

Images: 3M™ Integrated Dose by Dose Counter

More Than Just a Dose Counter

By Adam Stuart at 3M Drug Delivery Systems

To the untrained eye, it may appear that adding a dose counter or indicator to a metered dose inhaler is a simple task, but there are a number of technical challenges and complex factors that need to be carefully balanced and assessed

Keywords

- Metered dose inhaler (MDI)
- Dose counter
- Dose indicator
- Valve travel

Aside from the fact that dose counters are becoming part of the Food and Drug Administration’s (FDA’s) regulatory guidance in the US, patients today have expressed the desire to know their medication levels at all times. However, pharmaceutical

companies are often deterred from adding a dose counter or indicator to a metered dose inhaler (MDI) due to the associated complexity and costs.

This article discusses important factors that pharmaceutical companies should consider when looking to add a dose counter or indicator, and overviews the

detailed requirements that make for a challenging manufacturing process.

Counter Versus Indicator

Although similar, a dose counter and a dose indicator differ in various ways.

Figure 1 (above): Dose counter – a numerical display indexes forward for each actuation

A typical dose counter has a numerical display, indexes forward for each actuation made and has a discrete display – factors that often lead to preference by patients over a dose indicator.

Dose indicators take many forms, but often count in multiples (for example, 10 or 20) or use colours to display remaining doses (see Figure 1). They often do not index every count and require some patient interpretation of the display. The appeal of dose indicators tends to be the larger display and lower cost, although they are not considered by patients to be as accurate as a dose counter.

Device Location

Another consideration is where the dose counter or indicator will be located. Options include the top, internal or side mounting of the device.

Top-mounted dose counters or indicators are attached to the MDI canister. An advantage of a top-mounted device is that it can be added to a design without affecting existing components or pre-existing drug delivery. The two disadvantages are the overall height of the MDI, which is extended and has the potential to create difficulty for patients with a limited hand span; and the fact that the counter itself is exposed to the patient, which therefore means it must be designed to withstand a higher level of tampering and abuse.

Internal dose counters or indicators sit within the actuator and are often visible to the patient via a window in the actuator (see Figure 2). Fitting a dose counter or indicator inside the actuator is a very difficult task, as the space envelope between the MDI valve

and actuator is typically very small. An internal dose counter or indicator sits in the upstream airflow of the MDI, which has the potential to disrupt the spray plume.

Despite this, the main advantages are that the counter is a contained, tamper-proof system and that the outward appearance of the actuator remains familiar to patients. This means that apart from having an additional viewing window, it has the appearance of a typical MDI.

Side-mounted dose counters or indicators can be viewed as a compromise between internal and top-mounted counters. Side mounts have the advantages of sitting outside of the airflow, and being enclosed and tamper proof. However, one disadvantage of a side mount is its bulky appearance and size, which patients may find ungainly to use. The addition of a side-mounted dose counter to an existing product can drastically change its appearance, which can have a negative impact on a product where maintaining patient familiarity is essential.

Displacement Versus Force

Once the decision has been made to incorporate a dose counter or dose indicator, and its location has been agreed upon, the next step is to determine how it will be driven. Dose counters can be actuated by the displacement of the MDI valve or, if top mounted, can be force-driven.

A force-driven dose counter works by having a smaller actuation force than that of the valve, so when the dose counter is depressed, it is actuated before the valve. There is a higher risk of accidental overcounting with

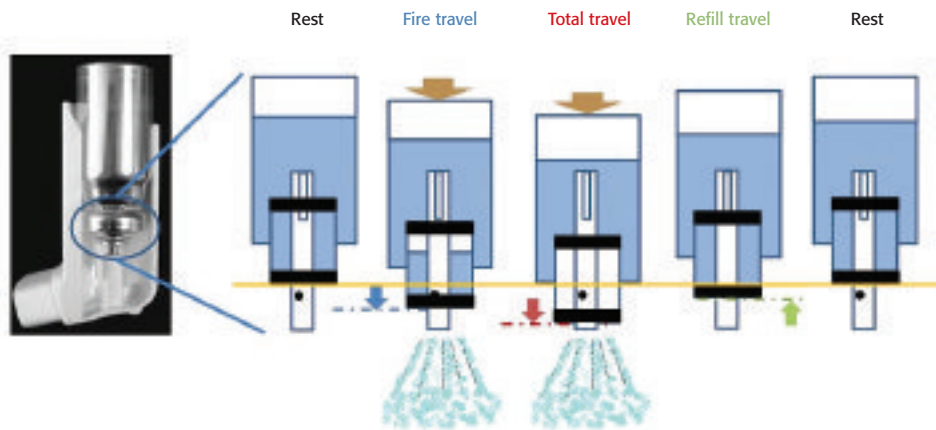


Figure 2: Internal dose counters sit within the actuator

a force-driven device, as it is inherently easy to actuate. This can lead to the counter displaying fewer doses than actually remain. This disadvantage alone has led to industry preference towards displacement-driven dose counters.

Displacement-driven dose counters are indexed after a set travel of the MDI valve and are therefore more robust to accidental actuation. The only disadvantage of a displacement-driven counter is the small amount of travel available to count in and the requirement to match valve travels – both of which can make designing and controlling the manufacturing process a challenge.

Figure 3: MDI valve stem depression



Valve Travel Matching

When an MDI valve stem is depressed, it travels through four key positions. The first is the rest position: the position it starts at and returns to after firing. On the down stroke, the valve reaches a point at which it delivers a dose – also known as the ‘fire travel’. Here, the valve continues to be depressed until it reaches a dead stop – known as the ‘total travel’. On the return stroke, the valve reaches a point at which its metering chamber refills and is ready to fire again – known as the ‘refill travel’. These travels are vital to the performance of the valve, and a dose counter or indicator needs to be designed to accommodate each travel variety.

Often, the biggest challenge when developing a dose counter or indicator is matching its function to the travels of one or more MDI valves. For products entering the US, the FDA guidance states that dose counters should be engineered to reliably track actuations and be designed to be as close to 100 per cent reliable as possible.

If some low frequency of error is unavoidable, the device should be designed to specifically avoid undercounting (where the MDI sprays but the counter does not advance). A typical MDI valve fires

with a travel of approximately 2mm (with varying tolerances) and the counter must be designed to count at the same point during an actuation. In addition, the counter must be allowed to reset, and therefore needs a clearance with the valve. The result of this is a very narrow window for counting, to which a counter must be designed to avoid undercounting (see Figure 3).

This issue becomes far more complicated when compatibility is required with multiple valves from a number of suppliers, all with differing travels and valve geometry. However, specific dose counters have been designed with an indexer that can be selected to match a group of valve designs. By simply switching the indexer from one to another, the counter becomes compatible with a wide range of valve geometries.

Robustness

Imagine the disruption that could be caused if a car’s fuel gauge was either inaccurate or completely faulty. It would be inconvenient, but would most likely not be described as life-threatening.

Now envision a potentially life-saving medication that requires a dose counter or indicator to display how much medication remains. In this

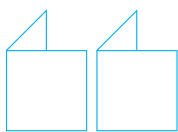
situation it is crucial for the device to be robust and accurate. This must be considered during the design phase of dose counter or indicator development, and thoroughly tested throughout design verification.


In ensuring the device is sufficiently robust, the key factors include:

- Count accuracy – ensuring that each count is registered, and that the device is designed to avoid undercounting, in accordance with FDA guidance
- Robustness to dropping – ensuring that the device can resist dropping from an industry standard height onto a metal plate. This replicates potential impacts that could occur in everyday life
- Tamper proof/tamper evident – making sure the dose counter cannot easily be artificially driven forwards or backwards, and ensuring that there is evidence of damage if this does occur

Dose Delivery

The most critical factor to be considered during the development of a dose counter for an MDI is the effect its presence will have on dose delivery performance. When adding a dose counter to an existing product, all efforts must be made to ensure its presence does not affect



Ensuring that a dose counter is robust to undercounting is critical from a regulatory stance and must be addressed during the design development. Matching a dose counter to a valve's travels is difficult due to the large manufacturing tolerances and small window of operation 

the delivery of the drug. At this point, airflow is a key consideration, as a change or restriction in airflow could lead to a significant change in the geometry of the spray plume and the efficiency of delivery to the lungs.

This criterion is less of a consideration for top- or side-mounted dose counters because the counter does not sit directly in the critical airflow path. Internal dose counters need to be designed so that they do not restrict airflow or considerably affect the flow profile between the valve and mouthpiece in the bottom of the actuator.

Size-Related Decisions

When designing a dose counter for an MDI, desired features can often be in conflict with each other. To achieve a suitable design, various factors must be carefully assessed and weighed up as necessary.

A prime example of this is balancing size, patient familiarity and function. It is desirable to a patient for the display to be as large and clear as possible, but there is a restriction on the size of an MDI, which must be readily portable and designed to fit in a standard pocket. A larger display requires larger components, so a compromise must be struck to achieve an optimal display size.

The device must remain readable to patients without compromising the overall size of the MDI. This

challenge is particularly difficult if designing an internal dose counter for an existing product because patient familiarity is important and the space envelope is already defined.

Another size-related decision is whether to opt for a smaller display dose counter or a larger display indicator. A dose indicator can have much larger text, tending to count in multiples of 10 or 20. This decision can sometimes be guided by the number of doses required. A product with a high number of doses will often be pushed to a dose indicator – an indicator is often the only choice when it is difficult to fit a numerical display that can count down in individual increments from 200 doses within the space limitations of a conventional MDI actuator.

Other Technical Issues

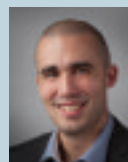
There are obvious aesthetic advantages of an internal dose counter or indicator, but its location creates the risk of affecting airflow through the MDI. If an internal device is chosen, great care must be taken to ensure its presence does not have an adverse effect on drug delivery. The effects of this can be predicted using computational fluid dynamics, but need to be confirmed with pharmaceutical testing.

Ensuring that a dose counter is robust to undercounting is critical

from a regulatory stance and must be addressed during the design development. Matching a dose counter to a valve's travels is difficult due to the large manufacturing tolerances and small window of operation. Tolerance optimisation and dimensional control are essential in ensuring that a counter always avoids undercounting, but has features which are large and robust enough to withstand everyday use.

Design Success

There are a number of technical challenges and decision factors that pharmaceutical companies need to carefully consider when adding a dose counter or indicator to an MDI. Choosing between a counter or indicator, the size and appearance of the MDI versus patient familiarity, and the importance of designing the counter to match key parameters of the MDI actuation are just a few issues in the design and development process to ensure success.



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