Drug delivery technologies enabling better patient care

Patients, practitioners and regulators for many years have expressed real concerns about the impact of poor regime assurance on the successful treatment of illness.

It is becoming clear, that in many cases, patient compliance can be better assured with assistance from within the device itself. Bespak, a global player in the design, development and manufacture of specialty medical devices, believes that in time, more and more regime assurance and assistance features will be incorporated into everyday drug delivery devices. It is becoming a regulatory requirement for certain features to be included and, as recently as 2001, the US Food & Drug Administration (FDA) issued draft guidance recommending that dose counters be considered for all future pMDI therapies. This article reviews the progress to date of dose counting and other technologies that will aid compliance such as regime assurance devices and new pMDI valve designs that allow patients to comply with their medication regime more easily.

This article will also review other recent delivery device developments, in particular, delivery via the nasal route, reviewing how these advancements have given pharmaceutical partners a unique point of difference and ultimately, how these other routes of administration may help patients comply more easily with their dosing regime.

The evolving role of drug delivery devices

As drug development costs continue to spiral and the generic therapies market becomes more competitive, the business case for developing devices that enable the non-invasive delivery of drugs and provide competitive advantage through a tangible patient compliance benefit is becoming increasingly obvious.

For some years device manufacturers have focused on developing additional patient features for Pressurised Metered Dose Inhalers (pMDIs) in order to offer a credible alternative to Dry Powder Inhalers (DPIs). Partially because of the relative ease of formulating combination therapies as stable powders and partially because many systemic therapies have initially been formulated as such, DPIs have progressed in design relatively rapidly whilst the bulk of development work on pMDIs has been focused on reformulation using more ozone friendly hydrofluoroalkane (HFA) propellants. Though there is evidence to suggest that pMDI technologies offer real benefits in terms of cost

effectiveness and speed through regulatory compliance to market, there remains some 'lag' in the development of the latest therapies in pMDI form. This is partly due to concerns that pMDIs remain difficult for some patient groups to use and this perception is enforced by the need for two-shot dosing and a lack of effective dose counting. Modern DPIs do offer much sought-after design and patient compliance features not offered by pMDIs but they are relatively expensive and still require some user training to be effective. The increasing potential to use the lungs as an access route to the systemic circulation may necessitate a change in basic inhaler design, but particularly pMDIs. It is estimated that by 2010 pain relief and other systemic drugs will account for up to 5% of the pMDI market and with more expensive therapies being delivered, the need to assist patients and prescribers to use the device correctly will become even greater.

Developments in valve technology

It can be argued that the most impactful technologies are those that provide benefit invisibly, that do not require the user to consider more information or learn further steps to gain advantage. If you accept this point of view then one of the most impactful regime assurance solutions lies within a part of the pMDI that few patients ever see. The development of a pMDI valve that guarantees a full dose with each actuation is a significant advance. Because of the internal design of conventional pMDI valves, an inhaler may require "priming" when it has been left inverted for a period of time or even shaken while being carried around. This is because conventional pMDI valves fill a metering chamber immediately after the last dose is fired and this chamber may partially empty if the inhaler is inverted or left. For the inhaler to then deliver an optimum dose, the patient should ideally fire one shot into the air to ensure the valve chamber is completely refilled from the main can reservoir. This requirement results in high levels of wastage and of course assumes that the patient has been shown how to use the inhaler properly or has read the easily ignored Patient Information Leaflet that came with their medication. Often, of course this is not the case, so the only reliable method to ensure a full dose is to recommend a regime based on two puffs from the inhaler. Because the 'Easi-fill' valve requires no priming, pharmaceutical partners can provide a drug delivery solution that gives a consistently accurate dose with a single actuation, resulting in greater regime compliance as patients need only take one puff of their inhaler rather than the two usually recommended. This also reduces waste and, with the growing likelihood of more expensive molecules being delivered from pMDI's, will almost certainly offer a significant economic advantage.

The valve also improves accuracy in dosage delivery as the core has been designed to provide an open channel in/out of the chamber in the 'at rest' position. This ensures that there is no flow of formulation back into the chamber, no chance of sediment settling within the body of the valve and therefore reducing the metering chamber volume and hence the next dose.

Enhanced actuators

Many patients find it difficult to co-ordinate the firing of their pMDI with the correct point of inhalation. This is made more difficult when the medication feels uncomfortable on the back of the throat and may even cause a gagging effect. Developments in the design of actuators, notably the use of actuators with smaller orifice diameters which produce a much slower, 'warmer' spray, make it easier for the patient to co-ordinate inhalation and therefore better ensure that the correct dose is administered to the correct part of the respiratory system.

Creating cost-effective dose counters

Dose counters enable patients to track the amount of medication they have remaining in their inhaler and aid compliance by reducing the likelihood of enforced breaks in the regime; this is brought about when a patient finds their pMDI is empty but cannot immediately get a replacement. Bespak, a leading manufacturer of valves and actuators, have a deep understanding of the interfaces and tolerances critical to accurate dose counting. They have been able to develop a cost-effective mechanical dose counter taking care to ensure the device will never under-count and so will never suggest there is dose remaining in an empty inhaler; the consequences of which clearly could be dire for a patient suffering from an asthma attack. Bespak have opted for a simple design with few components so that high volumes can be manufactured using automatic machinery, a critical consideration if dose counters are to be universally adopted for low cost or generic therapies.

Current designs have been very much developed with both the patient and prescriber in mind, with mooted features including a removable, washable spray nozzle, a clear plastic outer casing so the cannister information can be seen by both parties and a security feature that means the cannister cannot be removed from the device. This means that the counter never shows an error because the pack has been changed i.e. a half empty drug pack exchanged for a full one. Further refinements including an anti-fire feature, to prevent accidental discharge, are currently in development.

The changing role of pMDIs

As already stated, the expectation is that pMDIs, though still a robust delivery mechanism in the treatment of asthma, will be increasingly utilised in pain relief and for other systemic therapies. For example, severe pain management may require the administration of controlled substances such as opioids, but only within certain pre-set limits. The consequences of over-dosing on these more powerful drugs may be far more severe and

the risk is greater too as patients may be disorientated through the use of other medications or be suffering such severe pain that they will take too much of the potentially lethal therapy. There is also the risk of accidental misuse or deliberate abuse.

In order to mitigate such risks pMDI design concepts have been developed to improve their safety and security.

Incorporated into the pMDI device itself, a Regime Assurance Device (RAD) can prevent access at 'non administration' times, which not only helps patients comply with the prescribed regimen but also enables prescribers to monitor usage and, of course, prevent easy access by unauthorised users.
Audible and/or visual reminders have been incorporated to provide patients with information on when the last and next dose should be administered. This feature has real benefits; particularly where preventative medication is being prescribed and there is a real risk that the patient will simply forget to take their medication because they are not experiencing any symptoms. The RAD design also incorporates a dose counter and is breath-actuated, removing the need for a patient experiencing discomfort or suffering disability to then have to coordinate the actuation with inhalation.

Helping patients to comply with their dosing regime is often about providing an appropriate alternative to the needle. Device developers have a role to play in devising the enabling technologies for pharmaceutical developers to accurately and reliably target other areas of the body like the lung or the nasal passages. Through an in-depth understanding of the relationship between the three key components of nasal drug delivery, namely: the formulation, the anatomy of the nose and the characteristics of the delivery device, drug delivery companies are now able to manufacture complex nasal devices for a whole range of formulations. Bespak has successfully combined its own knowledge of device development with computer models that predict deposition in the nose. By varying particle size and even the exact point in the nostril where particles are released, Bespak have been able to demonstrate the more efficient targeting of certain areas in the nose. This may be useful when administering systemic therapies to the highly vascularised nasal turbinates or in avoiding certain areas, such as the olfactory region.

Conclusion

The demands placed on modern device manufacturers to deliver even greater compliance aids will inevitably increase in the coming years as organisations look to deliver more systemic therapies. The breadth and depth of regime assurance features is

substantial and as technology evolves, the cost effectiveness of such features will make them more accessible and desirable to pharmaceutical companies.
It is however essential that the advanced functionality is both discrete and easy to operate. The overall design of any regime assurance device should not stand out from the traditional pMDI and therefore become too cumbersome, complicated or, if controlled substances were to be delivered, a recognisable target for would-be abusers. The device should be developed from the patients' perspective, though clearly any technology should

be able to be manufactured in sufficient numbers with sufficient ease to prevent it from being cost-prohibitive.

Developments in valve technology, particularly the 'Easi-fill' valve, can be incorporated into new pMDI designs relatively easily and offer immediate benefits in terms of patient compliance. Other technologies perhaps require a greater degree of planning and assessment and do increase the cost of the device. That said the benefits to the patient and the savings in terms of wasted formulation might well outweigh that cost.