A Shaking Control Space Study for a Fluticasone/Salmeterol Metered Dose Inhaler Based on Spray Pattern Analysis

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Background

Determining and defining the proper shaking regime for suspension metered dose inhaler ("MDI") products that allows the formulation to be properly mixed and deliver the correct dose is a difficult challenge for product developers. It is well known that the spray pattern areas will change as a device is fired through life if the device is not shaken properly or the canister/valve temperature is not allowed to recover (i.e. the device is not operating isothermally). The change in spray pattern area is a function of the ratio of the formulation to propellant which changes in an unshaken or non-isothermal device. In this study, we took advantage of Proveris's automated shake and fire actuation technology for MDIs to explore a shaking control space for the product based on a Design of Experiments model. Identification of the proper shaking routine as evidenced by stable spray pattern areas through life would allow the application of the spray pattern test for fast screening of the correct formulation fill level.

Purpose

The purpose of the study was to identify conditions where a stable spray pattern could be produced using pMDIs. We chose a QbD approach to determine the effects of shaking on spray pattern performance of a fluticasone/salmeterol MDI product and used the results to determine if an optimal shaking regime for the product exists within the product's control space. Because there is no known spray pattern size associated with "good shaking", a decrease in the variability of the spray patterns was used as the indication of a good shaking routine.

Methods

Products Tested: Samples from one (1) production batch were used in this study with a minimum of one (1) device per shaking regime. Each sample was primed with ten (10) consecutive actuations a few minutes prior to each study.

Baseline: A baseline method was developed to determine the "no shake" performance of the product in terms of spray pattern area, and isothermal valve temperature (within about 0.25°C). Isothermal conditions were achieved by waiting in between actuations for the valve temperature to recover to its pre-actuation level. Automated actuation parameters previously developed using a QbD-based ergonometric study were used as follows:

- Stroke length = 4.1 mm; AS Velocity = 59 mm/s; AS Acceleration = 5351 mm/s^2; Hold time = 362 msec.

Shaking Control Space: A shaking method was developed from the baseline where the automated shaking parameters of the system were systematically varied using a set of control spaces derived from a standard 2-parameter X 3-level DoE approach [1] and measuring the following performance metrics:

- Spray pattern at 30 mm from the mouthpiece edge using the patented SprayVIEW® instrument [2];
- Canister/valve temperature; and
- Canister/valve temperature recovery time (time for the canister/valve temperature to reach its starting value).

A rotary shaking regime was used with a fixed rotation angle of +/- 45°, shaking frequencies of 0.2, 3.8 and 7.5 Hz; and shaking repetitions of 5, 10, and 15 (normal range) and 20, 40 and 60 (extended range).

Test Methods and Instrumentation: The samples were tested using a Proveris Scientific (Marlborough, MA) SprayVIEW® SFMDI automated spray pattern measurement instrument with an integrated Proveris Vereo® SFMDx automated shake-fire actuation system. The SprayVIEW instrument was programmed to shake each device at the prescribed conditions and then immediately actuate the device while simultaneously collecting spray pattern data/measurements.

Results

The baseline method results indicate that the product's spray pattern performance was consistent (mean = 232.8 mm^2; S.D. = 31.2 mm^2) under no-shaking and isothermal valve temperature conditions. However, the recovery time for the product ranged from nearly 2 minutes at the beginning of life to about 30 seconds at the end of life. The control space results show a strong dependence between the spray pattern performance and shaking regime, while running the tests in an isothermal manner.

High shaking frequencies coupled with high repetitions produced remarkably consistent spray pattern performance for the product indicating that these conditions may indeed form an optimal shaking regime for the product.

Conclusions

- The results show a strong dependency between spray pattern performance and recovery time vs. shaking for this product.
- High shaking frequencies coupled with high repetitions appears to be the optimal shaking regime for the product based on low variability spray pattern performance.
- The DoE approach produced a wide range of useful performance metrics for the product in terms of its spray pattern area sensitivity to shaking under isothermal valve conditions.
- Further experiments that couple these shaking regimes, identified by spray pattern analysis, with dose uniformity analysis will add further validity to the findings.

References

[1] The Design of Experiments module included with JMP software from SAS Institute.

[2] FDA-CDER (2003) "Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action".

Baseline Performance: No Shaking with Isothermal Valve Temperature

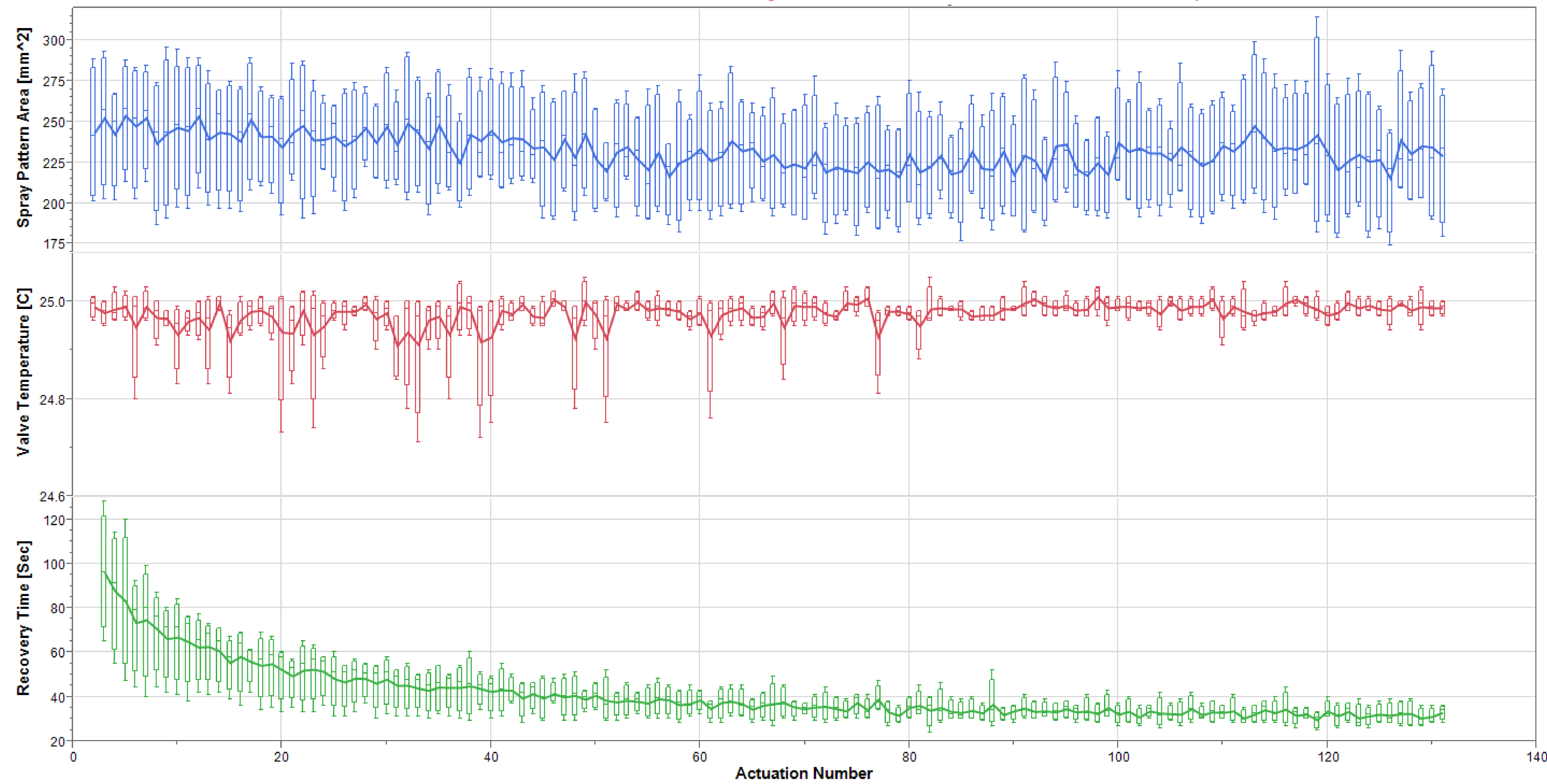

Figure 1. Boxplots of through-life baseline performance measured from four (4) product samples under isothermal valve conditions. Notice the dramatic drop in Recovery Time starting at about 2 minutes initially to about 30 seconds at the end of life. Through-life spray pattern area performance had a mean of 232.8 mm^2 with a S.D. of 31.2 mm^2.

Spray Pattern Area Performance Sensitivity to Shaking with Isothermal Valve

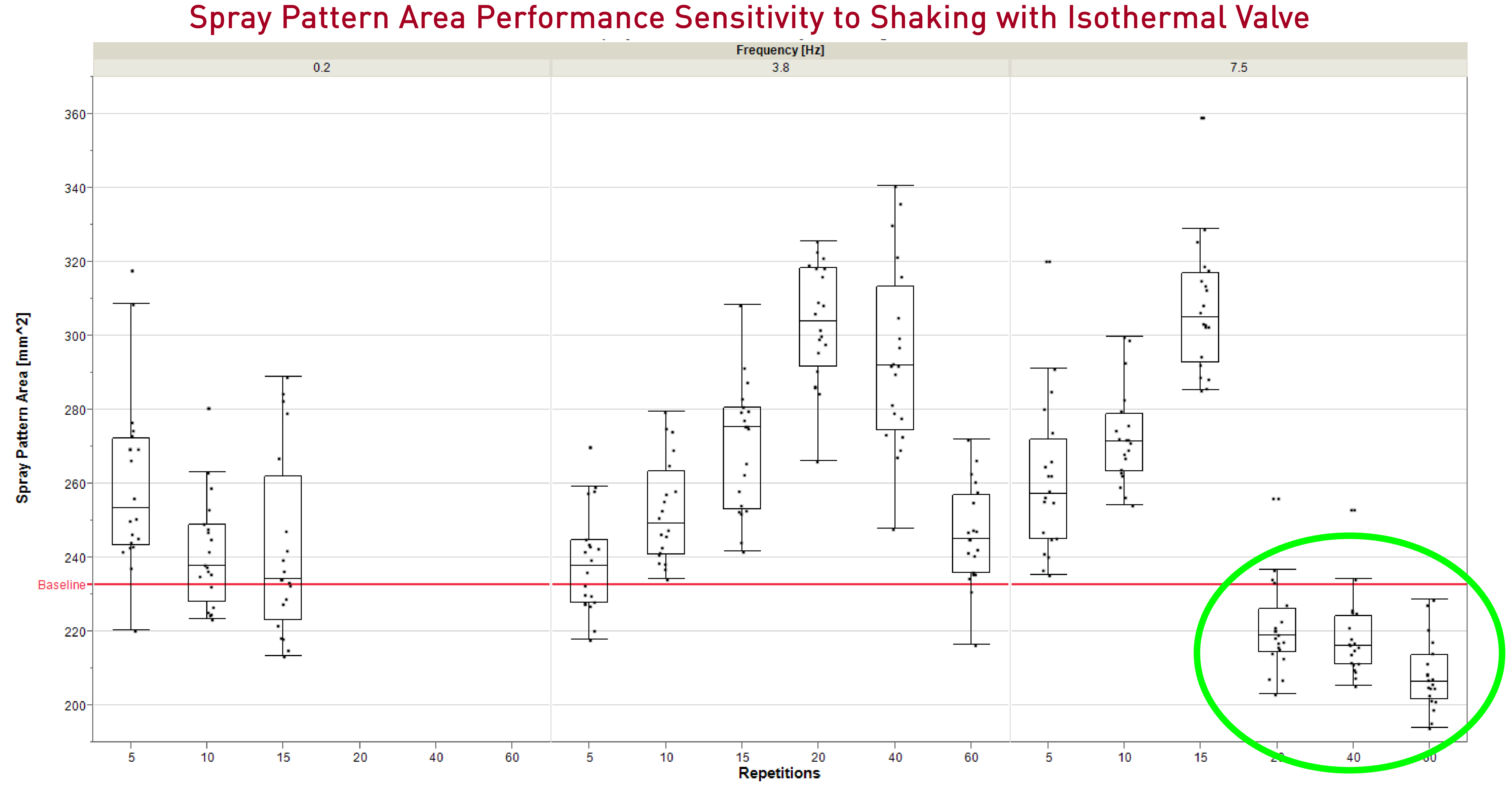

Figure 2. Boxplots showing mid- to high-shaking Frequency and Repetitions having a dramatic impact on the spray pattern area performance for the product relative to Baseline under isothermal valve conditions. Low frequency shaking appears to have little effect on performance, while the mid- to high-frequencies produce parabolic results as a function of Repetitions. Maximum spray pattern areas are achieved at frequency = 3.8 Hz/Repetitions = 20 and also at frequency = 7.5 Hz/Repetitions = 15. High frequencies coupled high repetitions (shown in the green oval) produce remarkably consistent spray pattern results and may indicate that this is an optimal shaking regime for the product.