Expert Opinion

informa
healthcare

Metered-dose inhalers: actuators old and new

David Lewis
Vectura Group Plc., Chippenham, UK

The actuator has been the patient interface of the metered-dose inhaler for the past 50 years. The original 1956 design remains a significant influence upon today's actuators and, moreover, its distinct geometry is still recognisable on the market. The actuator has contributed to the metered-dose inhaler's success as a clinically effective and cost-effective device. This review focuses upon developments since the actuator's introduction as an integral part of the metered-dose inhaler and discusses key aspects of its design that influence lung deposition potential. The ability of the actuator to reduce unwanted oropharyngeal drug deposition, facilitate correct patient use and provide valuable patient feedback is highlighted.

Keywords: actuator design, hydrofluoroalkane, metered-dose inhaler

Expert Opin. Drug Deliv. (2007) 4(3):235-245

1. Introduction

During the last 50 years, the success of the metered-dose inhaler (MDI) has led to its availability to deliver virtually all drugs used in the treatment of respiratory diseases. The MDI's cost-effectiveness, portability, apparent simplicity and convenience have facilitated a widespread acceptance by both patients and clinicians, making it the most common device used to deliver drugs to the lungs [1,201]. The story of the creation of the MDI has been published by its inventor Charles Thiel [2]. The first MDI clinical study was performed in June 1955; the results are reported by Freedman [3]. On the 12th January 1956, new drug applications for two MDI products were submitted to the FDA for approval. On the 9th March 1956, the FDA approval was granted and a month later, Riker Laboratories launched the first MDIs (Medihaler™ – adrenaline and isoprenaline).

The operational principle of present MDIs remains similar to the original 1950s push-and-breath design, which dispensed each dose from a metering chamber fed by a formulation reservoir, contained within a glass or metal container (Figure 1A). Drug is either homogeneously dissolved (in solution) or micronised and suspended in the formulation. On actuation of the MDI (Figure 1B), the MDI's metering chamber becomes closed to the formulation reservoir and opens to the atmosphere, resulting in the expansion of the propellant-based formulation and atomisation through the actuator orifice. The MDI has seen significant developments during recent years as the original chlorofluorocarbon (CFC) propellants are replaced by the non-ozone-depleting hydrofluoroalkane (HFAs) propellants HFA 134a and HFA 227ea in accordance with the Montreal Protocol (1989). This review focuses on the developments of the actuator since its introduction as an integral part of the MDI and its role in delivering drugs to the lungs. For the purpose of this review, the actuator is considered to be the patient-interface that couples directly to the can-valve assembly. In addition, integrated devices (e.g., the spacer, counter, actuation mechanism) will be considered as part of the actuator. Non-integratal add-on devices will not be considered as part of the actuator.

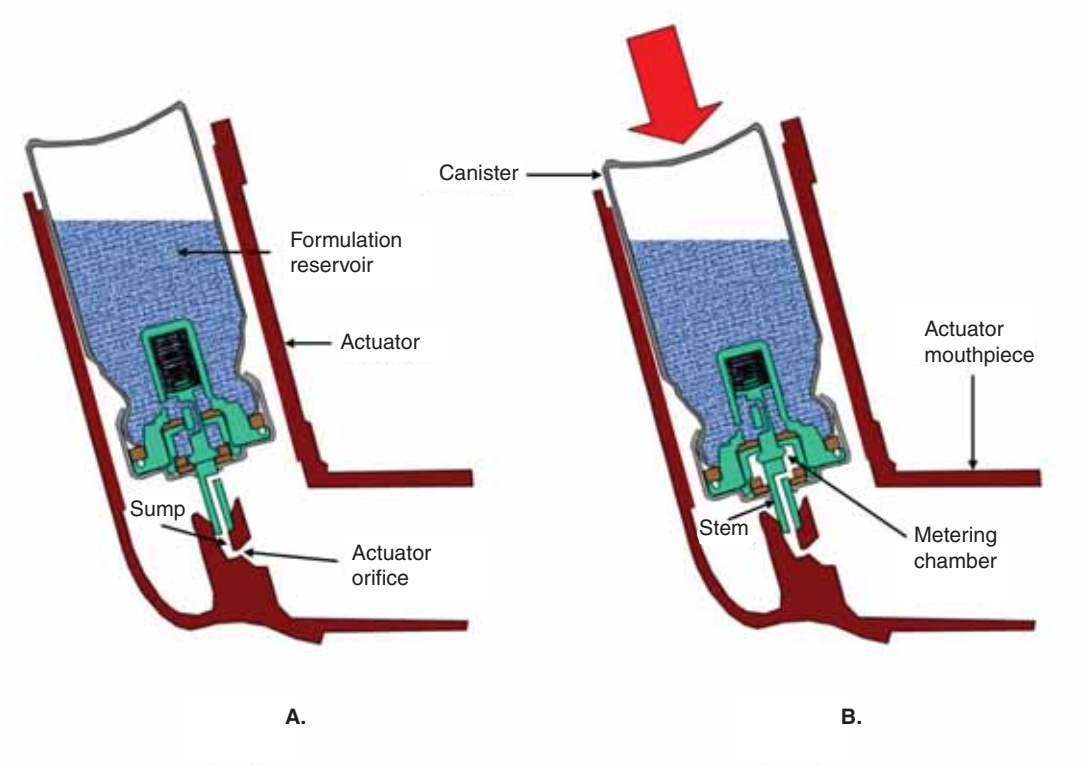

Figure 1. Illustration showing MDI's dose discharge route. A. MDI in rest position – metering chamber open to formulation reservoir. **B.** MDI in actuation position following dose discharge from metering chamber – metering chamber open to atmosphere.
MDI: Metered-dose inhaler.

2. Drug delivery

Depending on the product, 9 – 50% of the drug mass metered by a correctly used MDI is able to reach a patient's lungs [4-9]. Drug that does not reach the patient's lungs is either deposited in the valve stem, actuator and add-on device (if present) or within the patient's oropharyngeal region. However, when MDIs are used incorrectly [10-15], patients are likely to receive a reduced or even a non-existent dose to the lungs. Therefore, since their introduction, MDIs have been developed to facilitate patient compliance and to enhance drug delivery efficiency. Some patient errors (e.g., the patient not continuing to inhale slowly after actuation of the MDI) require correction by regular instruction and check-ups of inhalation technique by appropriately trained clinical professionals [11,16]. However, over the last 50 years, the increased understanding of the actuator's role as the patient interface and its ability to facilitate correct patient use of the MDI have led to significant physical developments in its design and practical execution.

2.1 Actuator geometry

Portability and convenience are of significant importance [12] and exert influence on the physical size of the actuator. Initially, the actuator's housing extended only to the top of the valve ferrule; the redesign of the actuator to encompass and support the canister did not occur until 1965 [101]. This modification introduced four equally spaced ribs to locate the container, and provided an annular passageway to draw air using the mouthpiece. The additional support provided by the modified actuator was introduced to prevent accidental opening of the valve as a result of unintentional axial movement of the valve stem. The updated design remains an important feature of present actuators.

Of significant interest is the original length of the actuator mouthpiece, which was 3- to 4-times longer compared with that commonly used today. The benefits of extending the actuator mouthpiece length have been reported to include increased lung deposition, reduced oropharyngeal deposition [7] and improved ability of patients to coordinate breathing with MDI actuation [17]. Although a shorter mouthpiece improves portability and reduces packaging size, it introduces the need for an add-on device to reduce unwanted oropharageal drug deposition and related side effects [18]. However, the use of an add-on device undermines the portability advantages of the MDI and, in particular, negates the gain obtained from reducing actuator mouthpiece

length. Although add-on devices are of significant value to the MDI with regard to optimising delivery of the therapeutic dose [19-21], the related inconvenience and bulk may result in non-compliance in patient use. In addition, patients may resort to homemade add-on devices when commercially produced devices are either unavailable or too costly [22-26].

The importance of actuator mouthpiece length is evident from the numerous publications reporting actuator designs with extended mouthpieces [14,27,102], mouthpiece attachments [103], collapsible/extendable mouthpiece designs [104-107] and integrated expansion chambers [108]. Such designs claim to overcome the commonly quoted disadvantages of the MDI: a high plume velocity, high oropharyngeal deposition and a poor ability of patients to coordinate breathing and MDI actuation. The effect of extending the mouthpiece length of a Bespak BK633 actuator upon the delivered dose of a beclometasone dipropionate (100 µg) solution MDI is presented in Figure 2 (Lewis *et al.*, unpublished data). This figure demonstrates that a modest increase in the length of an actuator's mouthpiece is able to reduce the delivery of the undesirable non-respirable dose (that leads to oropharyngeal deposition), while broadly maintaining delivery of the respirable dose (drug mass with particles ≤ 5 µm aerodynamic diameter). As an alternative to extending the actuator mouthpiece, modifications to control [109] or inhibit airflow in the vicinity of the actuator orifice [110] have also been reported to reduce plume velocity and oropharyngeal deposition.

The first CFC-free MDI (Airomir™ – albuterol) was launched by 3M Pharmaceuticals in 1995. Appropriately, Airomir's actuator re-introduced key geometrical features from the original Medihaler™ (3M Pharmaceuticals) MDI design. In addition to the sleeve supporting the can, Airomir and the later Qvar™ (beclometasone dipropionate; 3M Pharmaceuticals) were launched with the round mouthpiece design and a modestly extended mouthpiece, highlighting the importance of the original 1956 actuator. The round actuator mouthpiece was described as a means of widening the patient's mouth and clearing the tongue and teeth from the path of the delivered dose [28]. The combination of the mouthpiece design with a reduced metering volume (25 µl) was reported to result in a 'softer puff' [28].

Although similar efficacy can be obtained by patients using alternative inhaler devices [29,30] patients do not always use their inhaler correctly [10-15]. The introduction of inhalation-responsive actuators represents a development that facilitates patient technique by addressing the inhalation/actuation event [30-32]. Improvements of this type were first described in the 1960s [2,111] and have continued over the years, and involve significant modifications to the actuator housing. The first breath actuated MDI (Duo-Haler™; 3M Pharmaceuticals) became commercially available in 1970 [2,33]. Development of the Duo-Haler resulted in the launch of the Autohaler™ (3M Pharmaceuticals) in 1989. According to a proportion of the patient population (34 out of the 40 patients in the study), Autohaler was claimed to be an easier-to-use MDI [34]. A number of other inhalation-responsive concepts have been published [35,112,113], although only one other MDI with integrated breath actuation (Easi-breathe™ – launched in 1995; IVAX) has so far reached the market. The US launch of MD Turbo™ (Respirics, Inc.) in 2006 introduced a prescribed add-on breath-actuated device compatible with several marketed MDIs [202]. When used correctly, patients using a breath-actuated MDI have been reported to have better control over their asthma [36], resulting in a preference by some patients when compared with the conventional push-and-breathe MDI [37].

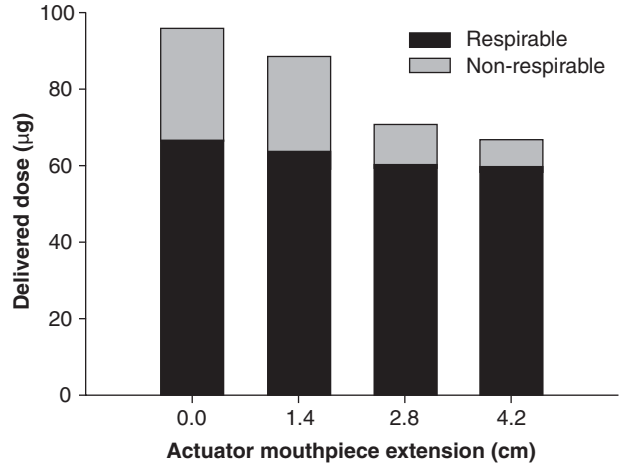

Figure 2. The effect of actuator mouthpiece length on the delivered dose of an ethanol-based beclometasone dipropionate (100 µg) solution HFA 134a MDI containing 10%w/w ethanol.

Data from Lewis *et al.*, unpublished data.
HFA: Hydrofluoroalkane; MDI: Metered-dose inhaler.

2.2 Atomisation

Atomisation of the MDI's formulation is of fundamental importance to the creation of a respirable dose, and occurs in the region of the actuator orifice (Figure 1A). The atomisation process begins as the formulation expands from the confinement of the metering chamber, forming vapour cavitations within the regions of the valve stem, actuator sump and over the length of the actuator orifice [8,38-40]. The process of liquid formulation expansion is followed by rapid flashing of the highly volatile propellant as the dose is emitted from the actuator's exit. The atomisation event typically occurs over a period of 0.1 – 0.5 s [38,40], although it is possible to extend this to 2 – 3 s (well within the range of slow, deep, inhalation) by reducing the actuator orifice diameter or increasing its length [18]. The duration of atomisation is also dependent upon a number of other factors, including the metered volume and composition of the formulation, as well as the dimensions of the valve stem and

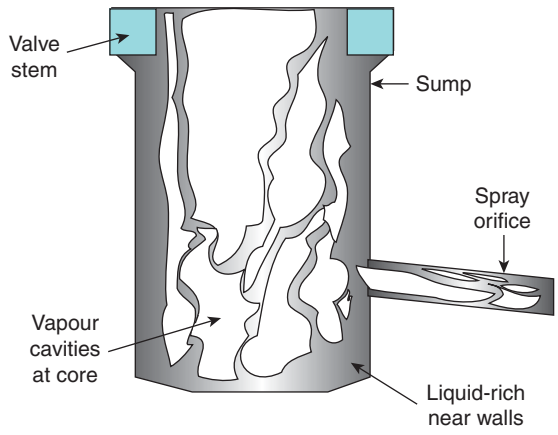

Figure 3. Illustration of vapour cavities within actuator sump and exit orifice.

actuator sump (Figure 1) [18]. The velocity of the emitted cloud decreases rapidly as the cloud moves away from the actuator orifice [18,41], typically leaving the mouthpiece of a conventional actuator at ~ 30 m/s [40,42]. Inhalation of the high-velocity cloud will result in selective removal of non-respirable particles by the oral cavity as a result of turbulent dispersion and inertial impaction [43-46].

2.3 Respirable dose

Many factors determine what proportion of an atomised dose is respirable. This is conventionally considered to be the drug mass composed of particles ≤ 5 µm aerodynamic diameter. Loss of 50 – 91% of the metered dose to the actuator's mouthpiece and patient's oropharageal region is not uncommon. This loss has been linked to the turbulent dispersion of high-velocity clouds within regions of restricted flow [42,43,46,47]. Control of the cloud dynamics can be achieved by careful selection of formulation and device variables. To this end, an understanding of the atomisation process is essential.

Finley [48] has emphasised the importance of propellant cavitations and bubble growth during the atomisation process, highlighting the importance of cavitation (or flashing) within the valve stem and actuator sump. Detailed cavitation and bubble growth observations within an actuator have been recently published by Versteeg and Hargrave [8]. Figure 3 illustrates their observations during the main spray event. They reported that a liquid-rich formulation flows downwards along the sump walls, to collect at the base of the sump, and a vapour-rich formulation occupies the sump's core. Throughout the spray event, variation in the detail was noted; for example, a liquid-rich formulation was reported to fill the sump until it reached the height of the spray orifice. Changes in the density and extent of the vapour core were apparent, as was the destruction and reformation of annular liquid flow within the spray orifice. During the main spray event, surging was observed, whereas pulsing of the spray (narrowing and widening) was observed at the end. They concluded that the formation of respirable particles (≤ 5 µm aerodynamic diameter) is a result of flash evaporation, and the formation of large, non-respirable particles is a result of either direct emission from the actuator orifice at the end of the spray event or break-up and re-entrainment of the formulation accumulating at the edge of the actuator orifice exit [8]. The observed accumulation of formulation at the edge of the actuator orifice may lead to actuator blockage as drug residual accumulates following cumulative doses. A number of alternatives have been used to resolve such issues. Redesign of the exit orifice to include a spout has been reported to prevent cumulative drug build-up [114]. Inclusion of a low volatility excipient to the formulation (e.g., ethanol) at a level that is sufficient to retard the flashing event may also prevent actuator blockage. This is exemplified in Figure 4, which shows the extent of deposition around the actuator orifice resulting from repetitive actuations of alternative estradiol dipropionate 200 µg solution HFA134a MDIs, formulated as a potential for hormone-replacement treatment in post-menopausal women [49,115]. Blockage of the actuator (Bespak BK634, 0.30 mm orifice) is avoided because the formulation's ethanol content is increased from 0 to 15% w/w (Lewis *et al.*, unpublished data). The actuator orifice geometry and actuator sump geometry have also been reported to be of significance with regard to understanding and reducing the risk of actuator blockage [50]. Of particular interest is the geometry of the actuator's sump which, for specific formulations, has an influence on the deposition and accumulation of drug within the actuator's pre-orifice region. Consequently, sump designs that ensure a smooth, rounded interior surface and promote a continuous flow path towards the spray orifice have been reported to improve drug delivery consistency and reduce issues of actuator blockage [116].

Actuator orifice and sump geometry also influence spray pattern [51]. However, the present FDA draft guidance requirement for the analysis of spray pattern and plume geometry within still air [203] does not consider complex plume dynamics and resulting plume shapes within restricted flow regions, which include a patient's respiratory system [42]. The clinical relevance of still air spray pattern measurements, therefore, remains unclear.

The ability to produce a respirable dose is dependent upon the MDI's formulation, valve and actuator characteristics [46,52]. Equation 1 provides an empirical correlation between respirable ex-valve fine particle fraction reported for ethanol-based HFA 134a solution MDIs [46], with actuator orifice diameter (a [mm]), metered dose volume (v [µl]) and HFA 134a content (C [% w/w]).

$$FPF = 2.1 \times 10^{-5} a^{-1.5} v^{-0.25} C^{3} \quad (1)$$

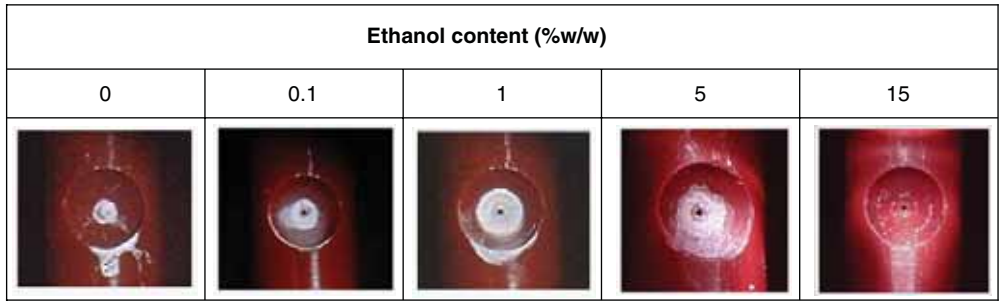

Figure 4. Effect of ethanol content on actuator blockage for estradiol dipropionate 200 µg solution HFA 134a MDIs. Actuator deposition is shown following discharge of 30 50-µl doses through Bespak BK634 (0.30-mm orifice) actuators.
Data from Lewis *et al.*, unpublished data.
HFA: Hydrofluoroalkane; MDI: Metered-dose inhaler.

Equation 1 predicts that MDIs with smaller actuator orifices and smaller metering volumes and high propellant contents will have the highest ex-valve fine particle fractions. Their high dependency on formulation volatility (i.e., propellant content) predicted by Equation 1 is concordant with Versteeg and Hargrave's observations that respirable particles are a result of flash evaporation [8]. Furthermore, the selective removal of larger non-respirable particles by the actuator and oral cavity [43,44,46] implies that Equation 1 may be applicable to estimating the efficiency of alternative actuator designs. However, the application of Equation 1 to predict the respirable dose emitted from an MDI used in conjunction with add-on chamber or spacer is not recommended. This is because there is a potential for such devices to alter the respirable drug mass as a result of the plume residence period [53,54], and/or their statically charged surfaces [55,56]. The choice of formulation, valve, canister and actuator also influence the electrostatic properties of a plume emitted from an MDI [57-59]. However, so far, there is no clear evidence that electrostatics affect the performance of a given MDI when no add-on device is used.

2.4 Particle size distribution

The primary determinant of capture in the lung is the aerodynamic size of a particle [40]. This characterises the particle's inertial behaviour (i.e., its ability to cross streamlines when entrained in an airstream, its rate of sedimentation in a gravitational field and diffusion). Control of the particle size distribution of the respirable dose is, therefore, of primary importance when designing a new MDI or replacing an existing MDI with a pharmaceutical/clinically equivalent product [40,60,61].

With regard to suspension formulations, the particle size distribution of the emitted drug is dependent on the particle size distribution of the micronised drug material [62-64], excipient addition [65], valve lubricant [66,67], MDI storage conditions [62,67] and actuator design [63,64]. However, for solution HFA MDI formulations, the particle size distribution of the respirable dose is generally less variable, being dependent mainly on propellant choice and the concentration of the non-volatile element of formulation [18,46,52,68,69]. The mass median aerodynamic diameter (MMAD) of the cloud delivered by an ethanol-based solution HFA 134a formulation or ethanol-based solution HFA 227ea formulation can be predicted using equations 2 and 3, respectively, where n is the non-volatile formulation content (% w/w) [18].

$$MMAD_{134a} = 2.31n^{1/3} \quad (2)$$

The simplicity of Equations 2 and 3 is striking, identifying particle size distribution to be independent of actuator design and metering valve characteristics. Furthermore, the lack of dependency on the formulation's liquid properties and/or device dimensions is again indicative of a flash atomisation process and furthermore, highlights the robustness of the process. This is further evidenced by the similarity of Equation 2 to that published contemporaneously by Stein *et al.* [69], which was derived using a different methodology, formulations and device hardware. The formation of vapour cavitations within the valve stem, actuator sump and exit orifice (Figure 3) [8,39,48,70] renders the particle size distribution of a solution MDI's respirable dose to be independent of the physical dimensions of these components.

$$MMAD_{227ea} = 3.26n^{1/3} \quad (3)$$

Table 1. The effect of actuator orifice diameter and metered-dose volume on the mean minimum plume temperature (± standard deviation, °C) for three HFA 134a solution MDIs [77].

Actuator orifice diameter (mm)	Metered dose volume (µl)	Mean minimum plume temperature, 2 cm from actuator mouthpiece (°C)		
		Ethanol content of MDI		
		0% w/w	*10% w/w*	*20% w/w*
0.22		+ 3 ± 1	- 2 ± 1	+1 ± 1
0.42	50	- 4 ± 2	- 12 ± 2	- 4 ± 3
0.58		- 33 ± 4	- 29 ± 2	- 20 ± 2
0.22		- 28 ± 4	- 4 ± 1	+1 ± 1
0.42	100	- 45 ± 4	- 25 ± 1	- 14 ± 3
0.58		- 48 ± 6	- 42 ± 2	- 24 ± 1

HFA: Hydrofluoroalkane; MDI: Metered-dose inhaler.

2.5 Actuator orifice design

The importance of actuator orifice design in determining drug delivery characteristics necessitates the tailoring of orifice dimensions to meet the requirements of each formulation. Present moulding processes limit the diameter of the exit orifice to ≥ 0.2 mm. Lewis *et al.* [18] used laser-drilling technology to overcome these moulding constraints, enabling unconventional orifice designs to be evaluated for potential performance advantages. In addition to single circular orifices (diameter of 0.12 – 0.42 mm), the performance of six non-conventional orifice designs, including two vertically stacked multiple (two or four) circular and four single non-circular orifice designs ('peanut', 'clover', 'cross' and 'slot'), were investigated. The particle size distribution of the respirable mass was found to be independent of orifice shape and the number of exit orifices. In agreement with previous work [40,46,52,71], reducing the total cross-sectional area of the orifice was found to increase the duration of the atomisation as well as increasing the ex-valve respirable fraction. In particular, the investigators noted that a 'complex' orifice design was found to increase the wall effect (viscous drag) of the orifice's surface area, retarding the expelled plume velocity and increasing undesirable drug retention within the pre-orifice volume – notably the valve stem. It was also concluded that complex orifice configurations seem to have no advantage over single circular geometry. For a specific formulation, reducing the orifice diameter from 0.22 to 0.14 mm (i.e., below that available from present moulding technology) was found to more than double the plume duration from 0.5 to 1.2 s, and increase the mean ex-valve respirable fraction from ~ 48 to 79%. This result is of particular interest with regard to developing MDIs with highly respirable slow-moving plumes which are comparable to that of electronic nebuliser devices such as Respimat® (Boehringer Ingelheim), which has a plume duration of 1.5 s for a unit dose of aqueous formulation [72].

The influence on performance characteristics of changing the length of an MDI actuator orifice (normally 0.6 – 0.7 mm) was also examined and found to be dependent on the formulation. For example, reducing the orifice length from 0.6 to 0.3 mm was found for one ethanol-based solution HFA formulation to have no effect on either the spray duration or delivery efficiency of the emitted dose. However, for another ethanol-based solution HFA formulation, an increase in the ex-valve fine particle fraction (< 5 µm) from 68 to 84% was observed.

2.6 Plume temperature

The temperature of a cloud emitted from an MDI can result in patient discomfort such that the patient stops inhaling prematurely (the cold Freon effect), resulting in inconsistent or non-existent dose delivery to the lungs [73-75]. Cooling of the MDI's cloud is a result of formulation flashing and evaporation, and it is coldest in the proximity of the actuator orifice, where the emitted cloud is highly dynamic. Pertinent design of the MDI to minimise cooling can result in the removal of patient discomfort and improved compliance and dose delivery to the lungs. The temperature of a cloud delivered to the patient may be raised by addition of co-solvents, such as ethanol, to suppress evaporation rate, an increase in drug concentration to reduce the unit dose metering volume, reduction of the actuator orifice diameter or an increase in the length of the actuator mouthpiece [76,77].

Table 1 illustrates the influence of formulation metering volume and ethanol content. Table 2 shows the use of a large-volume add-on device (e.g., Volumatic™ [750 ml]; GlaxoSmithKline) results in the temperature of the emitted plume approximating to ambient and that use of smaller devices, such as the Chiesi Jet™ (125 ml) or Aerochamber Plus™ (150 ml; Forest Laboratories, Inc.), also significantly increases the temperature of the emitted plume.

2.7 Patient feedback

Since 1972, there has been significant interest in the development of dose counters [78,79,117-123] to overcome difficulties encountered by patients when determining if their MDI is empty [48,80,81]. This has led to the FDA's 2003 recommendation that dose counters be integrated into MDI products [204]. The launch of Seretide Evohaler™ (GlaxoSmithKline) introduced the first MDI with a built-in dose counter in 2004. Electronic monitors that can be attached to MDIs to track and give feedback on patient dosing have been described [82-84]. The SmartMist™ system (Aradigm Corp.) [85] is an advanced electronic device, able to analyse an inspiratory flow profile and automatically actuate the MDI when predefined conditions of flow rate and cumulative inspired volume coincide. Other electronic concepts that use an electromagnet to actuate the dose on activation have been reported [124], as well as data loggers that

Table 2. The mean minimum plume temperature for six drug formulations discharged through conventional actuator, Chiesi Jet actuator with integrated spacer, or conventional actuators in conjunction with add-on devices [77].

	Actuator/add-on device (device volume)			
	Conventional actuator	***Actuator with integrated spacer: Chiesi Jet™ (125 ml)***	***Conventional actuator + Aerochamber Plus™* (150 ml)***	***Conventional actuator + Volumatic™* (750 ml)***
Mean minimum plume temperature (°C)	-8 to -1	+10 to +15	+10 to +13	+17 to +19

*GlaxoSmithKline.

assist, record and restrict patient use [125-127]. These developments represent significant modifications to the MDI actuator as a patient interface, and clearly require careful analysis of the patient benefits and justification of the additional final unit cost.

3. Conclusions

Over the last 50 years, the development of the actuator as the patient interface has resulted in significant capability to control drug delivery characteristics from an MDI. In particular, control of the respirable dose can be achieved by pertinent selection of actuator orifice design. A decrease in the orifice length and/or the orifice cross-sectional area will result in an increase in the respirable drug mass.

Modest extension of the actuator mouthpiece will delay exposure of the drug cloud to the patient, resulting in the inhalation of the cloud at reduced velocity and at a temperature closer to the ambient condition. This can result in reduced oropharyngeal drug deposition, reduced patient discomfort, an improvement in the ability for patients to coordinate breathing and MDI actuation, and an increase in respirable dose.

Correct geometry of the actuator housing is essential; the housing must encompass and support the canister to prevent accidental opening of the valve as a result of unintentional axial movement of the valve stem. Developments within the actuator housing have resulted in the introduction of inhalation responsive actuators and integration of dose-counter mechanisms, solving two commonly encountered drawbacks of the MDI. Further advances in technology have led to the development of actuators that actuate the dose at predefined inhalation conditions and log patient dosing to assist, record and restrict patient use. Each of these represents a significant modification to the MDI and highlights the actuator as the patient interface.

Fifty years on, the MDI remains the most popular and cost-effective device for delivering drugs to the lungs. Since its introduction, there has been an increase in the understanding of the MDI's atomisation process, making it now possible to develop highly efficient MDIs that are able to match the 'soft' clouds delivered from non-pressurised, mechanically powered devices [72]. This increased versatility, in addition to the improved patient interface mechanisms, will keep the MDI as the delivery drug system of choice ahead of alternative less cost-effective systems.

4. Expert opinion

The MDI has now been with us for 50 years. Its low cost, portability, convenience and popularity with both clinicians and patients continue to maintain it as an important inhalation delivery system [1,201]. The introduction of inhalation responsive systems and integrated dose counters has expanded the actuator's role as a patient interface. During the last decade, the ability to characterise and quantify drug delivery performance has improved significantly. There is now greater insight into how to optimise formulation, valve and actuator performance. MDIs able to deliver low velocity 'soft' highly respirable clouds have already reached the marketplace (e.g., Qvar), and the industry has successfully replaced a large number of CFC products. Moreover, MDIs with drugs and drug combinations previously unavailable as CFC products have now been launched.

A greater understanding of how to develop efficient MDIs has led to a number of publications and patents relating to the development of the MDIs for the potential treatment of non-respiratory diseases [49,86-88,115,128]. Furthermore, it has been proven that an MDI is able to deliver a respirable dose that is 80 – 96% of the ex-valve dose [18,46,60]. Coupled with the advantages of a fast onset of action and the avoidance of first-pass hepatic metabolism, the application of the MDI to target drug delivery to the lower airways as a portal to systemic delivery is inevitable.

The concept of using the MDI to deliver insulin dates back to 1956 [2]. The technology and, in some cases, the formulations already exist that are able to deliver drugs systemically [49,86,87]. Proving the safety and efficacy of these products remains the greatest hurdle and risk to capital investment. However, encouragement can be drawn from the recent FDA approval of Exubera® (Pfizer; an active dry power inhaler) to deliver inhaled insulin for the treatment of adults with Type 1 and Type 2 diabetes. Such encouragement is already stimulating the development of new therapeutic applications by inhalation, which may well unleash the full potential of the MDI.

With regard to the future development of the MDI and its actuator, much of the original 1950s concept still plays a

major role. Although this demonstrates the robustness and success of the original design it also reflects a significant lack of development. This scenario is fraught by the ever increasing amount of data required to gain marketing approval. Presently, the MDI represents the fastest route to the market for an inhalation product [205]. The introduction of new concepts and designs will inherently introduce additional capital investment risks, as well as increasing the likelihood of undesirable delays and costs of product development and approval. In addition, cost-effectiveness evidence generally favours the cheapest clinically effective inhaler as a means of first-line treatment [1,89]. It is, therefore, necessary that new MDI developments be both clinically effective, as well as cost-effective, if they are to be a favoured means of treatment. Furthermore, realisation of the MDIs full technological advantages requires optimisation of the formulation, device and inhalation technique. Such developments would focus on the respirable dose rather than the metered dose and align formulation design, device design and inhalation technique to optimise clinical benefit. However, it is likely that changes to the MDI's hardware will be driven by the requirement to overcoming technical or regulatory hurdles rather than as a means of 'improving' a readily available, functional drug delivery device.

In summary, the MDI is a clinically effective and cost-effective device, making it the preferred choice over rival systems such as dry powder inhalers and electronic nebuliser systems (e.g., Respimat®, Boehringer Ingelheim [72]; Aerx®, Aradigm Corp. [90]). Although the MDI and its actuator have considerable potential for further optimisation, it is essential that pharmaceutical and clinical considerations be considered as a priority to the development of an already highly successful product.

Acknowledgements

The author would like to thank B Meakin, Vectura Group Plc., Chippenham, UK and G Brambilla, Chiesi Farmaceutici SpA, Parma, Italy for their discussions regarding the manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. BROCKLEBANK D, RAM F, WRIGHT J *et al.*: Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. *Health Technol. Assess.* (2001) 5(26):1-149.
2. THIEL CG: From Susie's question to CFC free: an inventor's perspective on 40 years of MDI development and regulation. *Proceedings of Respiratory Drug Delivery V.* Phoenix, AZ, USA (1996):115-124.

• Provides an account of the MDI's invention and development.

3. FREEDMAN T: Medihaler therapy for bronchial asthma: a new type of aerosol therapy. *Postgrad. Med.* (1956) 12:667-673.
4. RAU JL: The inhalation of drugs: advantages and problems. *Respir. Care* (2005) 50(3):367-382.

•• Provides a description of high-speed images within an MDI's expansion chamber and in the close proximity to an actuator's exit orifice.

5. NEWMAN SP, NEWHOUSE MT: Effect of add-on devices for aerosol drug delivery: deposition studies and clinical aspects. *J. Aerosol Med.* (1996) 9(1):55-70.
6. NEWMAN SP: Principles of metered-dose inhaler design. *Respir. Care* (2005) 50(9):1177-1190.

• Provides a technical description and evaluation of the MDI as a delivery device for the future.

7. RICHARDS J, HIRST P, PITCAIRN G *et al.*: Deposition and pharmacokinetics of flunisolide delivered from pressurized inhalers containing non-CFC and CFC propellants. *J. Aerosol Med.* (2001) 14(2):197-208.
8. VERSTEEG HK, HARGRAVE G: Fundamentals and resilience of the original MDI actuator design. *Proceedings of Respiratory Drug Delivery X.* Boca Raton, FL, USA (2006) 1:91-100.
9. EVERARD ML: Aerosol therapy past, present, and future: a clinician's perspective. *Respir. Care* (2000) 45(6):769-776.
10. RAU JL: Practical problems with aerosol therapy in COPD. *Respir. Care* (2006) 51(2):158-172.
11. VAN BEERENDONK I, MESTERS I, MUDDE AN, TAN TD: Assessment of the inhalation technique in outpatients with asthma or chronic obstructive pulmonary disease using a metered-dose inhaler or dry powder device. *J. Asthma* (1998) 35(3):273-279.
12. HENDELES L, HATTON RC, COONS TJ, CARLSON L: Automatic replacement of albuterol nebulizer therapy by metered-dose inhaler and valved holding chamber. *Am. J. Health Syst. Pharm.* (2005) 62:1053-1061.
13. GROSSMAN J: The evolution of inhaler technology. *J. Asthma* (1994) 31(1):55-64.
14. GUNAWARDENA KA, SOHAL T, JONES JI, UPCHURCH FC, CROMPTON GK: The Spacehaler for delivery of salbutamol: a comparison with the standard metered-dose inhaler plus Volumatic spacer device. *Respir. Med.* (1997) 91(5):311-316.
15. CROMPTON GK: Problems patients have using pressurized aerosol inhalers. *Eur. J. Respir. Dis. Suppl.* (1982) 119:101-104.
16. SONG WS, MULLON J, REGAN NA, ROTH BJ: Instruction of hospitalized patients by respiratory therapists on metered-dose inhaler use leads to decrease in patient errors. *Respir. Care* (2005) 50(8):1040-1045.
17. BLOOMFIELD P, CROMPTON GK, WINSEY NJ: A tube spacer to improve inhalation of drugs from pressurised aerosols. *Br. Med. J.* (1979) 2(6203):1479.
18. LEWIS DA, MEAKIN BJ, BRAMBILLA G: New actuators versus old: reasons and results for actuator

modifications for HFA solution MDIs. *Proceedings of Respiratory Drug Delivery X*. Boca Raton, FL, USA (2006) 1:101-110.

•• An evaluation of MDI delivery performance, including some unconventional actuator orifice designs.

19. LOUCA E, LEUNG K, COATES AL, MITCHELL JP, NAGEL MW: Comparison of three valved holding chambers for the delivery of fluticasone propionate-HFA to an infant face model. *J. Aerosol Med.* (2006) 19(2):160-167.

20. DUBUS JC, DOLOVICH M: Emitted doses of salbutamol pressurized metered-dose inhaler from five different plastic spacer devices. *Fundam. Clin. Pharmacol.* (2000) 14(3):219-224.

21. LEE H, EVANS HE: Evaluation of inhalation aids of metered dose inhalers in asthmatic children. *Chest* (1987) 91(3):366-369.

22. KISSOON N, TEELUCKSINGH S, BLAKE KV, KESSER B, MURPHY SP, GELLER D: Plastic bottles as spacers for a pressurized metered-dose inhaler: *in vitro* characteristics. *West Indian Med. J.* (2001) 50(3):189-193.

23. OBGANDZE TN, NEMSADZE KP, CHKHAIDZE IG, PERADZE DI: Effectiveness of treatment of bronchoobstruction in children with acute respiratory infections using home-made spacer. *Georgian Med. News* (2005) 118:46-49.

24. SINGHAL T, GARG H, ARORA HS, LODHA R, PANDEY RM, KABRA SK: Efficacy of a home-made spacer with acute exacerbation of bronchial asthma: a randomized controlled trial. *Indian J. Pediatr.* (2001) 68(1):37-40.

25. SAMARANAYAKE SW, PERERA BJ: Paper spacers coupled to metered dose inhalers in family practice. *Ceylon Med. J.* (1998) 43(3):147-150.

26. ZAR H, STREUN S, LEVIN M, WEINBERG E, SWINGLER G: Randomised controlled trial of the efficacy of a metered dose inhaler with bottle spacer for bronchodilator therapy in acute lower airways obstruction. *Arch. Dis. Child.* (2006) (In Press).

27. NEWMAN SP, STEED KP, HOOPER G, JONES JI, UPCHURCH FC: Improved targeting of beclomethasone diproprionate (250 micrograms metered dose inhaler) to the lungs of asthmatics with the Spacehaler. *Respir. Med.* (1999) 93(6):424-431.

28. ELVECROG J: Metered dose inhalers in a CFC-free future. *Pharm. Tech. Eur.* (1997) 9:52-55.

29. DOLOVICH MB, AHRENS RC, HESS DR *et al.*: Device selection and outcomes of aerosol therapy. *Chest* (2005) 127(1):335-371.

30. NEWMAN SP, WEISZ AW, TALAEE N, CLARKE SW: Improvement of drug delivery with a breath actuated pressurised aerosol for patients with poor inhaler technique. *Thorax* (1991) 46(10):712-716.

31. PEDERSON S, FROST L, ARNFRED T: Errors in inhalation technique and efficiency in inhaler use in asthmatic children. *Allergy* (1986) 46:118-124.

32. CROMPTON GK: Problems patients have using pressurized aerosol inhalers. *Eur. J. Respir. Dis.* (1982) 63(Suppl. 119):101-104.

33. COADY TJ, DAVIES HJ, BARNES P: Evaluation of a breath actuated pressurized aerosol. *Clin. Allergy* (1976) 6(1):1-6.

34. KELLOWAY JS, KOCHEVAR JW, SVEUM RJ, HAHN MA: Evaluation of the Autohaler actuator: the effect of written patient instructions on correct use. *J. Asthma* (1993) 30(5):373-379.

35. BACON RJ, MCDERMENT I, BELL J: A new breath operated actuator. *Proceedings of Respiratory Drug Delivery VIII.* Tucson, AZ, USA (2002) 2:403-406.

36. PRICE D, THOMAS M, MITCHELL G, NIZIOL C, FEATHERSTONE R: Improvement of asthma control with a breath-actuated pressurised metred dose inhaler (BAI): a prescribing claims study of 5556 patients using a traditional pressurised metred dose inhaler (MDI) or a breath-actuated device. *Respir. Med.* (2003) 97(1):12-19.

37. CHAPMAN KR, LOVE L, BRUBAKER H: A comparison of breath-actuated and conventional metered-dose inhaler inhalation techniques in elderly subjects. *Chest* (1993) 104(5):1332-1336.

38. CLARK AR: Metered atomization for respiratory drug delivery. *PhD Thesis.* Loughborough University of Technology (1991).

39. DUNBAR CA, WATKINS AP, MILLER JF: An experimental investigation of the spray issued from a pMDI using laser diagnostic techniques. *J. Aerosol Med.* (1997) 10(4):351-368.

40. GANDERTON D, LEWIS D, DAVIES R, MEAKIN B, BRAMBILLA G, CHURCH T: Modulite: a means of designing the aerosols generated by pressurized metered dose inhalers. *Respir. Med.* (2002) 96(Suppl. D):S3-S8.

41. CLARK AR: MDIs: physics of aerosol formation. *J. Aerosol Med.* (1996) 9(Suppl. 1):S19-S26.

42. DAVIES RJ, LEWIS DA, GANDERTON D, MEAKIN BJ, BRAMBILLA G, MURPHY SD, NICHOLLS TR: Velocity profiling of a new HFA budesonide pMDI. *Proceedings of Respiratory Drug Delivery VIII.* Tucson, AZ, USA (2002) 2:759-762.

43. STEIN SW, GABRIO BJ: Understanding throat deposition during cascade impactor testing. *Proceedings of Respiratory Drug Delivery VII.* Tarpon Springs, FL, USA (2000) 2:287-290.

44. STEIN SW, MYRDAL PB: A theoretical and experimental analysis of formulation and device parameters affecting solution MDI size distributions. *J. Pharm. Sci.* (2004) 93(8):2158-2175.

45. MEAKIN BJ, GANDERTON D, PANZA I, VENTURA P: Drug delivery from pressurised metered dose inhalers (pMDIs) containing BDP using the Chiesi Jet actuator. *Proceedings of Respiratory Drug Delivery V.* Phoenix, AZ, USA (1996):370-373.

46. LEWIS DA, MEAKIN BJ, BRAMBILLA G: Theory and practice with solution systems. *Proceedings of Respiratory Drug Delivery IX.* Palm Desert, CA, USA (2004) 1:109-115.

47. VERSTEEG HK, HARGRAVE G, HARRINGTON L, SHRUBB I, HODSON D: The use of computational fluid dynamics (CFD) to predict pMDI air flows and aerosol plume formation. *Proceedings of Respiratory Drug Delivery VII.* Tarpon Springs, FL, USA (2000) 2:257-264.

48. FINLAY WH: *The Mechanics of Inhaled Pharmaceutical Aerosols.* Academic Press, San Diego, CA, USA (2001).

49. BRAMBILLA G, DAVIES RJ, LEWIS DA, GEORGE SC, GANDERTON D, MEAKIN BJ: Formulation of oestrogens as HFA solution pMDIs. *J. Aerosol Med.* (2003) 16(2):211.

50. TANENBAUM MF, BRAMANTE T, SHU F, ANGEL A, PARK J: Minimization of actuator (mouthpiece) clogging for solution inhalation aerosol products.

Proceedings of Respiratory Drug Delivery VI. Hilton Head, SC, USA (1998) 2:429-434.

51. SMYTH H, BRACE G, BARBOUR T, GALLION J, GROVE J, HICKEY AJ: Spray pattern analysis for metered dose inhalers: effect of actuator design. *Pharm. Res.* (2006) 23(7):1591-1596.
52. MEAKIN BJ, LEWIS DA, GANDERTON D *et al.*: Effects of actuator orifice diameter on beclomethasone dipropionate delivery from a pMDI HFA solution formulation. *Proceedings of Respiratory Drug Delivery VI.* Hilton Head, SC, USA (1998) 2:363-366.
53. MEAKIN BJ, LEWIS DA, CHURCH TK, GANDERTON D, RICHARDS J, BRAMBILLA G: A comparative formoterol HFA pMDI delivery performance from an integral device. *Proceedings of Respiratory Drug Delivery IX.* Palm Desert, CA, USA (2004) 2:845-848.
54. MEAKIN BJ, LEWIS DA, CHURCH TK, GANDERTON D, BRAMBILLA G: Budesonide 200 HFA Modulite delivery from the Chiesi Jet. *Drug Deliv. Lungs* (2003) 14:126-128.
55. MITCHELL JP, NAGEL MW: Spacer and holding chamber testing *in-vitro*: a critical analysis with examples. *Proceedings of Respiratory Drug Delivery VII.* Tarpon Springs, FL, USA (2000) 1:265-274.
56. KWOK P, CHAN HK: Electrostatic charges of metered dose inhaler aerosols sampled from plastic spacers. *Proceedings of Respiratory Drug Delivery X.* Boca Raton, FL, USA (2006) 1:121-132.
57. KEIL JC, KOTIAN R, PEART J: Using and interpreting aerosol electrostatic data from the electrical low pressure impactor. *Proceedings of Respiratory Drug Delivery X.* Boca Raton, FL, USA (2006) 1:267-278.
58. KOTIAN R, PEART J: Influence of formulation components on inherent electrostatic properties of HFA propelled solution pMDIs. *Proceedings of Respiratory Drug Delivery X.* Boca Raton, FL, USA (2006) 3:947-950.
59. PEART J: Influence of static charge on dynamic performance of inhaled drug products. *Proceedings of Academy of Pharmaceutical Sciences Inhalation.* (2007) Bath, UK.
60. BRAMBILLA G, GANDERTON D, LEWIS DA, MEAKIN BJ, GARZIA R: The modulation of clouds generated by pMDIs. *J. Aerosol Med.* (1999) 12:119.
61. MEAKIN BJ, LEWIS DA, GANDERTON D, BRAMBILLA G: Countering challenges posed by mimicry of CFC performance using HFA systems. *Proceedings of Respiratory Drug Delivery VII.* Tarpon Springs, FL, USA (2000) 1:99-107.
62. BERRY J, KLINE LC, SHERWOOD JK *et al.:* Influence of the size of micronized active pharmaceutical ingredient on the aerodynamic particle size and stability of a metered dose inhaler. *Drug Dev. Ind. Pharm.* (2004) 30(7):705-714.
63. BERRY J, HEIMBECHER S, HART JL, SEQUEIRA J: Influence of the metering chamber volume and actuator design on the aerodynamic particle size of a metered dose inhaler. *Drug Dev. Ind. Pharm.* (2003) 29(8):865-876.
64. SMYTH HD: The influence of formulation variables on the performance of alternative propellant-driven metered dose inhalers. *Adv. Drug Deliv. Rev.* (2003) 55(7):807-828.
65. WILLIAMS RO, LIU J, KOLENG JJ: Influence of metering chamber volume and water level on the emitted dose of a suspension-based pMDI containing propellant 134a. *Pharm. Res.* (1997) 14(4):438-443.
66. BERRY J, KLINE L, NAINI V, CHAUDHRY S, HART J, SEQUEIRA J: Influence of the valve lubricant on the aerodynamic particle size of a metered dose inhaler. *Drug Dev. Ind. Pharm.* (2004) 30(3):267-275.
67. BERRY J, KLINE LC, HART JL, SEQUEIRA J: Influence of the storage orientation on the aerodynamic particle size of a suspension metered dose inhaler containing propellant HFA-227. *Drug Dev. Ind. Pharm.* (2003) 29(6):631-639.
68. GUPTA A, STEIN SW, MYRDAL PB: Balancing ethanol cosolvent concentration with product performance in 134a-based pressurized metered dose inhalers. *J. Aerosol Med.* (2003) 16(2):167-174.
69. STEIN SW, MYRDAL PB, GABRIO BJ, OBEREIT D, BECK TJ: Evaluation of a new aerodynamic particle sizer spectrometer for size distribution measurements of solution metered dose inhalers. *J. Aerosol Med.* (2003) 16(2):107-119.
70. DOMNICK J, DURST F: Measurement of bubble size, velocity and concentration in flashing flow behind a sudden constriction. *Int. J. Multiphase Flow* (1995) 21(6):1047-1062.
71. BRAMBILLA G, GANDERTON D, GARZIA R, LEWIS D, MEAKIN B, VENTURA P: Modulation of aerosol clouds produced by pressurised inhalation aerosols. *Int. J. Pharm.* (1999) 186(1):53-61.
72. HOCHRAINER D, HOLZ H, KREHER C, SCAFFIDI L, SPALLEK M, WACHTEL H: Comparison of the aerosol velocity and spray duration of Respimat® Soft Mist® inhaler and pressurized metered dose inhalers. *J. Aerosol Med.* (2005) 18(3):273-282.
73. NEWMAN SP, STEED KP, HOOPER G, JONES JI, UPCHURCH FC: Improved targeting of beclomethasone diproprionate (250 micrograms metered dose inhaler) to the lungs of asthmatics with the Spacehaler. *Respir. Med.* (1999) 93(6):424-431.
74. GABRIO BJ, STEIN SW, VELASQUEZ DJ: A new method to evaluate plume characteristics of hydrofluoroalkane and chlorofluorocarbon metered dose inhalers. *Int. J. Pharm.*(1999) 186(1):3-12.
75. ROSS DL, GABRIO BJ: Advances in metered dose inhaler technology with the development of a chlorofluorocarbon-free drug delivery system. *Int. J. Pharm.* (1999) 12(3):151-160.
76. BRAMBILLA G, CHURCH T, KEEBLE C, LEWIS D, MEAKIN B: The determination of the plume temperature for budesonide HFA metered dose inhalers. *Proceedings of Drug Delivery to the Lungs 17.* Edinburgh, Scotland, UK (2006):94-97.
77. BRAMBILLA G, CHURCH TK, LEWIS DA, MEAKIN BJ: Control of plume temperature emitted from metered dose inhalers. (In Press).

•• An empirical evaluation of solution MDI performance characteristics.

78. WILBY M, PURKINS G: The 3M™ integrated dose by dose counter for pMDIs. *Proceedings of Drug Delivery to the Lungs 17.* Edinburgh, Scotland, UK (2006):288-291.
79. BRADSHAW DR: Developing dose counters: an appraisal based on regulator, pharma, and user needs. *Proceedings of Respiratory Drug Delivery X.* Boca Raton, FL, USA (2006) 1:121-132.
80. CAIN WT, OPPENHEIMER JJ: The misconception of using floating patterns as an accurate means of measuring the contents of metered-dose inhaler devices. *Ann. Allergy Asthma Immunol.* (2001) 87(5):417-419.

81. HOLT S, HOLT A, WEATHERALL M, MASOLI M, BEASLEY R: Metered dose inhalers: a need for dose counters. *Respirology* (2005) 10(1):105-106.

82. JULIUS SM, SHERMAN JM, HENDELES L: Accuracy of three electronic monitors for metered-dose inhalers. *Chest* (2002) 121(3):871-876.

83. O'CONNOR SL, BENDER BG, GAVIN-DEVITT LA: Measuring adherence with the Doser CT in children with asthma. *J. Asthma* (2004) 41(6):663-670.

84. APTER AJ, TOR M, FELDMAN HI: Testing the reliability of old and new features of a new electronic monitor for metered dose inhalers. *Ann. Allergy Asthma Immunol.* (2001) 86(4):421-424.

85. FARR SJ, ROWE AM, RUBSAMEN R, TAYLOR G: Aerosol deposition in the human lung following administration from a microprocessor controlled pressurised metered dose inhaler. *Thorax* (1995) 50(6):639-644.

86. BRAMBILLA G, BERRILL S, DAVIES RJ *et al.*: Formulation of leuprolide as a HFA solution pMDI. *J. Aerosol Med.* (2003) 16(2):209.

87. BRAMBILLA G, DAVIES RJ, LEWIS DA, GEORGE SC, GANDERTON D, MEAKIN BJ: Formulation of an analogue of apomorphine as an HFA solution pMDIs. *J. Aerosol Med.* (2003) 16(2):209.

88. SMYTH HD: Propellant-driven metered-dose inhalers for pulmonary drug delivery. *Expert Opin. Drug Deliv.* (2005) 2(1):53-74.

•• A review of the MDI's ability to continue to develop and dominate the pulmonary drug delivery market.

89. RAM FS: Clinical efficacy of inhaler devices containing β(2)-agonist bronchodilators in the treatment of asthma: cochrane systematic review and meta-analysis of more than 100 randomized, controlled trials. *Am. J. Respir. Med.* (2003) 2(4):349-365.

90. NOYMER P, SCHUSTER, J, HOLST, P *et al.*: AERx®-Essence™: efficiency and breath control without electronics. *Proceedings of Respiratory Drug Delivery IX*. Palm Desert, CA, USA (2004) 1:255-262.

Patents

101. RIKER LABORATORIES, INC.: GB994755 (1965).

102. SCHERING CORPORATION: WO9305837A1 (1993).

103. WILLIAMS JW: US5746197 (1998).

104. ALLDREDGE, AL: US5571246 (1996).

105. ABBOTT LABORATORIES: WO199220391A1 (1992).

106. BESPAK PLC: US6230704 (2001).

107. FISONS PLC: US4509515 (1985).

108. CHIESI FARMACEUTICI SPA: WO200149350 (2001).

109. BESPAK PLC: GB2279879A (1995).

110. 3M INNOVATIVE PROPERTIES CO: WO200050112 (2000).

111. DART INDUSTRIES, INC.: US3456644 (1969).

112. DART INDUSTRIES, INC: US3456646 (1969).

113. RIKER LABORATORIES, INC.: US5069204 (1991).

114. FISONS PLC: US5682875 (1997).

115. CHIESI FARMACEUTICI SPA: WO03074058 (2003).

116. IVAX CORP: WO03002169 (2003).

117. GLAXO GROUP LTD: US4817822 (1989).

118. TRUDELL MEDICAL INTERNATIONAL, INC.: US7100530 (2006).

119. GLAXO GROUP LTD: US7107986 (2006).

120. GLAXO GROUP LTD: EP0988077B1 (2003).

121. VALOIS SA: US5988496 (1999).

122. MINNESOTA MINING AND MANUFACTURING COMPANY: US5349945 (1994).

123. ONEIDA RESEARCH SERVICES, INC.: US5676129 (1997).

124. BESPAK PLC: GB2413498 (2005).

125. ARMSTRONG PHARMACEUTICALS, INC.: US5284133 (1994).

126. CIRCADIAN, INC.: US5363842 (1994).

127. ARADIGM CORPORATION: US5392768 (1995).

128. CHIESI FARMACEUTICI SPA: WO2003074023A1 (2003).

Websites

201. http://www.pharmiweb.com/PressReleases/pressrel.asp?ROW_ID=1625
'Metered Dose Inhalers Still the Workhorse of Respiratory Drug Delivery', Greystone Associates, Posted on: 25 Aug 06.

202. http://www.mdturbo.com/index.html
MD Turbo™ (handheld companion to metered dose inhalers) website.

203. www.fda.gov/cder/guidance/2180dft.pdf
FDA guidance for industry: metered dose inhaler (MDI) and dry powder inhaler (DPI) drug products, chemistry, manufacturing, and controls documentation.

204. www.fda.gov/cder/guidance/5308FNL.pdf
FDA guidance for Industry: integration of dose-counting mechanisms into MDI drug products.

205. http://www.ptemag.com/pharmtecheurope/article/articleDetail.jsp?id=176027
PRITCHARD J: The future of metered-dose inhalers. *Pharmaceutical Technology Europe* (1 September 2005).

Affiliation

David Lewis BSc, MSc, PhD
Head of HFA Programmes, Vectura Group Plc., Chippenham, UK
Tel: +44 (0)1249 667623;
Fax: +44 (0)1249 667701;
E-mail: david.lewis@vectura.com