

An Application of Quality by Design (QBD) and Process Analytical Technology (PAT) to the Development of Force-Driven Dose Counters for Pressurized Metered Dose Inhalers

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Summary

The principles of Quality by Design (QbD) require the aerosol drug delivery device developer to define the critical quality attributes and process parameters that have impact on the safety, efficacy, and quality of the product. The Force-to-Actuate (FT_A) and Force-to-Reset (FT_{RS}) of the Top Mounted Actuation Indicator (TMAI), developed by Trudell Medical International (Trudell), are the defining critical quality attributes of the device. In combination with the pressurized metered dose inhaler (pMDI) Force-to-Fire (FT_F) and Force-to-Refill (FT_{RF}), it defines the sequence of events that affect the count accuracy of the system.

Trudell completed a simulated patient handling study to evaluate the design space around the FT_A and FT_{RS} of the TMAI-200 Series; a second generation device design modified for use with rescue medications. The study revealed that the design space around the FT_A and FT_{RS} for the TMAI-200 Series device was robust with a count accuracy of over 99%.

To monitor and improve the control space, Process Analytical Technology (PAT) was developed to facilitate continuous real time monitoring of the FT_A of each device produced. Not only does this ensure that all TMAI leaving the facility were produced within the control space but the data captured can be applied to continuous improvement efforts and the development of up-stream manufacturing processes including injection moulding of the plastic components and spring winding.

Introduction

The term “dose counter” for pMDI, generally adopted by industry and regulators, can be considered misleading. There is no intent by any of the devices that are commercially available to give the user information about whether they have received a “dose” of their medication. Certainly a scan of the crowded IP landscape in dose counting will reveal concepts that come close. However, most dose counters, by the nature of their designs, cannot determine whether the full capacity of the metering chamber was delivered along with the correct amount of drug. It has been shown, and will be discussed later in this paper, that user technique can affect the magnitude of the mass of medication released from the pMDI. For the discussion in this paper, the implications of variation in shot weight will be restricted to the use of gravimetric measurement in determining the count accuracy of a dose counter-pMDI system.

The count accuracy of a dose counter cannot be discussed in the context of the dose counter alone, where the concept of counter precision would be more appropriate. Instead, count accuracy is a system level attribute that must be assessed from the perspective of the end-user. In this context the “system” is considered to be the complete inhaler comprising: the dose counter mechanism, inhaler actuator, and the filled canister complete with metering valve. The dose counter platforms available today vary significantly in complexity, integration, and mode of operation yet all must meet an acceptable count accuracy requirement in the context of the system.

The Top Mounted Actuation Indicator (TMAI) developed by Trudell is named so to recognize that by itself it does not register the delivery of a dose, as its purpose is to record “actuations” of the system. Therefore, for the discussion in this paper, count accuracy will be defined as the system level requirement for an actuation to be registered by the dose counter when a bolus of aerosol is released. Also, unless referring specifically to the TMAI by Trudell, the generally accepted term of dose counter will be used.

Count accuracy of the system is recognized in this paper as a critical quality attribute due to the intended purpose of the device and the risks to the end user that inaccuracies could pose. Typically, most dose counter technology is evaluated for count accuracy in either a handling study or a clinical trial.

In theory as the FT_A increases above the FT_F in a force-drive dose counter, the potential for under-counting may increase due to the effect that higher forces have on the timing of events. Theoretically the inverse is also true whereby over-counting may increase with FT_A values below the FT_F for the same System. The theory is predicated on the assumption that the user releases the inhaler canister immediately following the release of the aerosol, or a count in the latter case, and that the canister is not fully depressed. If the TMAI System is fully depressed, the TMAI and the valve will bottom out causing the force within the System to rise eliminating any small difference between the FT_A and FT_F . Thus it is important to assess count accuracy in a way that includes user-induced variation so that the design space can be properly developed.

Count Accuracy Requirements for Rescue Medications

Most dose counter developers will inherently strive to achieve a device design that counts accurately regardless of the type of formulation being delivered. However, it is important to recognize that there are different conditions of use and certainly different severities associated with different classes of medication. For instance, the severity of a patient running out of a bronchodilator (rescue medication) can be life threatening, whereby the severity is lower on an anti-inflammatory (controller) medication.

In the rescue class of medication, patients may reach for their inhaler after the onset of asthma symptoms. The symptoms may be severe in nature and may, in some cases, result in increased feelings of anxiety and panic. A patient under this duress may actuate their pMDI differently than a patient who is calmly taking a controller medication as directed by the instruction leaflet (PIL). Although most PILs instruct the user to fire their inhaler once-per-breath, fully depress and hold for a period of time, followed by the release of the pMDI canister between actuations, a dose counter that can maintain accuracy in light of patient variation to instructions would be preferable. It then becomes important to assess what is "intuitive" to the user and what abusive situations exist whereby what seems intuitive to many may go against the instructions in the PIL.

While the PIL is unlikely to advise multiple actuations in rapid succession for rescue medications, in a state of panic or exasperation a patient may undertake this manoeuvre and not fully release the canister between successive actuations. Such a scenario could impact the count accuracy of the system, as most dose counters, including the TMAI from Trudell, require two events to take place in order to register an actuation. In the case of the TMAI, the actuation on the compression stroke and the reset of the counter on the release are required to register one complete cycle of the system. The Force to Reset (FT_{RS}) is described as the force applied to the device the moment the TMAI mechanism resets on the release. Similarly, the dose is delivered from the metering valve of the inhaler on the compression stroke and the refilling of the metering chamber on the release.

A dose counter should register a count (actuation) with the delivery of an aerosol, and register any successive counts by resetting when the metering chamber can refill. In the context of the TMAI, for an under-count to occur in the above scenario, the user must be able to maintain enough force on the system so that between successive, repeated, actuations the user allows the metering chamber to refill but prevents the TMAI from resetting. For this to occur the TMAI must have a FT_{RS} that is lower than the FT_{RF} . If the user were able to do this repeatedly the outcome would be only one actuation recorded by the TMAI for multiple actuations of the inhaler, leading ultimately to under-counting.

The TMAI 200 Series

The first generation TMAI, currently referred to as the 100 Series, and approved by the FDA in the United States, has a plastic return spring mechanism. This design had been proven to be very robust, reliable, consistent, and suitable for use for the delivery of a variety of formulations where a rescue condition is not present. However, a risk analysis of the TMAI-100 design for application on rescue medications, identified the plastic spring mechanism as a design limitation, since the mechanism could not provide a FT_{RS} that would be high enough to ensure that under-counting would be prevented in the rapid/repeated actuation scenario. In response, the second generation TMAI device, the 200 Series, was designed such that the plastic spring mechanism was replaced with a precision stainless steel coil spring. Metal springs are able to tolerate pre-load over time without suffering the slow creep possible with plastic springs. The metal spring affords custom tailoring of the FT_{RS} and the FT_A independently in order to match a wide range of forces associated with different filled pMDI canisters.

The increased severity of under-counting in a rescue medication also led to improvements on FT_A consistency when the device is actuated intuitively by a patient. The TMAI incorporates internal geometry to guide the movement of the parts, and it is necessary to evaluate how this mechanism functions in the case of likely inadvertent mis-use by actuating the pMDI canister off-centre. Under a condition of off-centre force application to the top of the TMAI, the guidance geometry develops a moment that creates surface pressure resulting in an increase in sliding friction. This friction is both cumulative with the FT_A on the compression stroke and subtractive with the FT_{RS} on the release and could result in greater force variation. In response to this consideration, design changes were made in the TMAI-200 to reduce both the moment that creates the contact pressure in the guidance geometry and the coefficient of friction between the sliding features. These changes combine to reduce force variation of the TMAI in patients that apply off-centre forces.

Simulated Patient Handling Study

Trudell recognized that to properly develop the design space around the FT_A and FT_{RS} of the TMAI-200 Series that in-vitro testing must be supported by an estimation of system level count accuracy in the hands of patients. Controlled laboratory testing would not suffice since it is patient behaviour that influences much of the variation in performance by nature of their firing method. Theoretically, laboratory methods could be developed to approximate worst case in-use conditions but due to the nuances of the patient interface it was decided that a

carefully executed handling study would provide more meaningful clinically relevant data to support the in-vitro analysis.

Trudell completed an internal Simulated Patient Handling Study that evaluated the count accuracy of the system. Participants of the handling study were instructed to fire their placebo pMDI without inhalation. Trudell employees, unfamiliar with the operation of the TMAI or objective of the study, participated as Simulated Patients (participants). The protocol instructed the participants to follow a firing regimen that required the rapid/repeated firing method intended to simulate a patient in an exacerbated state.

Before the TMAI-200 series device could be evaluated in the study, a method for estimating count accuracy had to be developed. A goal was set to achieve a high degree of precision for the chosen method of ± 1 actuation. In order to drive out human error, it was determined that participant logs would only be used to support and cross reference the primary method. The primary method was also required to avoid influencing participant-induced variation in grip and firing methods as would be the case with video monitoring or one-on-one evaluation of the participants during a study.

Gravimetric shot weight analysis of the pMDI canister was chosen as a means of determining whether an aerosol was released. It was determined that it had the potential for the required accuracy and yet could be done behind the scenes of the study without influencing the participants. The key challenge in using gravimetric analysis is that it is prone to variation in the shot weight of any given actuation and the accumulation of shot weight variation can lead to measurement errors. Several variables had an impact on shot weight, including manufacturing variation of the pMDIs, through life variation, and participant-induced shot weight variation influenced by differences in firing technique. Participant-induced variation caused the most significant change in shot weight whereby certain participants consistently had average shot weights that were much different than others.

In order to minimize the potential for error in the measurement technique, it was determined that the gravimetric average must be calculated on each inhaler individually and that the measurements must be taken at 6 shot intervals to reduce the error as a result of cumulative shot weight variation. Also, each inhaler would remain with the same participant for the duration of the study to take advantage of the tendency of each participant to maintain a consistent technique and therefore consistent shot weight.

Handling Study Protocol

The goal of the handling study was to correlate the in-vitro work used to define the design space around the FT_A and FT_{RS} and to do so while inhalers were exposed to an in-use handling protocol that would be considered "worst case". Firstly, participants were instructed to fire each inhaler in the study twice in quick succession, three times for a total of 6 shots per session. At the beginning of the study, an instructional session was held to explain to the participants the details of the protocol. The primary reason for this detailed instruction was to improve protocol compliance to reduce instances of deviations (e.g. a participant firing a device 4 times when they were supposed to fire it 6 times). A study coordinator demonstrated the firing sequence. The demonstrator unit was held in a way that complied with a rescue therapy PIL instruction but no specific instruction was made as to exactly how to hold the inhaler. The participant was not corrected if they adopted their own technique that deviated from the PIL. This encouraged an intuitive technique that was recognized to be more variable and thus more indicative of real in-use behaviour.

Three different TMAI-200 configurations were observed in the study, each at a different nominal FT_A and FT_{RS}, but all mounted on the same placebo and inhaler system. This was achieved by developing custom metal coil spring components to generate the intended force profile for each version of the device. The forces were selected to represent the design space of the FT_A and the FT_{RS} of the TMAI-200 and to evaluate their impact on count accuracy as part of the inhaler system.

To coincide with the frequent gravimetric weight checks of the pMDI canisters, the TMAIs were evaluated frequently through the study to determine their exact count. The frequent count verification and gravimetric weight checks also allowed for a running count accuracy evaluation to determine whether any count "cancelling" was taking place as would be the case in a device that experienced both over-counting and under-counting. If evaluation of a device was only performed at the end of the study, count cancelling could result in a device that appeared to be more accurate than it actually was. With the goal of developing the design space around the FT_A and FT_{RS}, a count error must be considered a singular event since the circumstances that lead to its occurrence are also singular. The fact that a cancelling errors might occur does not minimize the significance of each individual error, unless the events are inherently linked. Thus, as the results of the study were tabulated, under-counting and over-counting were tabulated independently.

Trudell's Simulated Patient Handling Study was intended to be clinically relevant, but not a replacement for a clinical study. Key differences are the emphasis of a "worst case" scenario, the 44 "simulated patients" or participants who took part in the study may not have been fully representative of a patient population, the participants did not inhale the medication (placebo), and inhalers remained in the study facility reducing exposure effects outside of a dosing regimen. The design of the study was intentional in order to limit the number of

variables to focus on the design changes and critical quality attributes while increasing count accuracy measurement and tracking. Other deviations were for practical reasons related to running a handling study economically and in a timely fashion.

Observations and Conclusions from the Handling Study

Three TMAI-200 configurations were evaluated in the handling study. It was expected that the theory would translate empirically with a proportional increase in under-counting and over-counting as the design moved from an optimal force setting profile. However, no performance reduction was observed within the nominal 7N range studied revealing a wider design space for force selection.

Overall count accuracy in the handling study performed with 44 participants was over 99% (n=132 devices, 200 actuations per device for a total of 26400 actuations). This confirmed that the design space was also robust when exposed to an abusive testing methodology. All actuations were performed in rapid succession and thus the scenario mentioned earlier that could result in under-counting on any dose counter, was not apparent on the TMAI-200 series. The design space around the FT_{RS} was also robust with an acceptable range of FT_{RS} values relative to pMDI FT_{RF} values without increasing under-counting as a result of the rapid fire scenario.

The protocol lead to high gravimetric precision throughout the study with less than 1% discrepancy of greater than +/- 1 shot was observed. In all cases, where a discrepancy was observed, the measurement error was recorded against the TMAI count accuracy. For instance, if it was indeterminate whether a participant fired the inhaler 1 or 2 times, it was biased in the direction that would result in greater inaccuracy from the TMAI. However, with less than 1% of measurements falling into this category it had a minimal effect on the outcome of the study.

The handling study proved successful in correlating in-use performance of the TMAI-200 in the design space with in-vitro Design Verification methods. It demonstrated that the design space around the FT_A and FT_{RS} of the TMAI is robust and that in-use, exposed to a worst-case firing regimen, the TMAI-200 maintains high count accuracy.

Force to Actuate Testing Utilizing Process Analytical Technology (PAT)

It was determined that it was necessary to add Process Analytical Technology (PAT) to the manufacturing process to monitor the control space of the FT_A real time during manufacturing. Trudell developed a method that would allow detection of the FT_A in process so that any manufacturing variation can be monitored to ensure the critical process parameter is controlled. The methods employed also provide the opportunity for continuous improvement by providing data for analysis of the manufacturing process and upstream processes including plastic injection moulding and precision spring winding. The high volume production assembly cell for the TMAI utilizes a high speed data acquisition system and precision load cells to measure the compression force exerted on each device during actuation. The FTA measurement method is sensitive enough to reliably identify the precise FTA within the cycle time of the high speed automated assembly cell. The TMAI produces a force signature at the precise point of actuation while all components of the TMAI are engaged and in motion. This force signature profile is identified and the force being exerted on the TMAI at that precise moment is determined. It is important to note that the force signature is a device generated profile that is the result of proper operation of the mechanism. It is not simply a compression test to a known displacement that would only capture variation in spring force and would not detect variations in the actuation point of the mechanism.

As Trudell embraces and increasingly applies QbD methodology throughout the development of the Top Mounted Actuation Indicator, the FT_A critical quality attribute will be qualified and controlled to the benefit of the end user.

References

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