PULMONARY DRUG DELIVERY:

INNOVATIONS IN DEVICE COMPONENTS, MANUFACTURING EQUIPMENT & INHALER TESTING

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"Pulmonary Drug Delivery: Innovations in Device Components, Manufacturing Equipment & Inhaler Testing"

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PERFORMANCE COUNTS

In this article about dose counters for pMDIs, Georgina Fradley, MBA, Global Technical Marketing Manager, 3M Drug Delivery Systems, discusses the need and drivers for dose counters for pMDIs, patients' points of view, dose counter selection criteria and pharmaceutical performance. She also describes 3M's Integrated Dose by Dose Counter, which recently received US FDA approval in conjunction with a pMDI product.

A simple question about why asthma medicine couldn't be dispensed from a spray can like hairspray created the evolution of the pressurised metered-dose inhaler (pMDI) and revolutionised the field of respiratory drug delivery. Today the pMDI remains the most popular delivery device for asthma and COPD medications,[1] offering a broad selection of therapies in a small, familiar device.

However, one of the most difficult challenges for patients using pMDIs is how to know when to replace their inhaler. Currently for pMDIs without a dose counter there are two main methods used to assess when patients should replace their inhaler. Patients either opt to keep a manual record of the doses taken or implement the popular float test, where the can is immersed in water to check for remaining content.

In reality, both of these methods are unreliable and can result in patients discarding a partly used inhaler, or even worse, finding their inhaler is empty when they need it most. The float test can add a further risk for medications that are not water soluble and many patient instruction leaflets now warn against using this method.

In primary research conducted by 3M Drug Delivery Systems, patients spontaneously requested a simple way to know when their inhaler should be replaced.[2] Patients revealed a wide variety of methods they use to make the decision currently, from keeping Post-It™ notes on the inhaler packaging, through shaking it next to their ear, to just "giving it a go" to see if any medication remains.

A 2003 US survey found that only 36% of 342 adult asthmatics reported having been told to keep track of their pMDI doses. Moreover, 25% had found their inhaler to be completely empty when they needed to use it, and 8% of these had ended up calling emergency services for help. The authors of this study recommended that all pMDIs be equipped with dose counters or indicators.[3]

> "AN INDICATION THAT A pMDI IS EMPTY WHEN IN FACT THERE ARE DOSES REMAINING MAY NOT BE LIFE THREATENING. NONETHELESS, IT COMPROMISES THE CONFIDENCE OF THE PATIENT IN THE PRODUCT."

Dose-counting mechanisms include dose counters and dose indicators. A dose indicator gives a graphical or numerical indication of the number of doses remaining in the inhaler (a graduated coloured band, or numerals in intervals of ten, for example) but does not give a precise measurement. A dose counter counts each individual dose and displays the exact number of doses remaining in the inhaler.

DRIVERS TO INCLUDING A DOSE COUNTER ON pMDI PRODUCTS

In 2003, the US FDA issued guidance on Integration of Dose-Counting Mechanisms into MDI Drug Products, which recommends that a dose-counting mechanism is included in all new orally inhaled pMDI products as an "accurate means of informing patients as to the remain-

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ing number of metered doses left in an MDI".[4] Whilst European guidelines do not explicitly require such a dose counter, it is encouraged.

However, regulatory drivers are not the only reason to consider a dose counter. Since the issuing of the FDA guidance, dose-counting mechanisms have been introduced across many countries and are becoming recognised as desirable to include in pMDI products to be competitive in the global market place.

The first dose counter to be incorporated into a pMDI product was introduced on Seretide™ (GSK) in Europe in 2004. In the US, Nycomed (on Alvesco®) and AstraZeneca (on Symbicort®) have included dose indicators, while GSK (on Advair® and Ventolin™) and Merck & Co (on Dulera®) have incorporated dose counters.

Dose-counting mechanisms are even considered beneficial in cost sensitive markets. Dr. Reddy's "Dose Counter Inhalers" include a visual mechanism that turns from green to red when the inhaler reaches the end of its life. Whilst in most countries these counters are not mandatory, they are recognised as adding benefit for the patient and are included to gain differentiation in the market.

In a study of patient satisfaction with a pMDI including a dose counter, LaForce *et al* found that an integrated dose counter was an important contributor to patient satisfaction. They found 92% of subjects agreed the dose counter helped them track doses, and that 75% would recommend the inhaler to a friend.[5]

Alongside the drive for product differentiation is the opportunity for generic alternatives. As key industry patents begin to expire, generic alternatives will enter to challenge innovator products. Where included on the innovator, a dose counter will be an essential factor in the success of the corresponding generic.

SELECTING A DOSE COUNTER: WHAT DO PATIENTS WANT?

In 2006, 3M conducted primary research with 100 patients across the UK and the US to understand the most important patient requirements when including a dose counter or indicator. This included the impact of inclusion on inhaler design as well as the benefits of dose-by-dose counting compared with indication and visual end of life displays.

The research found that patients preferred options that did not alter the external appearance of their pMDI, retaining familiarity and giving patients confidence their inhaler will work when they need it most. Options that added size and changed the appearance were often seen by patients as bulky and an unnecessary addition compared with integrated options, which retained both the look and feel of their current inhaler.

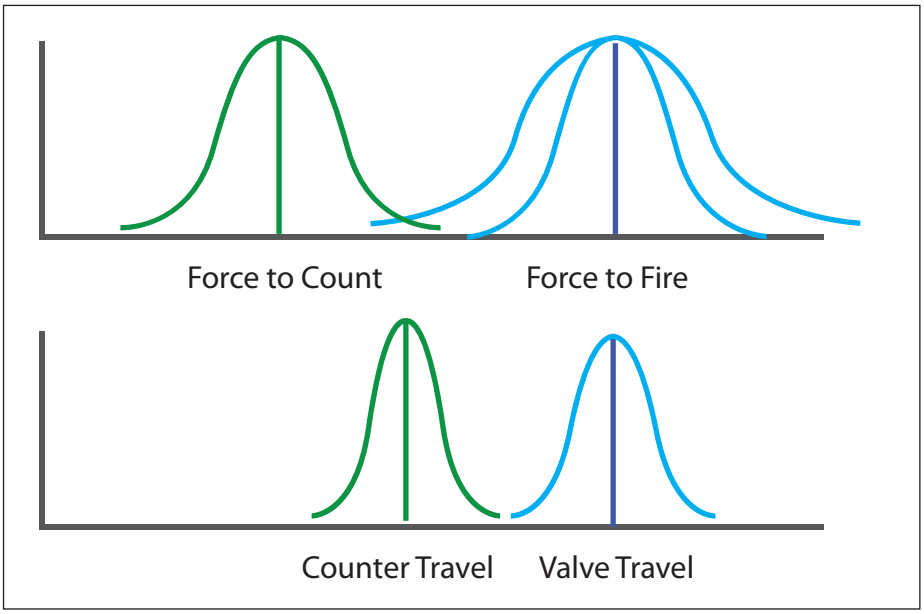

Figure 1: Schematic representing variability of count-fire points using force to fire *versus* valve displacement mechanisms.

When it came to the display, a means to know when to order a new prescription was clearly the primary driver for patients, and both dose counters and indicators were perceived as acceptable. However dose counters were expected to provide additional benefits, enabling patients to monitor their intake of medication. This was seen as helpful for preventer medication as patients felt they could use a counter to work out whether they had taken their required doses that day. For relievers, patients felt they could use the dose counter to assess whether they were taking the inhaler more frequently and should go and see their doctor for advice.

Additionally, parents felt the dose-by-dose counting option would enable them to monitor their child's use of inhalers better, especially with inhalers kept at school. School nurses or teachers could be instructed to send a note home to inform parents of increased use as well as giving plenty of notice of when the pMDI is about to run out.

SELECTING A DOSE COUNTER: TECHNICAL DECISIONS

When it comes to selecting the right dose counter for your pMDI product there are several technical factors to consider in addition to the market and patient drivers discussed above.

It is important to conduct a technical assessment to reduce the risks of including a dose counter in terms of regulatory approval and commercial viability.

Dose-counting mechanisms use either a displacement or force-driven approach. Force-driven mechanisms match dose counter indexing to the force required to actuate the pMDI. Displacement driven mechanisms use the movement of the valve to trigger indexing at a fixed point in the valve travel.

The force required to index a force driven counter is fundamentally more variable than the displacement required to index a displacement driven counter. [6] This is because the force to fire a pMDI changes both through the life of a unit and over the product shelf life, especially when the range of operating temperatures is taken into account. Displacement driven mechanisms use the movement of the valve to trigger indexing at a fixed point in the valve travel. Whilst there can be variability in travels between valves, this can be controlled to within acceptable limits through specifications in key manufacturing parameters. The differences in variability between force and displacement mechanisms are illustrated in Figure 1.

Accuracy of count is a critical parameter for dose counters. It is essential that the count point of the dose counter is closely matched to the fire point of the pMDI aerosol to avoid the counter display showing doses remaining when the pMDI has dispensed the number of doses claimed on the label (undercounting).

It is also important to reduce overcounting as this can lead to the inhaler reading zero when there are multiple doses remaining. In these circumstances, the indication that a pMDI is empty when in fact there are doses remaining may not be life threatening. Nonetheless, it compromises the confidence of the patient in the product and thus impacts patient preference and product differentiation. Weinstein *et al* conducted a study to compare the accuracy of the dose counter in a mometasone furoate/formoterol fumarate HFA pMDI and found discrepancies in only 0.13% of patients using dose counters to track doses.

Figure 2: The 3M™ Integrated Dose by Dose counter is now US FDA approved in conjunction with a pMDI product.

PHARMACEUTICAL PERFORMANCE

It is essential the addition of a dose counter does not negatively impact pharmaceutical performance. For new products this is easily managed through selecting the dose counter early in development and incorporating the appropriate actuator during *in vivo* and *in vitro* studies. For retrofitting to existing products, and for those progressing through later phase studies, it is important to consider the impact of switching to the new actuator style required for incorporation of a dose counter. Where possible the actuator change should be minimised by incorporating a dose counter with similar dimensions and airflow to the existing product. This will minimise the impact on critical pharmaceutical parameters such as dose uniformity and particle size distribution, as well as reducing the impact to manufacturing lines.

THE 3M INTEGRATED DOSE BY DOSE COUNTER

3M has developed the Integrated Dose by Dose Counter (shown in Figure 2). It is designed to prevent undercounting and minimise over counting.

The counter operates using a split-count principle which makes half of the count irreversibly on the firing stroke of the aerosol just before the metering valve releases spray, and completes the second part of the count on the aerosol return stroke close to the point where the metering valve refills ready for the next actuation. The approach, illustrated in Figure 3, ensures that the counter will not undercount (it always counts before fire) but the count point is not so far in advance of the fire point that it is easy to make a count without releasing a spray.

The 3M Integrated Dose by Dose Counter is now US FDA approved in conjunction with a pMDI product.

CONCLUSION

The addition of an accurate dose counter to an inhaler can improve patient satisfaction by offering reassurance and added confidence that their medication can be relied upon, as well as reducing the risk of patients taking a subtherapeutic dose by using the inhaler past the label claimed number of doses.

Selection of a dose counter that retains a familiar look and feel alongside excellent technical performance can offer benefits to pharmaceutical companies through aiding regulatory approval, enabling product differentiation to protect and grow market share or simply providing a competitive generic alternative to existing innovator products. As a result an accurate, patient-preferred dose counter is a desirable addition to new and existing pMDI products.

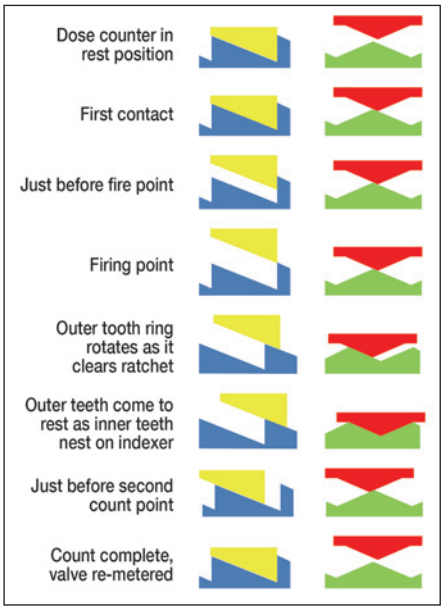

Figure 3: Diagrammatic representation of the split-count principle.

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TEN FACTORS TO CONSIDER WHEN SELECTING A DOSE COUNTER

1. Is the incorporation of a dose counter a regulatory requirement?
2. Will a dose counter enhance product differentiation?
3. For generic products, is a dose counter included on the innovator product?
4. Is the dose counter proven to be accurate and robust?
5. Does the dose counter provide patient reassurance through retaining a familiar look and feel?
6. Is the dose counter already approved in the chosen markets?
7. Can the dose counter be integrated into the product whilst retaining pharmaceutical performance parameters?
8. Is the dose counter suitable for use by all patient groups (children, adult, elderly)?
9. Is end of life dose indication sufficient or would dose by dose count and display offer a competitive advantage?
10. Is the dose counter/actuator combination compatible with existing manufacturing and packaging lines?

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REFINING INHALED PRODUCT TESTING

Reliable and relevant analytical data provide a robust foundation for the efficient development and manufacture of efficacious products. For pharmaceuticals, secure relationships between *in vitro* test data and *in vivo* behaviour (*in vitro-in vivo* relationships – IVIVRs) are especially useful, but they remain a challenge in the area of inhaled drug delivery. Here, Mark Copley, Sales Director at Copley Scientific, considers how inhaled product testing is being refined towards the goal of better *in vivo* representation, and greater overall productivity. The focus of the article is cascade impaction, the technique used for aerodynamic particle size distribution measurement for all orally inhaled and nasal drug products (OINDPs).

UNDERSTANDING REQUIREMENTS FOR INHALED PRODUCT TESTING

Accelerating time to market and developing better manufacturing practice are ongoing goals for the pharmaceutical industry. The efficient extension of knowledge and understanding is seen as critical, setting clear criteria for the assessment of analytical tools such as: "Do they provide relevant information?" and "Are they as productive as possible?"

Inhaled product development presents some unique challenges, intensifying the need to optimise the analytical approach. The difficulty of precisely correlating drug deposition behaviour with clinical efficacy, the impact of patient-to-patient variability on drug delivery and the complex interaction between formulation and device, all complicate the acquisition of greater understanding and, more generally, product development. Better IVIVRs have long been an industry goal, but the current climate clearly adds impetus to the desire for progress.

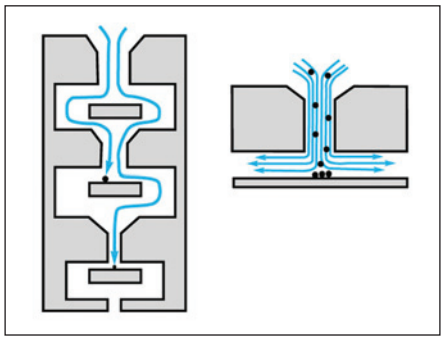

Figure 1: Multistage cascade impactors size fractionate a sample, particles with sufficient inertia breaking free of the airstream and impacting on the collection surface at specific stages.

The monographs relating to inhaled product testing reference two core techniques: delivered dose uniformity testing and aerodynamic particle size distribution measurement. Dose uniformity testing verifies that the quantity of drug delivered is consistent from batch to batch, and for multi-dose systems from dose-to-dose. Particle size information is gathered to confirm the consistency of dose dispersion and to gain some insight into likely *in vivo* deposition behaviour.

Dose uniformity testing is relatively straightforward and there have been no significant developments since the inhaler testing monographs were last revised in 2005. Cascade impaction, on the other hand, has been the subject of considerable efforts towards refinement, with new instrumentation introduced and new methodologies proposed.

Multistage cascade impaction size-fractionates a dose on the basis of particle inertia.[1] The sample is separated by successively accelerating it through a series of stages. At each stage progressively smaller particles acquire sufficient inertia to break free of the prevailing airstream and impact on a collection surface (see Figure 1). The resulting series of samples is analysed, typically by HPLC, to determine a particle-size distribution specifically for the active rather than for the formulation as a whole.

This unique ability of cascade impaction to generate an *aerodynamic* particle size distribution (APSD) *specifically* for the active makes it highly relevant for the study of inhaled

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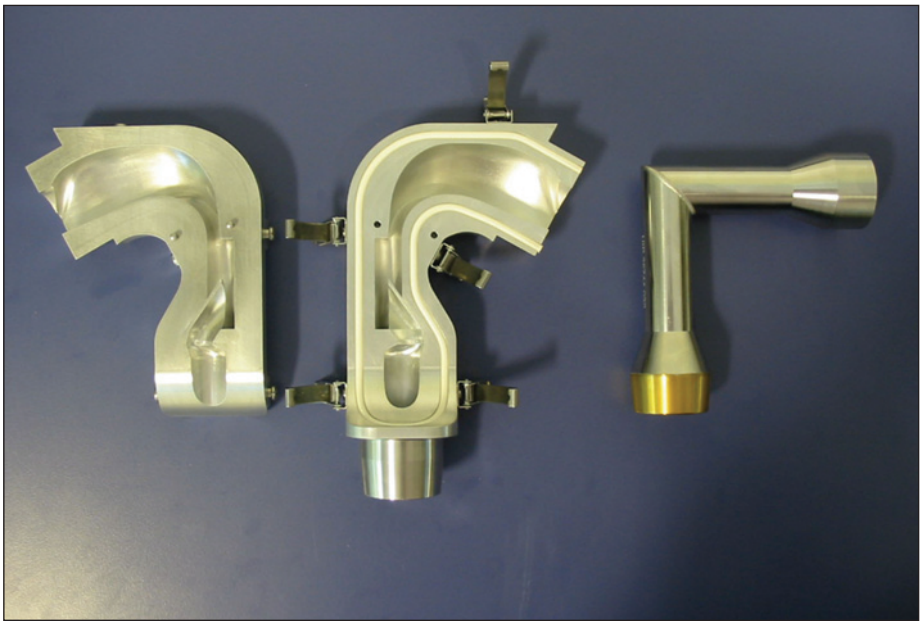

Figure 2: The AIT has a more human-like geometry than the USP/Ph Eur induction port but is easily manufactured to very close tolerances for consistent analysis.

Figure 3: Use of a mixing inlet decouples flow through the test device from flow through the impactor extending options for more relevant inhaled product testing.

products, but the practicalities of measurement are less appealing. Cascade impaction can be time consuming and, because it is complex and expensive to automate, it remains a largely manual technique, increasing the possibility of analytical error. Work on refinement has a dual focus: to improve *in vivo* representation and to streamline, accelerate and, ideally, automate analysis.

BETTER IVIVRS

One strategy for improving the significance of cascade impaction data is to modify the test set-up to mimic the drug delivery process more closely. Improving the interface between the device and the impactor is seen as important, as is the application of more realistic breathing profiles during testing.

Developed with testing standardisation in mind the USP/Ph Eur induction port used to interface device and impactor has a simple well-defined geometry. It is easy to manufacture and gives consistent performance, essential for QC testing. However, it is widely accepted that this port does not provide an accurate *in vitro* realisation of aerosol transport through the upper respiratory tract, and consistently under-predicts the amount of material captured.[2,3]

The Alberta Idealized Throat (AIT) is a new impactor/device interface (see Figure 2). Developed over the course of a decade at the Aerosol Research Laboratory of Alberta (University of Alberta, Canada), the AIT lies some way between a human throat cast and the USP induction port, thereby combining the advantages of reproducible manufacture and flow rate independent performance, with better *in vivo* representation.[4]

Early experimental studies with dry-powder inhalers (DPIs) and pressurised metered-dose inhalers (pMDIs) confirm that the AIT captures more of the emitted dose than the standard induction port,[3,5] supporting the proposal that it may lead to better IVIVRs.

Applying more representative breathing profiles during testing is complicated by the fact that impactors operate at constant flow rate. Furthermore, the lower limit of calibrated performance for cascade impactors (15 L/min with the Next Generation Impactor (NGI) and 28.3 L/min with the Andersen Cascade Impactor (ACI)) is a potential obstacle to low flow rate testing.

Mixing inlets decouple the flow rate applied across the device from the air flow drawn through the impactor, thereby enabling more representative testing. Utilising geometry that encourages gentle mixing they allow the introduction of a secondary air stream that creates a sheath flow to supplement the flow applied across the device, thereby entraining the sample aerosol before entry into the impactor (see Figure 3). This makes it possible, for example, to operate the product under test at a very low flow rate but boost airflow through the impactor to achieve the calibrated steady-state flow rate required. Alternatively, a sinusoidal breathing profile can be applied across the device, and offset by effectively generating an out-of-phase secondary sinusoidal flow prior to APSD measurement.

In this way, mixing inlets in combination with increasingly sophisticated breathing simulators offer scope to investigate the performance of inhaled products under conditions that more closely mimic those applied during patient use. With DPIs for example, especially those with high resistance, examining performance at very low flow rates may provide clearer information about the likely product performance as the inhalation strength falls. In turn this may suggest limits as to the appropriateness of a device for certain groups of users.[6]

Looking beyond the initial stages of drug delivery a further consideration in the development of better IVIVRs is *in vivo* uptake. Several recently published papers, including a USP Stimuli to the revision process, address the issue of dissolution testing for inhaled drugs, and specific dissolution testing equipment is now commercially available.[7,8]

Particles delivered to the lung are by necessity extremely fine, so there has long been an assumption that they dissolve rapidly despite the fact that conditions in the lung are far from optimal for dissolution. As the development of larger, less soluble molecules such as proteins and vaccines as OINDPs becomes more common, this assumption is being questioned. In the future, dissolution testing could become more routine as efforts towards better IVIVRs intensify.

INCREASING PRODUCTIVITY

As well as improving the relevance of inhaled product testing, increasing productivity is a major concern; ideally both would be achieved simultaneously. The drive for greater efficiency is stimulating debate as to whether multistage cascade impaction needs to be

Figure 4: The Fast Screening Impactor (MSP Corp) is based on the Next Generation Impactor (NGI) pre-separator and was developed specifically for AIM.

applied to the extent that it is currently. The multistage cascade impactors used most widely normally produce seven or eight size fractions in each experiment, resulting in significant sample work-up. Some now argue that this level of detail is not always necessary for effective decision-making.

During the early stages of device development or formulation, for example, the goal may simply be to identify parameters that enhance drug delivery, and so it may be enough simply to detect shifts in the fine particle fraction (FPF), typically defined as the sub-five micron dose. Post-production effectiveness in QC similarly depends on an ability to sensitively differentiate between samples, to detect one that is out of specification. The argument is that meeting these criteria is crucial, but full resolution of the APSD may not be necessary unless a detailed investigation is required.

These ideas support the adoption of abbreviated impactor measurement (AIM), characterisation of the emitted dose using just two or three size contributions. AIM can be implemented in one of two ways: either by combining the material collected on different stages of a multistage impactor,[9] or by using specially designed equipment (see Figure 4).

Evidence suggests AIM could reduce overall analysis times by at least 50%,[10] and there are other potential benefits. Returning to the issue of better IVIVRs, AIM offers the prospect of higher precision, because of the removal of stages on which very little material collects. More practically the possibility of using simpler apparatus that is easier to operate and automate, and the potential for reduced solvent usage during sample work-up, are both appealing. However, the crucial question is whether AIM can reliably supply the required information.

There is significant experimental activity in this area, both academic and industrial, and understanding of the AIM concept has grown rapidly over the last few years. Results suggest that simplified metrics associated with AIM (Efficient Data Analysis – EDA) sensitively detect changes in APSD, as long as the boundary figure segregating the size fractions is set somewhere within the central region of the typically uni-modal APSD. Sensitivity increases as the boundary figure approaches the mass median aerodynamic diameter (MMAD) of the formulation.[11]

Based on this finding, twin approaches to AIM have evolved: AIM-pHRT (AIM- (potential) Human Respiratory Tract) and AIM-QC. Using AIM-pHRT the boundary between the fractions is set in line with the figure used to define FPF at five microns, which typically is taken as an upper size limit for material entering the lung. An additional stage is included to separate out the sub-one micron fraction usually considered to be too small to deposit in the lung and therefore exhaled. In contrast, AIM-QC configurations have a single stage with a cut-off as close to the MMAD as the commercial availability of stages allows, to optimise sensitivity.

Experimental data indicate that such set-ups should be able to detect changes in MMAD of the order of just tenths of a micron, indicating that this approach is highly differentiating,[11] a primary concern for QC testing requirements.

Published studies with dedicated AIM apparatus,[12-15] show that these systems provide data closely comparable with full-resolution, multistage cascade impaction, for the majority of OINDPs, providing that appropriate test methodologies are applied. However, the regulators have yet to formalise the use of AIM; and there is a further issue. To swap between multistage cascade impaction and AIM at different points in the development cycle, the transfer of specifications between the two must be extremely simple, with the preference being for complete parity. Any discrepancies between multistage and AIM data, however well-understood, will inhibit the uptake of AIM techniques and significantly complicate the adoption of a twin-track approach.

MOVING FORWARD

The inhaled product sector is a dynamic one with pulmonary drug delivery becoming feasible for increasing numbers of drug entities. That said, the mechanisms of drug delivery via the lung and nasal cavity are complex and continue to challenge our understanding. Greater efficiency in inhaled product testing is becoming increasingly important for the successful application of these relatively new technologies.

Testing can be made more efficient by improving the relevance of the information gathered and/or by streamlining and simplifying test equipment and methodologies. The attainment of better IVIVRs is a goal shared by regulators and industry since it enables faster more efficient product development and simultaneously reduces risk, an increasingly important regulatory concern.

Innovations such as the AIT, mixing inlets and increasingly sophisticated breathing simulators, introduce the possibility of more representative test methods, as already implemented in the recently revised nebuliser guidance.[16] However, the USP and Ph Eur will need to be convinced that there is sufficient understanding, data and benefit to support any broader changes in future revisions of the monographs relating to other OINDPs, as they begin deliberations on this matter.

AIM/EDA is perhaps the biggest idea to develop in recent years, certainly since the development of the NGI. It could potentially transform testing and offers numerous potential benefits, but there remains considerable debate within the community about application. This debate centres on how closely AIM and full resolution impaction data correlate for different device types, most especially DPIs, and the practicalities of applying both techniques at different points in the development/production cycle.

What is clear is that there is both appetite and drive to continue to develop inhaled product testing. This bodes well for the efficient development of new inhaled products that meet societal requirements for better, more effective, easier to use pharmaceuticals.

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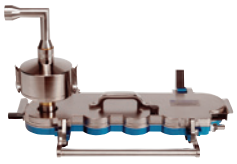

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Coster is a leading provider of both aerosol components and filling machines for the pharmaceutical, personal care and cosmetics industries. Founded in the early 1960s, now with an annual turnover of €150 million, Coster has more than 40 years' experience in the design and manufacture of high-quality packaging systems.

Coster is the sole company worldwide supplying integrated aerosol and spray solutions, including:

- MDI valves and inhalers for HFA and CFC
- 20 mm & one-inch valves and actuators
- Bag-On-Valves (BOV) and actuators
- Filling lines for inhaled, nasal, oral, and topical products

Coster's robust and reliable technology allows it to meet the pharmaceutical industry's stringent quality standards and product safety features, while maintaining competitive prices.

Coster's R&D Centre offers formulation and re-formulation services for selected aerosol and spray OTC products. Customised aerosol courses can be hosted in-house or on-site.

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Coster's range includes the following products:

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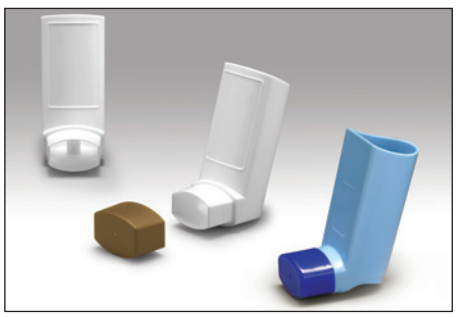

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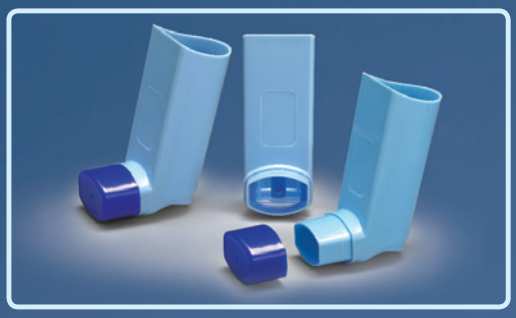

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team technik
PRODUCTION TECHNOLOGY

Medical products such as inhalers and pens make it possible for chronically sick people to live largely unrestricted lives. Inhaler systems allow asthmatics fast access to their medication, and diabetics are able to inject themselves with their daily dose of insulin quickly and safely thanks to their insulin pens.

The fact that they are so easy to use means that these devices have long been in great demand, and are produced in high volumes - and the trend is growing.

The requirement for increasingly flexible solutions to automate the manufacture of medical products from assembly to the complete packaged unit, including functional testing, is therefore also increasing. teamtechnik Group is one of the leading suppliers developing and implementing turn-key production systems for medical devices.

teamtechnik has been making intelligent and reliable automation solutions for the automotive and solar technology and for medical and pharmaceutical industries for over 35 years. With their focus on assembly and testing, the systems are distinguished by their consistently modular and standardised process-oriented structure.

teamtechnik, based in Freiberg, Germany (Figure 1), is considered an international leader in highly flexible automation technology. With a total of 700 employees throughout the world, the company achieves sales

Figure 1: teamtechnik's Facility in Freiberg, Germany.

of over €130 million (£111 million). The teamtechnik Group has production sites in Germany, Poland, China and the US.

teamtechnik develops innovative process-optimised production solutions for medical technology that meet customers' requirements right up to serial production. The systems are designed with a modular approach, a highly-flexible concept which allows the manufacturers of medical devices to adapt their production quickly and economically to changes in the market.
In the new TEAMED system, its latest system platform, the company has brought to market a highly flexible and upgradeable linear system for assembly and testing, realising almost 80% of all customer solutions in the medical technology sector. Sophisticated process technology and 100% end-of-line testing can be integrated in the platform specifically for the assembly of medical devices and pharmaceutical products.

TEAMED (shown in Figure 2) allows production compliant with global guidelines and monitoring systems such as GAMP 5, FDA and CE and meets class 6 clean-room

Figure 2: A TEAMED Production Line.

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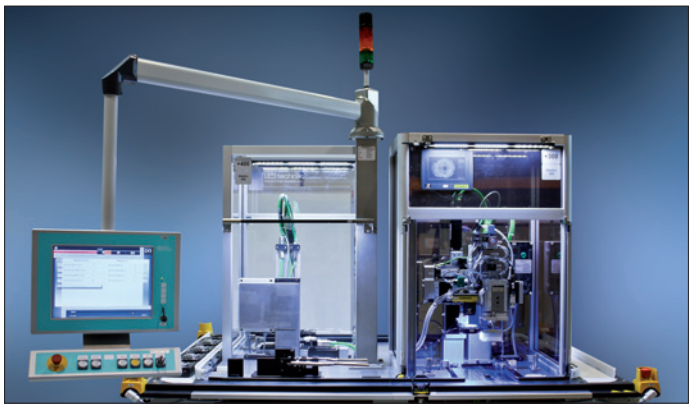

Figure 3: teamtechnik Prototype Production Unit.

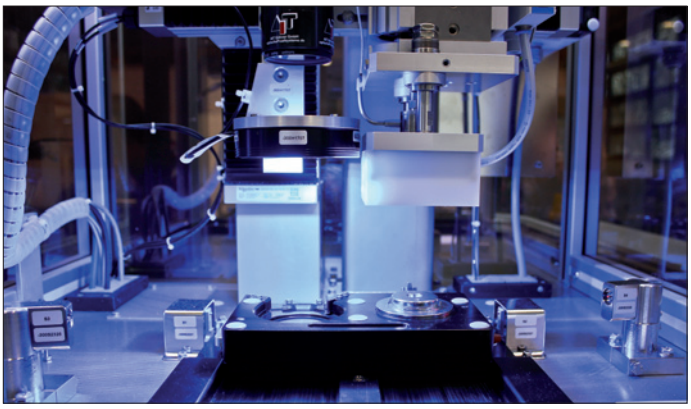

Figure 4: Fully Monitored Process Application.

specifications. The special feature is that TEAMED also incorporates processes from clinical Phase I and II prototype production directly in serial production, thus verifying critical processes in advance of the original configuration later on and providing the person responsible with reassurance for future serial production from the start. TEAMED-based systems can be adjusted to accommodate increasing unit numbers quickly and with little extra effort, as in the case study that follows.

FROM PROTOTYPE TO HIGH-VOLUME PRODUCTION: A DPI ON THE PATH TO MARKET SUCCESS

First Stage: Protoype Production
The assembly of a dry-powder inhaler (DPI) normally includes many complex processes which must be monitored whilst the process is underway, or else the result must be verified after the process.

To reduce time-to-market, the customer ideally needs a complete final device assembly line from the outset (Phase I clinical trials). In practice though, factors such as cost and risk used to mean this was usually impossible. However, teamtechnik – one of the leading suppliers developing and implementing turn-key production systems for medical devices – now offers exactly this option.

Having the critical processes automated in a very early phase of development is made possible with the TEAMED platform. The machine will typically be a small, manually operated unit with only some selected processes and tests performed automatically (see Figure 1).

In the following case study, the customer came to teamtechnik with a device still in development. We designed a TEAMED workstation for one to five operators working at the machine at the same time. The number of operators depends on the output the customer likes to get from the machine. Output is one unit per minute with one operator up to six per minute with five operators.

All parts are fed manually by the operator into the nests of the carrier or direct into the device. For a delicate assembly process the operator moves the carrier manually into the process station where the fully monitored assembly process (Figure 4) is performed automatically. After a successful process, the operator pulls out the carrier and pushes it to the next station where minor assembly operations are done by the next (or by the same) operator(s). Before closing the device (another monitored automatic process) a camera system checks completeness and correct positions of all parts. Finally, the assembly of the lid is done automatically to avoid an operator influence after this check of completeness. The lid assembly is path force monitored also.

Next Level: Small-Volume Production
Due to flexible modular TEAMED design of the process units, teamtechnik integrates the same process units into the next-level machine: a semi automatic assembly line with material input by one or two operators.

The process stations are connected via a flexible carrier system. The carrier still has the same design as in the first prototype machine, now with some additional nests for manual preloaded parts. Almost all assembly operations are performed by automatic stations, and the delicate process stations are still the same as in the prototype machine for Phase I clinical trial products. Output is at 20 parts per minute now, working with two or three operators.

Market Level: High-Volume Production
The next stage is a four-up fully automatic high-volume line with all parts fed by bowl feeders or palletizing systems. Output is at 120 parts per minute now, the machine is running 24/7 with one operator and one milk runner.

teamtechnik designs the carrier back to the roots of the prototype machine where only a main nest and an intermediate nest was necessary. The delicate processes have been validated at the prototype machine in the Phase I clinical trials and are still identical in design and function. This saves a lot of time in the complete path to market and due to the early market entry the time to return-on-investment (ROI) is reduced dramatically.

This has only been made possible by a very strong modular medical TEAMED design from teamtechnik. In a non-critical, high-speed assembly satellite of a pre-assembly unit teamtechnik selected a two-up PFUDERER RTS dial system with 60 cycles per minute.

A final 100% function test with all data stored to the customers network proves the product quality before the device gets a final data matrix code by a label. The trays for the final product are also printed online by an inkjet system

An inhaler on its path to the market - a story of success - developed and manufactured by teamtechnik.

SANOFI

LEVERAGING THE BENEFITS OF BIG PHARMA TO SUCCESSFULLY INDUSTRIALISE & MANUFACTURE THIRD-PARTY PRODUCTS

Sanofi has undertaken third-party manufacturing for a number of years and is best known for its contract manufacture of pharmaceutical ingredients. Here, Nigel Hilton, Head of Manufacturing at Sanofi Holmes Chapel, UK, describes the contract manufacture for secondary pharmaceutical processing, including industrialisation and manufacture of MDIs, DPIs and nasal sprays, that the company offers at the Holmes Chapel site. He gives an insight into the necessary expertise to achieve a successful product launch and is based on recent experience gained from industrialisation of a third-party product.

Most of the current range of blockbuster inhalation products, which includes GlaxoSmithKline's Advair (fluticasone/salmeterol) and AstraZeneca's Symbicort (budesonide/formoterol), was developed by traditional multinational pharmaceutical companies.

Whilst these companies continue to develop and launch new products, a number of smaller development companies have emerged in the past few years, focused on gaining a share of this lucrative market. These products often involve the industrialisation of new delivery technology or new approaches to formulation, frequently using established active ingredients formulated either as a pressurised metered dose inhaler (pMDI) or a dry-powder inhaler (DPI).

By their very nature, these smaller development companies are initially focused on early development and proof of concept. As they progress through to late-stage development and thoughts turn to supply of the product at commercial quantities there is a need to look outside their organisations towards Contract Manufacturing Organisations (CMOs) with the appropriate capabilities to help them successfully industrialise and manufacture their products.

The availability of big pharma as a CMO presents an opportunity for these smaller development companies to take advantage of the benefits that come from working with a large pharmaceutical company, well versed in the regulatory requirements for attaining and maintaining manufacturing licences. Sanofi is one such company offering contract manufacture. The UK site where this takes place is shown in Figure 1.

To industrialise and supply new inhalation products successfully at any CMO there are a number of basic elements that both parties must work to address, being clear on the scope and responsibilities for each.

These are:

- Manufacturing strategy, including scale, concept and layout
- Equipment specification and procurement
- Analytical testing and stability testing
- Device component industrialisation and supply
- Process transfer and scale-up
- Regulatory considerations
- Supply chain management and product maintenance

Developing a sound manufacturing strategy is the single greatest contribution a CMO can make to the development company's industrialisation programme. Here an understanding of the factors that influence the finished product batch size and manufacturing throughput is fundamental to determine capacity and unit price. The aim is always to strike the optimum balance between the financial value of a single batch, the level of

Figure 1: Sanofi inhalation manufacturing facility.

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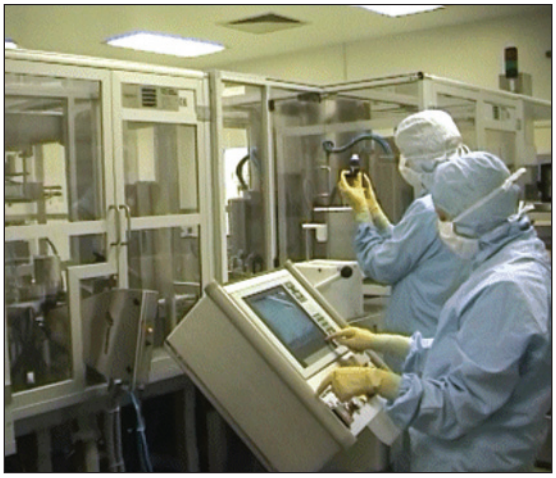

Figure 2: DPI filling and final assembly equipment.

Figure 3: MDI filling line.

capital investment, the available capacity and the unit cost of the finished product.

For DPI products, batch size is usually governed by blend scale. However, there can be other considerations such as the capacity of the filling and assembly equipment (see Figure 2) or its impact on the blend and finished product performance due to, for example, powder compaction or segregation. Invariably some form of conditioning may be required, typically a hold time for either the blend or filled product.

Furthermore, the end-to-end manufacturing process is often separated into discrete stages, allowing confirmatory testing to occur before adding further value to the product. Clearly, these requirements need to be factored into the logistics of the manufacturing process.

The manufacturing strategy for MDI products can be more straightforward. Recognising the relatively universal design of MDIs it is rarely necessary to commission a manufacturing operation around a bespoke product. Instead, the usual way forward is to utilise existing equipment such as that shown in Figure 3. In these cases batch size may be dictated by the capacity already installed at the CMO.

Other considerations include the level of automation and associated capital investment provided for within the manufacturing process. This always involves striking a compromise between the relatively high initial investment associated with automation, such as that shown in Figure 4, versus a lower capital but higher ongoing labour cost solution.

As well as financial considerations, there is much to be done here to ensure that equipment design, layout of facilities and ways of working satisfy cGMP regulatory requirements as well as Health & Safety needs, including containment and emissions.

Having agreed a manufacturing strategy, there will be capital investment and associated one-time costs required to industrialise or transfer the product to the CMO. Cost and timescale certainty is usually critical and can only be achieved from having the proven skills and experience to support the specification, procurement and qualification of what is often bespoke or modified equipment and facilities.

Whilst analytical method transfer is well understood within the pharmaceutical industry, the challenge in industrialising a new inhalation or nasal product is to ensure that the process can routinely produce a product that meets exacting regulatory standards, especially for delivered dose and aerodynamic particle size distribution.

The selection and control of starting materials and manufacturing processes are critical in maintaining this capability. Similarly, a robust test method is required that minimises variability and provides both a precise and accurate result.

Equipment such as the Next Generation Impactor (NGI), shown in Figure 5, is now routinely used because of the improved precision that it affords. Environmental control within the laboratory is especially important in maintaining consistent evaluation of product performance and is particularly relevant for DPIs. Test method automation is becoming more commonplace, once again affording improved precision with the additional benefit of increased laboratory throughput.

Experience shows that analytical method transfer is especially important for MDIs and DPIs because of the challenging specifications required by regulatory authorities. In some cases this is the point when the true variability within the method is understood and may be found to be unacceptable. In such cases, the analytical method development expertise within a CMO can be essential in order to improve the problematic method.

Stability study management also presents some specific challenges due to the resource intensive nature of the testing and the tight product specifications which must be applied. The laboratories in a big pharma CMO are well placed to manage the shifting resource requirements, given a larger resource pool. Additionally the risk of out-of-specification results occurring is reduced in a laboratory staffed by analytical chemists experienced in

Figure 4: High speed automated packing line.

Figure 5: Next Generation Impactor (NGI).

Figure 6: DPI automated assembly equipment.

testing inhalation products. These laboratories are typically also familiar with the specific needs of testing excipients and active ingredients, such as propellant impurity testing or physical characterisation of active ingredients.

The delivery devices used for MDIs and DPIs are integral parts of the product. When the new product is a DPI and involves a bespoke device, product industrialisation has an added level of complexity due to the need to industrialise the device componentry at the same time as the manufacturing process.

The development company will possess an in-depth knowledge of the device design, often gained from single or low cavity injection mould tools and manual or semi-automated assembly processes. It is essential that the development company has identified the critical features and dimensions within the device and has performed tolerance analyses to ensure that the device has been appropriately specified. Ideally the CMO should be able to bring experience of mould tool scale-up and device assembly industrialisation, such as that shown in Figure 6.

Working with a CMO that possesses this level of expertise can free-up valuable resources within the development company to focus on competing activities such as product registration.

Where the product is an MDI, the CMO should as a minimum have a thorough knowledge of valve and can componentry and should be able to help refine the actuator design to ensure compatibility with automated packing processes, where actuator cap fit and dose counter security can be an issue.

Having established supply of the device componentry, completed method transfer and installed the manufacturing equipment, the CMO must be able to support successful process transfer, scale-up and validation.

Clearly the product has to comply with the specification routinely. With this in mind, one prerequisite for a robust process is to ensure that the development company defines the product's specifications based on manufacture and testing of an appropriate number of batches, utilising multiple lots of input materials and components. By following such an approach, potential difficulties encountered during process scale-up can be minimised.

Whilst development of a robust product is the responsibility of the development company, the CMO needs to possess the skills to understand the sources of variability within the manufacturing process that influence critical parameters such as assay, particle size distribution and dose. Application of statistical tools is essential to identify, isolate and minimise these sources of variability during scale-up. This statistical approach is most powerful when applied within a six-sigma infrastructure.

In parallel with the product transfer and scale-up, the development company will typically progress their submissions to regulatory authorities. Our experience is that a big pharma CMO is well placed to provide invaluable input into the regulatory package, ensuring that its content is completely consistent with the installed process. Additionally, since big pharma is experienced in authoring successful regulatory dossiers, it can offer dossier preparation as an additional service.

When selecting a CMO, the development company should carefully consider the compliance pedigree of the proposed facility to achieve successful inspection results, without experiencing potential delays from unfavourable observations.

An important aspect of industrialising any new pharmaceutical product is establishing and managing a reliable supply chain. The entire supply chain starting with raw material procurement through to finished product distribution needs to be understood in order to ensure risks are identified and effectively mitigated. A competent CMO should be able to help establish (and even operate) the supply chain, utilising technical, quality and commercial personnel to optimise raw material and device componentry supply in terms of both cost and quality. Depending on size and buying leverage, the CMO may also be able to obtain financial savings on behalf of the development company.

Inhalation and nasal spray products are relatively complex and inevitably, even with careful management of the supply chain, there will be times when a supplier needs to modify or substitute a material. This type of product maintenance activity is particularly prevalent in the case of delivery devices, where consolidation within the polymer industry has (and continues to) result in rationalisation of polymer grades.

In such cases, a CMO with a thorough understanding of the regulatory requirements, complemented by the technical capability to qualify the new material is a useful partner for any developer.

It is clear that selection of an appropriate CMO is an important decision for a development company seeking contract manufacturing services. Making the correct decision is even more critical when the product is relatively complex, as is the case with inhalation and nasally delivered products.

Working with an established big pharma CMO can allow the developer access to a broader range of technical and commercial expertise, effectively a "one stop shop" for product industrialisation and marketed product support. This not only provides additional assurance that their product will be reliably manufactured and supplied, but it also provides assurance that there will be support capabilities to respond to the inevitable technical challenges that arise and to deliver rigorous control of change and product maintenance throughout its life cycle.

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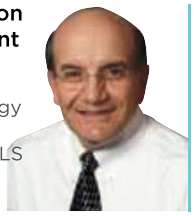

R&D Budget Cuts and the Effect on Drug Delivery Partnering

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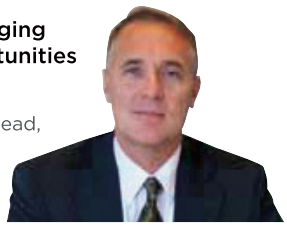
SVP and Head, Worldwide Licensing & Knowledge Management, MERCK

Uncover Emerging Market Opportunities

Chris Jones
VP and Global Head, Pharmaceutical Development, ASTRAZENECA



Overcome Barriers to Commercialize Products Overseas

Christopher Seaton
SVP, Global Licensing, BAYER PHARMACEUTICALS

Drug Delivery Devices as a Growth Mechanism

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CONFERENCE REPORT: DRY POWDER INHALERS

JUNE 29-30, 2011, LONDON, UK

***Dry Powder Inhalers*, a two-day conference from Management Forum, was held in London. The meeting brought together scientists, manufacturers and suppliers who have a special interest in developing dry-powder inhalers (DPIs). Here, Steve Nichols, PhD, an independent OINDP Consultant based in the UK, and Andrea James, Conference Director, Management Forum, report some of the highlights.**

The Dry Powder Inhalers conference was opened with a review by Dr Steve Nichols (OINDP consultant) of the key industrial, scientific and clinical advances that have been reported over the last 12 months. A key message was that there has been a significant amount of activity during this period, both in the traditional asthma/COPD area, but also developments progressing inhaled systemic drugs.

Day 1 started with a keynote address by John Bell (Stewart Erl Associates, Loughborough, UK), entitled: "*Upping the game; the next 25 years – what, why, how, who when?*" Interestingly, he focused on how inhalation technology could be "sustaining", "disruptive" or "revolutionary". It seems that most DPIs are sustaining and add little innovation, that there is occasional new disruptive technology introduced, but that very rarely has there been any revolutionary technology introduced. He challenged us to consider that the future will need more of the latter DPI technology if major advances in treatment are to be made.

David Vodak presented results on a feasibility study that assessed the inhaled delivery of a peptide, PYY_{3-36} that is responsible for appetite suppression. The peptide was delivered using a dextran excipient. In an *in vivo* model in mice, appetite suppression was successfully demonstrated.

Staying with systemic delivery of macromolecules, new concepts in the delivery of peptides (insulin), and device technology tailored to meet the specific drug and dosing requirements, were presented by Dr Andrea Leone-Bay (Mannkind Corporation, Valencia, CA, US). The company's insulin technology uses a novel excipient (fumaryl diketopiperazine; FDKP) to form Technosphere® particles that provide protection to the peptide. The technology could be applied to other peptides too. New concepts of simple devices that could be optimised to a particular drug-formulation and were easy to use were illustrated.

Continuing the formulation/powder theme Dr Marie-Pierre Flament (Université Lille – Nord de France, Lille, France) illustrated her group's latest research examining how the measurements of air permeability could be related to other physical factors of aerosol delivery such as fine particle dose. Good correlations were found for several of the measurements that could aid formulation development and optimisation.

David Hipkiss (Prosonix, Oxford, UK) illustrated how engineered particles can be used in dry-powder formulations to provide enhanced delivery over micronised drug substance. He illustrated how the Prosonix technologies can be used to provide matching performance in generic products, but with added benefits including, for example, reduced side effects, lower metered doses, and how "combination" particles can be formed, which may work in a enhanced synergistic manner.

Prof Hartwig Steckel (Christian-Albrechts-Universität zu Kiel, Kiel, Germany) provided an insight into drug and indication considerations that have to be made for selecting the right inhaler. He illustrated his considerations by referring to three inhalers in development and how these can provide the necessary delivery and user features for different potential therapeutic indications.

"DR PHIL SEENEY ILLUSTRATED HOW THE FUTURE MAY LOOK WITH REMOTE MONITORING AND FEEDBACK PROCESSES TO THE PATIENT CONCERNING DOSING AND COMPLIANCE"

"*The inhaler of the future*" was the subject covered by Dr Phil Seeney (PA Consulting, London, UK). He illustrated how electronic technologies have been added to other drug delivery devices, but have not been adopted by inhaler technology companies. He illustrated how the future may look with remote monitoring and feedback processes to the patient concerning dosing and compliance. This might include some reward system to the patient. Interestingly, he was predicating it may be 25 years before such technologies are widely seen in inhaled drug technologies. Dr Andy Clark (Novartis Pharmaceuticals Corporation, CA, US) provided an overview of how the TOBI® Podhaler® product was developed and the challenges faced. This is a high-mass delivery product which uses PulmoSphere™ particle technology and an optimised device to deliver effective doses to CF patients.

The final presentation of day 1 was by Dr Carsten Niederlaender (Almirall Sofotec, Bad Homburg vor der Höhe, Germany), who charted the history of the Genuair® inhaler from single cavity to commercial supply. It was fascinating to hear about the specific challenges presented when developing a multidose reservoir inhaler that is "complicated", including the various aids incorporated to improve patient compliance and ease of use.

Day Two began with a review of the key messages from the previous day by Dr Ian Smith (H12 Consulting Ltd, Cambridge, UK). The first presentation of the day was by David Howlett (Pharmadelivery Solutions, Grimston, Norfolk, UK), who discussed "*Opportunities and Challenges in Emerging Markets*". He focused on the BRIC countries (Brazil, Russia, India and China) and noted that not only are the western countries attempting to enter these markets but that the BRICs are also entering western markets. It was interesting to see that a number of DPIs are coming out of these countries that physically look like many of the current market leaders. One of the key issues to consider, Dr Smith said, is the price that can be commanded in the BRICs compared with the manufacturing cost required to ensure a profitable product.

The "*Demonstration of Therapeutic Equivalence*" was discussed by Dr Anders Fuglsang (Fuglsang Pharma, Rudolstadt, Germany). Regulatory requirements in the EU and the US were discussed, and the challenges that these present. Potential practical ways of dealing with these were presented, highlight-

ing the areas where difficulties still exist when designing studies.

The development processes of a new multi-dose DPI was presented by Duncan Bishop (Cambridge Consultants, Cambridge, UK). It was very interesting to see how the design programme developed, and how the working practices with an Indian pharma company were organised and managed. From the time of agreeing development to providing commercial supplies device (single cavity, manual assembly) took five-and-a-half years.

Another case history of device development, "*Inhalation in Influenza Therapy: the TwinCaps® Story*", was provided by Dr Peter Villax (Hovione FarmaCiencia, Loures, Portugal). This technology was developed specifically to deliver an avian influenza vaccine being developed by Sankyo Pharmaceutical Co in Japan. The simple, two-capsule, deposable device was conceived in November 2005 and the market product was approved in Japan in October 2010. The device development programme was conducted together with the drug testing, demonstrating just how fast an inhaled product can reach the market when the drug and device combination is specifically co-developed.

Not forgetting the patients, Jane Leyhson (Education for Health) presented on "*Views of an Asthma Nurse – Patient Experience*". She described how providing the right drug in a good device, but without considering patient practices (i.e. training in proper use of the inhaler), leads to an uncertain treatment outcome. She concluded that given all the improvements in science, we have not "cracked it" yet and that, in the absence of training and without ensuring compliance, just giving patients "well researched and tested inhalers" does not itself improve the patient outcome.

"IN THE ABSENCE OF TRAINING AND WITHOUT ENSURING COMPLIANCE, JUST GIVING PATIENTS 'WELL RESEARCHED AND TESTED INHALERS' DOES NOT ITSELF IMPROVE THE PATIENT OUTCOME"

Orest Lastow (Zenit Design Group, Malmö, Sweden) discussed, "*Electrostatics: Real Solutions*". He began by describing the source and issues associated with electrostatics in DPIs. He provided a number of practical examples of the effect electrostatics can have and then looked at ways of removing or reducing the effect of charge during the manufacture of powder blends and filling DPIs.

To close the day, Dr KarlHeinz Seyfang (Harro Höfliger Verpackungsmaschinen, Allmersbach, Germany) spoke on, "*Current DPI Filling Technology: the Challenge of Powder Dosing*". He described the challenges of filling small masses into devices, especially for pre-metered DPIs, which may require as little as 2-40 mg metering in to a blister or capsule. The various technology approaches which have been used for metering the doses were discussed. Dr Seyfang also described the way these have been scaled to commercial-scale filling processes and in-line monitoring tools.

The 2011 Dry Powder Inhalers conference was a great success with new and thought-provoking material being presented. The meeting had a very positive response from attendees. Additionally, good opportunities for peer networking and discussion with several suppliers who exhibited were possible.

The next "Dry Powder Inhalers" conference will be held in London on June 19-20, 2012.

CONFERENCE REPORT: RDD EUROPE

MAY 3-6, 2011, BERLIN, GERMANY

RDD® Europe, jointly organised by RDD Online® and Aptar Pharma, took place in Berlin, Germany on May 3-6, 2011. Here, Guy Furness, Publisher of ONdrugDelivery, reports comments on and highlights of the meeting from two of its key organisers, Richard Dalby, PhD, Professor of Pharmaceutical Sciences at the University of Maryland School of Pharmacy, and Pierre Carlotti, MBA, Vice-President of Marketing and Communication at Aptar Pharma.

The annual *Respiratory Drug Delivery* conference (RDD), which alternates between European and North American cities each year is, in my opinion, one of the two most important events in the inhalable drug delivery calendar. It is important on various levels including: the quality and significance of the scientific and technical presentations; the quality and number of attendees; the size and importance of the exhibit hall; and the excellent standard of event production and seamless organisation. The latter, anyone who has attended will have noted, is always carried off apparently effortlessly, yet the amount of hard work that goes on behind the scenes is of course appreciated.

As the publisher of two issues of ONdrugDelivery a year focussing wholly on Pulmonary & Nasal Drug Delivery (you are reading one such edition) it is a priority for me to attend RDD whenever possible. However, this year I was unfortunately unable to make it to RDD in Berlin, so I did the next best thing and arranged to speak with two of people that make RDD happen – Professor Richard Dalby of the University of Maryland, and Aptar Pharma's Pierre Carlotti – to find out what I'd missed!

Mr Carlotti began with some general attendance data from the event. There were 465 attendees, making 2011 the largest RDD Europe to date. There were 59 industry sponsors and 65 posters. Attendees travelled to Berlin from 30 countries and there was a marked increase in the number of non-European delegates, especially from India, Bangladesh, China and Latin America. Breaking attendees down by broad geographic region, 70% were from Europe, 23% came from the US, and 8% from other areas.

Changes underway in the industry's geographic dynamic were reflected at RDD, Dalby noted, saying that this year's event seemed "more global". For example, he observed Indian companies buying the services of Western vendors at the exhibit tables. And amongst the posters, the first Chinese poster at RDD was presented this year.

Another general observation he made was that modelling software companies were emerging strongly. The quality-by-design software developer, S Matrix Corporation (Eureka, CA, USA), was one such company.

On a qualitative level, Mr Carlotti said that people like the format of RDD. Being focused on a well defined and very well connected industry segment, he described the event feeling "like a club, but not at all a closed club". Also, although "everyone" is there, the event layout ensured that one could navigate the entire event with only a small distance to walk between the various things going on.

"THE FIRST STEP TOWARDS BETTER UNDERSTANDING OF ASTHMA IS TO ACCEPT THAT IT IS NOT A SINGLE DISEASE ENTITY, BUT A CONGLOMERATE OF SEVERAL DISTINCT DISEASES PRESENTING WITH SIMILAR SYMPTOMS. "PHENOTYPES" OF ASTHMA CAN BE RE-DEFINED USING RICH DATA SETS, THROUGH THE FUSION OF COMPUTATIONAL THINKING AND NOVEL MATHEMATICAL APPROACHES WITH GENETICS, BIOMEDICAL AND ENVIRONMENTAL SCIENCE"

These sentiments were echoed by Professor Dalby, who said that the level of interaction between people was particularly noticeable in Berlin. He attributed this in part to the good location – the auditorium and the exhibition hall.

I asked both Professor Dalby and Mr Carlotti what or who created the biggest buzz in the presentation hall, and they both gave the same response without hesitation. It was Adnan Custovic, MD, PhD, FRCP, Professor of Allergy and a Head of Respiratory Research Group in the School of Translational Medicine at the University of Manchester (UK), who's fine delivery of the opening plenary lecture, "*Genetics and Environment: Their Influence on Rational Drug Therapy for Asthma*", drove home the point that asthma is not the same disease in everybody, particularly in terms of the different responses to certain drugs, and that there is likely a genetic basis for the variation. Indeed I asked Professor Dalby later in our conversation what he had learnt at RDD this year that readers of ONdrugDelivery who didn't make it to the conference might particularly benefit from knowing, and he chose this same point.

Here follows the abstract of Professor Custovic's talk: "Despite considerable effort by the pharmaceutical industry and academia to develop novel therapeutic agents, little has changed in the approach to asthma management in the last five decades, and inhaled corticosteroids remain the cornerstone of treatment. One of the problems in the search for novel targets is the relatively poor understanding of the mechanisms underlying asthma. This is due in part to phenotypic heterogeneity and poor phenotype definition, and to the existence of numerous gene-environment interactions. This makes reproducible studies aiming to understand the mechanisms of asthma extremely difficult (if not impossible).

"The first step towards better understanding of asthma is to accept that it is not a single disease entity, but a conglomerate of several distinct diseases presenting with similar symptoms. "Phenotypes" of asthma can be re-defined using rich data sets, through the fusion of

computational thinking and novel mathematical approaches with genetics, biomedical and environmental science. These novel phenotypes may better reflect the different underlying pathophysiological processes and molecular pathways underpinning each of the diseases in the "asthma" syndrome, and may be more relevant for genetic and environmental association studies. This strategy may lead to the development of methods for prevention and new drugs for treatment of different "asthmas" that are genotype and phenotype-specific, and identification of target molecules for drug discovery."

The full paper, which was published in the *Proceedings of RDD Europe 2011*, is available to purchase at www.rddonline.com.

In addition to these points raised in the plenary lecture, Dalby cited innovations in aids to treatment adherence training and spacer devices amongst the significant topics he learnt more about at this year's conference. The poster, "*Developing Patient Friendly Devices for Inhalation Therapy*", was presented by Jolyon Mitchell, Mark Nagel and Robert Morton of Trudell Medical International (London, ON, Canada). Also from Trudell, Rudi Mueller-Walz, Lisa M Fueg, Anne Brindley and Geraldine Venthoye presented their study: "*Delivery from Flutiform HFA pMDI With and Without Valved Holding Chamber*".

Another key topic raised was how technology is being used to make inhaler testing more efficient, requiring less data. Dalby commented that the job is to educate the FDA to accept these developments. Cascade impactors with fewer stages provide a good example of an area where progress was being made in this respect. [Mark Copley of Copley Scientific discusses abbreviated impactor measurement (AIM) in more detail in his article "*Refining Inhaled Product Testing*" in this issue, pp 8-12.]

Amongst the signficant subjects that Pierre Carlotti highlighted was that of new propellants for MDIs. More than 600 million pMDIs are used per year compared with 200 million DPIs, he said, and whilst the switch from CFCs to HFAs limited damage to the ozone layer, HFA is still a greenhouse gas, implicated in global warming.

A poster from Barbara Decaire, Kekin Ghelani, Stephen Conviser, Segolene Sarrailh, Bruno Le Corre, Chris Baron, arising from a collaboration between Aptar Pharma and Honeywell, and entitled "*Materials Compatibility Testing of New Low Global Warming Potential Propellants*", was one of five top posters selected for oral presentation at RDD in the "Posters on the Podium" section of the programme.

The others were:

- *Influence of L-leucine Coating on Drug Dissolution from Carrier-Free Powders*
  Teicos Pharma (Espoo, Finland)
- *Imaging Particle and Drug Deposition in Airways of Laboratory Animals*
  University of California, Davis
- *Evaluation of Delivery Efficiency from Valved Holding Chambers with Facemasks Under Simulated Use Conditions*
  University of Maryland, Baltimore
- *Biodegradable Particles for Local and Prolonged Delivery of an Oligonucleotide Decoy to Nuclear Factor-kB in the Lung*
  University of Napoli

"The sector took a beating after Exubera and there was nobody talking on systemic delivery for some time afterwards," Dalby said. Other negatives for the industry he referred to were the "black box" warning on GSK's Advair in the US, and equivalent warnings in other countries, and continuing the lack of a clear path for generics, particularly for DPIs.

"Yet the sector is gradually becoming more bullish." he said, pointing out that the innovations and analyses presented at RDD showed that there was "still room to grow" and spaces where money could be made. There are still opportunities, he said

"The need for systemic delivery of biologics still exists," he added, "but we're not back to where we were four years ago. There was a huge buzz then."

Similarly cautiously optimistic, Pierre Carlotti summed up the mood at RDD as good and positive. "The respiratory market is healthy," he said. One positive trend in particular was that regulators had reduced approval times for inhaled products from more than two years prior to 2000, to 14 months after 2004.

However, the late-stage clinical pipeline is "dry" and the industry faces a patent cliff, Carlotti said. The generics companies are aware and opportunities abound in the future for firms such as Teva and Cipla, which are strong in the sector at present. New generic entrants are being seen also.

Other trends that Mr Carlotti forecast based on what had been seen and heard at RDD included: increased drug delivery product differentiation through devices and device components such as dose counters; a general increasing focus in patient adherence studies; and a convergence of the inhalable drug delivery market with consumer goods markets such as cosmetics, food and cell phones. Finally, he observes market sensitivity to price becoming more important. "More people were presenting their points at the conference in terms of cost," he said.

Based on his observations at RDD, Professor Dalby gave three succinct predictions for the sector for the coming year or two: "closure on the acceptability of new more efficient cascade impactor methods; the genetic insights about the nature of asthma coming to the fore; and an upswing in systemic drug delivery via the lung."

The next Respiratory Drug Delivery conference (RDD 2012) will be held in Phoenix, AZ, US, on May 13-17, 2012.

"CASCADE IMPACTORS WITH FEWER STAGES PROVIDE A GOOD EXAMPLE OF AN AREA WHERE PROGRESS WAS BEING MADE IN THIS RESPECT"

The exhibition was also an important aspect of the show. It is worth noting that the exhibition at RDD is governed by strict rules that give this event's exhibit hall a distinctive – perhaps even unique – character. Every exhibitor – whether they be a huge multinational corporation or the smallest start-up or niche provider – has a simple table top. The tables are all the same size and are arranged to avoid some tables being more prominent than others. Setting up elaborate or extensive kit on or around the table is closely controlled and, indeed, Professor Dalby personally acts as the "exhibit policeman" on the ground, circulating the hall to enforce the rules!

This special set-up levels the field and there are no huge commercial props, said Mr Carlotti. It is not possible for the larger firms to draw all the attention as they do at so many other events with elaborately lit double, triple or corner stands. It sounds restrictive perhaps but having the same simple table-top for all exhibitors means that the smaller companies have a very good chance of people stopping to find out more, and those manning the tables of the larger companies, stripped of their massive stands and flashing lights, need to make just as much effort to engage passing visitors.

The effect is ultimately extremely positive with success depending more on the substance of what an exhibitor is offering rather than the size of their exhibition budget. "We want to keep this format of an exhibit *within* a scientific conference and not alongside it," Carlotti said. Professor Dalby too is a keen proponent of this system. "We hope to be offering a few free exhibit tables at RDD in Arizona next year," he said.

My final questions to Professor Dalby and Mr Carlotti concerned how they perceived the general mood in the pulmonary and nasal drug delivery sector as reflected by the mood at RDD Europe, and what the future has in store.

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