



Developments in pMDI valve technology ensure better patient compliance

Background

Over a number of years, patients, practitioners and regulators 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. In time, more and more regime assurance and assistance features will be incorporated into everyday drug delivery devices. Indeed, as recently as 2003, the US Food & Drug Administration (FDA) issued draft guidance¹ recommending that dose counters be considered for all future pMDI therapies. The FDA and other regulatory authorities have also emphasised the need to produce less variable pMDIs that deliver doses more accurately than the current requirement in the United States Pharmacopoeia (USP)^{2,3}.

Many devices in development now feature dose counters, but perhaps the most impactful technologies in drug delivery regime assurance are those that provide benefit invisibly, that do not require the user to consider more information or learn further steps to gain advantage.

Loss of prime (LOP) and dose content variability are major patient compliance issues associated with all capillary retention valves fitted to pressurised metered dose inhalers (pMDIs)⁴. 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 some time. 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 (often ignored) Patient Information Leaflet that came with their medication. Often, this is not the case, so the only reliable method to ensure a full dose is taken is to recommend a regime based on two puffs from the inhaler.

Many believe that other more expensive systemic therapies will account for an increasing share of the pMDI market in the coming years. As pharmaceutical companies consider delivering more expensive drugs via pMDI and generic equivalents compete with more and more of the molecules that have historically been delivered in pMDIs, the high wastage issue becomes of greater concern.

A new valve designed to eliminate loss of prime and improve dose accuracy

Bespak, a leading designer, developer and manufacturer of specialty medical devices, has developed a unique pMDI valve to eliminate loss of prime and improve dose content uniformity. The BK361 'Easi-fill' valve is designed to have fast fill/fast drain characteristics that allow the metering chamber to fully refill after actuation or storage, eliminating LOP, reducing dosing variability and therefore helping to improve patient compliance. The following paragraphs detail the methodology and results of testing the BK361 'Easi-fill' valve against a conventional capillary retention valve.

Figure 1 shows a cross-sectional diagram of the BK361, which has a larger flow path than the standard metering valve and therefore is able to fill and drain easily.

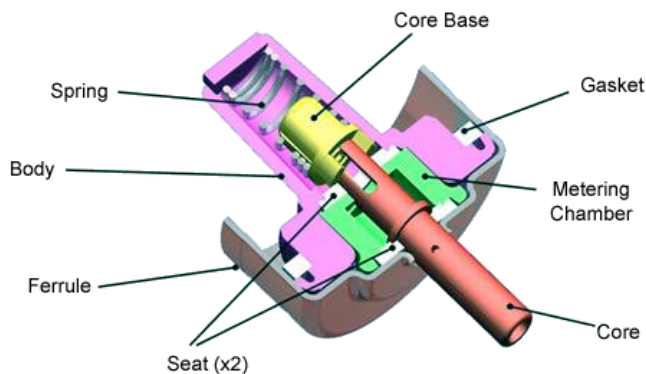


Figure 1: Schematic of the Bespak BK361 'Easi-fill' valve.

Methods

The performance of 'Easi-fill' 50 µl valves fitted with RB700 EPDM elastomers was investigated using a model 0.4% salbutamol sulphate HFA 134a formulation containing 15% ethanol and oleic acid. A comparative priming study of BK361 and a conventional HFA valve was performed to assess each valve's ability to re-prime from empty. The procedure involved test firing each inhaler with 3 shots using a 5-second shake between shots. Shot 4 was fired, valve down. The nominal shot weight was established and indicated that the valves were primed. The device was then inverted (valve up) and shots 5 to 9 were fired, without shaking, to empty the metering chamber. The mass of shot 9

was noted to indicate exhaustion of the valve metering chamber. Shots 10, 11 and 12 were fired valve down to establish whether the valve could deliver a full shot from empty. The procedure was repeated at the end of the pMDI life (nominal 100 doses).

Dose content uniformity (DCU) was assessed for pMDIs fitted with a BK361 valve at time = 0 and following storage at 40°C/75% RH (valve down) for 3 months. DCU was assessed through the life of 10 units at the beginning (3 shots), middle (4 shots) and end (3 shots) of the unit life according to USP methods. Salbutamol content was determined using a reverse phase HPLC method.

Results and Discussion

Figure 2 summarises the results of the priming study and shows that following exhaustion Shots 10 and 85, actuated from pMDIs packaged with 'Easi-fill' valves, delivered a full dose. In contrast, pMDIs fitted with standard HFA valves did not deliver a full dose when fired from empty.

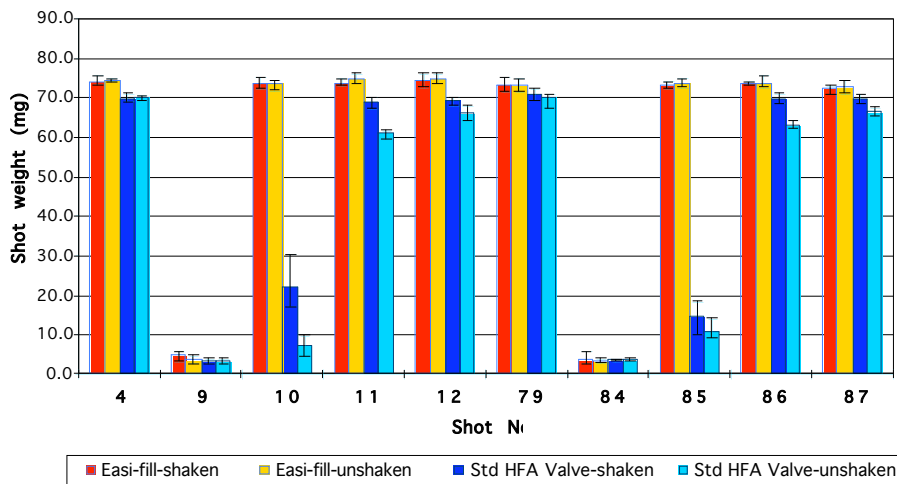


Figure 2: Through Life Shot Weight Data for Salbutamol pMDIs fitted with BK361 'Easi-fill' and Conventional HFA Valves (n=5)

Figures 3 and 4 illustrate through life dose content uniformity of Salbutamol pMDIs packaged with BK361 'Easi-fill' valves at time = 0 and following 3 months' storage at 40°C/75% RH, respectively. The results indicate that the DCU remains within the $\pm 20\%$ target limits through the life of the product.

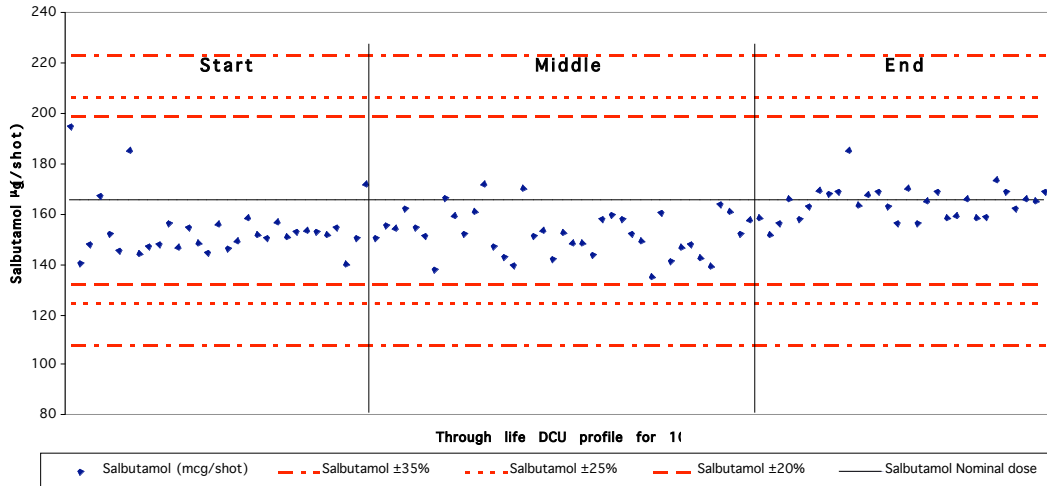


Figure 3: Through Life Dose Content Uniformity for Salbutamol pMDIs fitted with BK361 'Easi-fill' Valves at initial (ambient) (Start: 3 shots, Middle: 4 shots, End: 3 shots from 10 pMDIs).

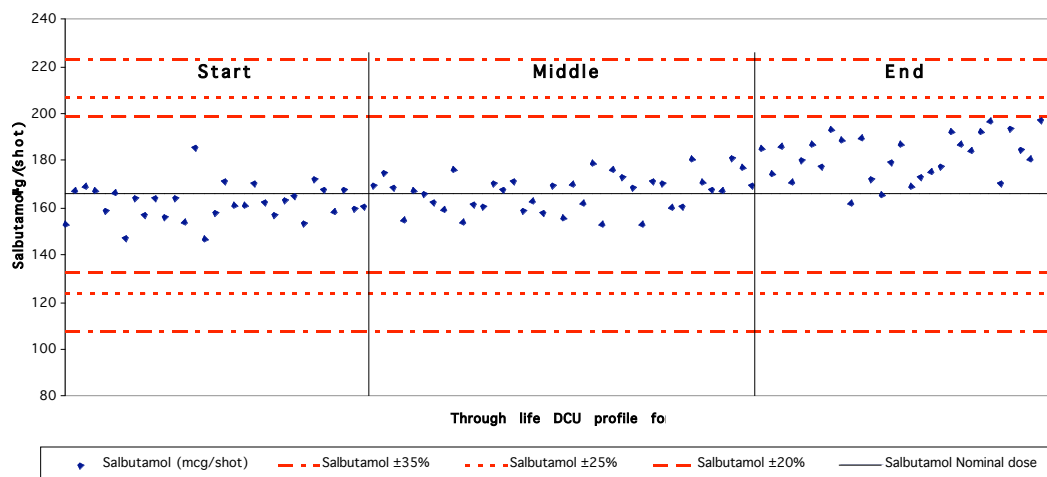


Figure 4: Through Life Dose Content Uniformity for Salbutamol pMDIs fitted with BK361 'Easi-fill' Valves following 3 Months' Storage (40°C/75% RH, valve down) (Start: 3 shots, Middle: 4 shots, End: 3 shots from 10 pMDIs)

Conclusion

The data indicate that the BK361 "Easi-fill" valve has fast fill/fast drain characteristics, that LOP has been eliminated and that pMDIs fitted with this valve do not require priming. DCU results at the start, middle and end of unit life for the initial and 3 months time points indicate that all data were within the specification outlined by the FDA and well within the specification detailed in the USP.

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 reduces waste and, with the growing likelihood of more expensive molecules being delivered from pMDIs, will almost certainly offer a significant economic advantage. Easily incorporated into new pMDI designs, the business case for using the 'Easi-fill' valve is further enhanced when considered in the context of the key benefits of pMDIs as a delivery route i.e. the flexibility to deliver to a range of formulations, enhanced delivery to the lungs, and historically a speedier route to market.

References

1. Guidance for Industry: Integration of Dose-Counting Mechanisms into MDI Drug Products; Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), March 2003
2. Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products – Chemistry, Manufacturing and Controls Documentation; U.S Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER), October 1998.
3. United States Pharmacopoeia (2006), USP 29 NF 24, monograph <601> Aerosols, page 2617.

4. Cyr, T.D., Graham, S.J., Li, K.Y.R., and Lovering, E.G. 1991. Low First Spray Content in Albuterol Metered-Dose Inhalers. *Pharm. Res* 8:658-660.