

# What is Needed From a NEXT-GENERATION INHALATION DEVICE?

*Reinventing familiar technologies*

systems, addressing needs of patients and regulators, and responding to the increasing prevalence of the disease states of COPD and asthma. These changes have included the following:

- Within component technologies, the industry has seen a transition to metallic containers with coatings to prevent deposition. Valves include metallic and plastic components, with and without coatings;
- An inhaler's activation method has moved from just press-and-breathe to breath-actuated;
- The 1987 Montreal Protocol led to a drive toward non-CFC propellants;
- We have seen the introduction of dose counters, with the recent FDA approval of 3M's Dose by Dose counter as the first integrated dose counter in conjunction with a partner product;
- Dry powder inhalers have introduced an alternative to MDIs;
- Nebulizers are primarily used to deliver fine aqueous solutions or suspensions, but traditionally are not portable;
- Other alternatives such as Respimat and the Staccato system have been introduced to provide further alternatives.

These changes have led us to where we are today, with three established and recognized groups of inhaled drug delivery devices, and some emerging developments. A brief overview of these groups will highlight their current strengths and weaknesses.

## **Nebulizers**

There is a growing move toward portable nebulizer technology for conditions such as cystic fibrosis, but these devices are still very expensive compared to DPIs and MDIs. This results in them being a very small part of the market.

## **Dry Powder Inhalers**

This technology, often favored by Big Pharma, relies on the strength of the patient's breath to deliver a dry powder formulation from either a blister strip, capsule or reservoir. Because of this, DPIs can hold multiple doses or a single dose, which can

3M Metered  
Dose Inhaler

Evidence shows that people have been using inhaled treatments from as far back as around 1000 BC. However, when we consider early inhaler devices, the squeeze bulb nebulizer is perhaps the earliest "technology" that comes to mind, and was introduced in the late 19th century. This method of delivery remained the best inhalation method available until the mid-1950s. It was then that Riker Laboratories introduced the pressurized Metered Dose Inhaler (MDI), with very similar components to those that are still used today.

Given that much of inhalation technology has stayed the same for nearly 60 years, it is worth evaluating now whether the market needs a reinvention. Can the same familiar technologies we are accustomed to continue their steady evolution, or does today's climate demand something closer to a revolution? How should the course be charted for the next 60 years?

## **A LOOK BEHIND**

While the basic building blocks of the technology have remained unchanged since the first MDI, there have of course been steady improvements. Changes have been driven by a number of needs—delivering different molecules, changing propellant

be an advantage for some therapy areas. No two DPI devices are really the same, which allows for added IP protection against true generic competition. Furthermore, we have recently seen these devices used for delivery of macro molecules such as insulin.

These devices often have a new, modern feel, which can add to the brand value. One drawback to the fact that these devices are all different, however, is that each requires device-specific training. This can lead to careful scrutiny of human factor considerations in the regulatory approval process.

For patients, DPIs offer the advantages of breath-actuation and a small size. However, the devices can be misused if the patient does not inhale properly. If the inhalation is too slow, particles may be deposited into the mouth instead of the lungs. The devices are also more expensive than MDIs.

### Metered Dose Inhalers

The original inhaler, the MDI, has a familiar look and feel, but is often described as old. The MDI, unlike DPIs, is fairly standardized on the outside, which is beneficial for patient familiarity. On the inside, however, formulation is still complex, as evidenced by the limited number of companies that have successfully commercialized MDI products. Additionally, this delivery mechanism has been limited to relatively small molecules, which has restricted its applicability in some therapeutic areas. Feasibility of new molecules for MDI formulation and delivery can be established as quickly and as cost effectively as DPIs by specialist MDI contract development and manufacturing organizations (CDMO).

The MDI is an inexpensive delivery system, which makes it ideal for use in developing markets and in cost-sensitive economies, typically being less than half the cost per dose of DPI delivery. Because the formulation is held in a sealed canister, product shelf life can be prolonged. A canister also has the ability to hold more than 200 doses. Both of these factors contribute to the cost benefit of the MDI.

In the patient's hands, an MDI's high reproducibility between doses, its short treatment time, and no need for preparation are all favorable attributes. The largest recognized issue with the MDI is around patient breath coordination. In fact, one large study found that 70% of patients misused MDIs, with nearly half of the misuse related to breath coordination.

### Soft Mist Inhalers

This newer type of inhaler is not quite a nebulizer, nor an MDI. It delivers a drug formulation via a fine liquid aerosol. This method of delivery has the advantage of greater deposition in the lower airway than MDIs, and also does not need a propellant. Because they are newer to the market than DPIs or MDIs, there is significantly less data on these devices, and they have not been used with a wide range of compounds. The compounds they deliver are targeted at COPD treatment so patient experience is limited to this one area.

## UNDERSTANDING THE STAKEHOLDERS

With this understanding of the current landscape, we can better consider where the industry needs to go next. In making this determination, we must keep in mind the complex array of stakeholders in the process—patients, healthcare professionals, payers, and the pharma industry. What does a next-generation

device need to deliver to each of these groups in order to be successful? Is it just as simple as maintaining the advantages of each of the devices described above, addressing the disadvantages, and combining everything into a single product? If so, why hasn't this been done already?

A metaphor might help us understand the relationship between the stakeholders involved. If we consider the situation as a restaurant, the CDMO can be seen as the chef. Pharmaceutical companies are the waiters who bring in the orders—either a molecule or a product, which can then be developed and commercially scaled up.

The term “customer” here applies to several different groups. In fact, the waiter and the chef are delivering a unique dinner for three. First, the health care professional is the person who places the order; second, the patient is the one who has to actually eat the meal; third, at the end of the meal, the bill is delivered to the insurance company or payer. This helps us understand the needs of payers, who are asked to pay for a meal they didn't order and didn't eat. Therefore, they need a compelling display of value to understand why they should pay. This is the complex environment in which CDMOs and pharmaceutical developers operate.

Recent research with these various stakeholders has yielded more insights into what is needed by each of the groups from new inhalation products.

### Patients

One-to-one interviews and a web-based survey were used to gather thoughts from asthma and COPD patients in both the U.S. and UK. These patients had experience using a range of MDI and DPI devices, and were asked a series of multiple-choice and short-answer questions. They were also asked to upload video footage of their inhalation technique.

This research revealed that although 100% of patients felt confident they used their device correctly, nearly half had problems with their technique. Patient questioning also found that 42% were worried about forgetting to take their medications, and 82% acknowledged that this had happened at some point already.

The patient-focused research identified a number of opportunity areas for inhalation devices:

- Improving handling and usability. Patients' varying levels of dexterity and strength led to difficulty with many devices. Physical problems observed during the research included fiddling with capsules, struggling with twisting and priming devices, and dropping or losing the caps off the end of devices. It was also determined that devices are rarely intuitive to use, and the initial training given to patients is limited. In fact, some patients reported looking to online videos and forums for advice.
- Feedback mechanisms. Patients revealed a desire for reassurance that a dose had been taken correctly, but also wanted this feedback to be discreet. Some current devices have unintentional feedback mechanisms that actually give patients the wrong signal. For example, one product clicks on activation, which leads many patients to stop inhaling when they should actually continue after the click. However, another product that is silent on actuation was disliked because it gives no feedback.

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- Technique was found to vary considerably across patients, from whether they breathed out before actuation, to the force of inhalation, to the time that the breath was held post-actuation. This is an important area for improvement in both devices and training.
- Condition management. Some patients managed their condition based on the cost of the medication, while others developed strategies to remind them when to take their dose. Dose counters on devices were seen as positive.
- Monitoring and patient support are increasing, allowing better management of the patient in the community and reducing the risk of expensive hospitalizations. Research found that patients had not considered data logging or smart connectivity to monitor their conditions, although some did see value in these techniques.

Cumulatively, this patient research underscored the fact that it doesn't matter how good a drug is in clinical trials—if poor technique means patients don't get the medication to the lungs, or a busy life means they forget to take it all together, the product will not result in a positive outcome. These findings reinforce a number of earlier studies.

### Health Care Professionals

One-to-one interviews were conducted with health care professionals—a combination of general practitioners, respiratory consultants

and respiratory nurses in the U.S. and UK—to determine their process of diagnosing and prescribing COPD and asthma treatments. These professionals voiced concern over the pressure they feel from payers and highlighted the strong importance of cost. Particularly in the U.S., clinicians stated that they are heavily influenced by insurers when prescribing medication. Within the UK, health care professionals have steps to follow, often based on guidelines of the National Institute for Health and Care Excellence (NICE).

Across the range of professionals, there was variation in knowledge of products and devices. Many of the GPs focused on the drug more so than the delivery device. The respiratory nurses were more familiar with various devices and training methods for patients, but also recognized that there wasn't always enough time to ensure correct use of devices. The nurses' main focus was on evaluating the patient's condition and adherence, and they stated that it would be useful to have information on when patients took their medication. The research found that in both the U.S. and UK, a focus on preventative health is driving the need for metadata, medication reminders, technique-improvements and education.

### Payers

Interviews were conducted with individuals with budget and payer control in the U.S., UK and Germany to get a broad range of insights across various payment systems.

The payer landscape is evolving across each of the markets considered. The research underscored the ongoing impact of the global economic recession, which has resulted in a greater focus on budgets. Austerity measures have been implemented in most countries, and this has increased the power of the payer in health systems across the world.

Within the UK, there is a shift towards a service-based model where reimbursement is intended to link to patient outcomes. The U.S. has an increased focus on community and preventative care programs that also focus on outcomes while ensuring that premiums are spent on care or quality improvements. The ongoing implementation of the Affordable Care Act will likely heighten payers' emphasis on outcomes. Payers in Germany were found to be focused on discounts relative to a reference-priced product, with final reimbursement linked to the performance of the product.

As expected, this research showed that safety, efficacy and cost remain of high importance. Developers of new products should engage with payers early in the process in order to begin educating them about the value of the product, and should always bear in mind that data is king.

### Pharma Industry

Finally, an analysis of the pharmaceutical industry was conducted to reconcile its stance relative to the other stakeholders listed here. As is well known, the industry has been waiting for the entry of generics that can attack the inhalation blockbusters. There has been recent movement in this area with launches or approvals for generic and new branded products to both attack and defend this market, including generic Advair, AirFluSal, Forspiro, Breo and Ellipta. One driver for growth of the DPI as a platform has been to provide further product IP protection for the industry, but this is something that may be delivered through any new platform device—MDI or DPI. The changing dynamics in the market and

the emerging strength of payers result in a growing need to collect unambiguous outcomes data relative to alternative products, and to turn this data into a convincing value proposition for the payer.

### WHERE DOES THE DATA LEAD?

This accumulation of data highlighted several themes that each group of stakeholders can benefit from:

- Patient centric approaches. A growing consumer mindset is being applied to the healthcare world. Devices that are difficult to use or that don't satisfy the needs of the patient as a consumer will struggle.
- Electronic integration. Devices are becoming smaller and smarter. Many new developments build on existing devices such as smart phones, helping to make them more cost effective. New integrated products are all trying to drive themes of "Wellness" and "Preventive Medicine."
- Low cost and differentiation. With continued austerity measures and generic competition, it is likely that the focus on cost and product differentiation will continue to maximize the value of any new developments.

Considered in total, the takeaways from this research showed five lessons for new product development:

1. Keep it simple.
2. Make it intuitive.
3. Ensure it provides improved efficacy.
4. Find a way to provide added-value services that better match the patient and the treatment.
5. Ensure all of the real world health-economic benefits can be proven to a payer.

### CONCLUSION

This stakeholder feedback provided a wealth of information regarding what works and what doesn't with today's devices. With this information in mind, we must ask ourselves if the latest products and those currently in development are poised to meet these needs. All of the products that are currently known provide an evolution on the theme that goes back 60 years, and none of them have managed to resolve the basic issues with both MDI and DPI inhaled drug delivery.

Therefore, the primary challenges that are facing the industry are to develop a device that allows patients to adhere to their

medication regimes and to comply with their use, maximizing delivery of the drug dose. This should result in improved patient outcomes. Furthermore, we need to be able to measure these positive patient outcomes in a real-world environment and demonstrate that they are real to the payer and health care professional. Achieving this should result in favorable market access and reimbursement. Finally, the industry needs a product that is differentiated in this competitive landscape, and that also enables protection against generic competition.

This evidence points to the conclusion that in order to serve a successful dinner for three, CDMOs and pharmaceutical developers can't just rely on evolution. In this case, what is really necessary may be a revolution. **CP**

#### References

1. Giraud V and Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *Eur Resp J* 2002;19:246-51.

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