivery (a joint ISAM/IPAC-RS (International Pharmaceutical Aerosol Consortium on Regulation and Science) workshop)
- Advanced lung cell culture models and microfluidic tissue chips in aerosol medicine and respiratory disorders.

The workshops will provide attendees with a full-day with experts in each scientific area.

NETWORKING EVENTS

Several networking events are scheduled during the conference to foster interactions between participants and to support and coach young female students:

- Poster session during breaks/evenings with refreshments
- Networking group meetings
- Student networking event
- "Women in Science" lunch session.

AWARDS PRESENTATIONS

During the congress, several ISAM awards will be presented, including the Thomas T Mercer Award, Career Achievement, Young Investigator, Student Research, Jurai Ferin and Best Oral Presentation. Details about each award and their submission guidelines can be found on the congress website.

EXHIBITION AND SPONSORSHIP

The ISAM congress offers companies a range of sponsorship and exhibition options, including the opportunity to showcase new products and provide face-to-face training. Interested companies are invited to contact the organising committee via the congress website.

CONGRESS VENUE

The conference will be held at the Montreux Music & Convention Centre (2m2c) in Montreux, Switzerland (Figure 1). The state-of-the-art building is located on the beautiful shores of Lake Geneva, surrounded by gardens and the principal hotels of the town.

ISAM 2019 promises to be a dynamic international meeting. The congress organising committee and the ISAM board encourage anyone interested in aerosols in medicine to consider attendance, submission of abstracts and sponsorship.

ABOUT THE SOCIETY

The International Society for Aerosols in Medicine (ISAM) is an international organisation, founded in 1970, focused on all areas of aerosol research, including pulmonary drug delivery, new and evolving technologies and the health effects of inhaled aerosols. The Society holds a congress every two years to engage with its membership and review the current state-of-the-art within aerosols in medicine. Between congresses, the society focuses on the advancement of the science of aerosols in medicine via publication, distribution and education. Much of its scientific publication is done through the official journal of ISAM, the *Journal of Aerosol Medicine and Pulmonary Drug Delivery*.

ABOUT THE AUTHOR

Prof Dr Barbara Rothen-Rutishauser received her PhD in 1996 in cell biology at the Swiss Federal Institute of Technology (ETH) in Zurich. From 1996 to 2000 she held a post-doctoral position in Biopharmacy at ETH and in 2000 she joined Prof Peter Gehr's research group at the University of Bern, Switzerland, as a postdoc. After promotion to group leader in 2006 she completed her habilitation in cell biology in 2009. Prof Rothen-Rutishauser has pioneered the development of 3D human lung models to assess effects of aerosolised drugs and nanoparticles. Since 2011, she has been the new chair in BioNanomaterials at the Adolphe Merkle Institute, University of Fribourg, Switzerland, equally sharing the position with Prof Alke Fink. Prof Rothen-Rutishauser has published more than 220 peer-reviewed papers and is an associate editor of the journal *Particle and Fibre Toxicology*, and is also on the board of many other journals, such as *Nanotoxicology* and JAMPDD. She served as a board member for ISAM from 2011–2015 and is the conference chair of the 2019 biennial conference in Montreux, Switzerland.

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