Reducing variability in test results for OINDPS with automated actuation

Proveris Scientific discusses the importance of automated actuation for testing inhalation and spray devices to avoid variability introduced by manual methods, and how Proveris' portfolio of instruments and services can ensure the accuracy and reproducibility of results.

Automated versus manual actuation

Inhalation or spray drug-device combination products are notoriously complex and difficult to develop and manufacture. Proper performance of these devices is sensitive to a large number of variables, which must be properly controlled. A lack of sufficient control can adversely affect data quality and reproducibility, which can in turn cause developmental delays or production quality issues. The formulation is often the primary focus of analysis and less attention is devoted to understanding the device usage. However, appropriate actuation and testing parameters are essential for combination products, and any variability will influence the accuracy and reproducibility of the data.

Human actuation of devices is prone to introduce variability, as using hand actuation for testing is neither consistent over time nor between different analysts. The ideal way to conduct testing is automated, mechanical actuation using a defined testing profile (stroke length, velocity, hold time, etc.) derived from human-usage data. This approach reduces variability and improves the correlation between *in vitro* tests and *in vivo* performance. It also makes it possible to avoid the inherent human error that arises due to operator fatigue and other influences when testing a high volume of samples. The result is a significant reduction in the number of deviations/investigations attributed to analyst error, thereby increasing the efficiency of the lab.

The range of variation in hand actuation can be seen in Figure 1. The data is derived from an Ergo™, a Proveris Scientific device which measures and records human-usage parameters. The figure shows the high variability in stroke length, actuation velocity, and hold time as recorded from a human actuation (right) compared with the option of controlling parameters consistently with automated actuation (left) for a pressurized metered dose inhaler (pMDI) device. Manual actuation could therefore lead to variability in test results for delivered shot weight, dose

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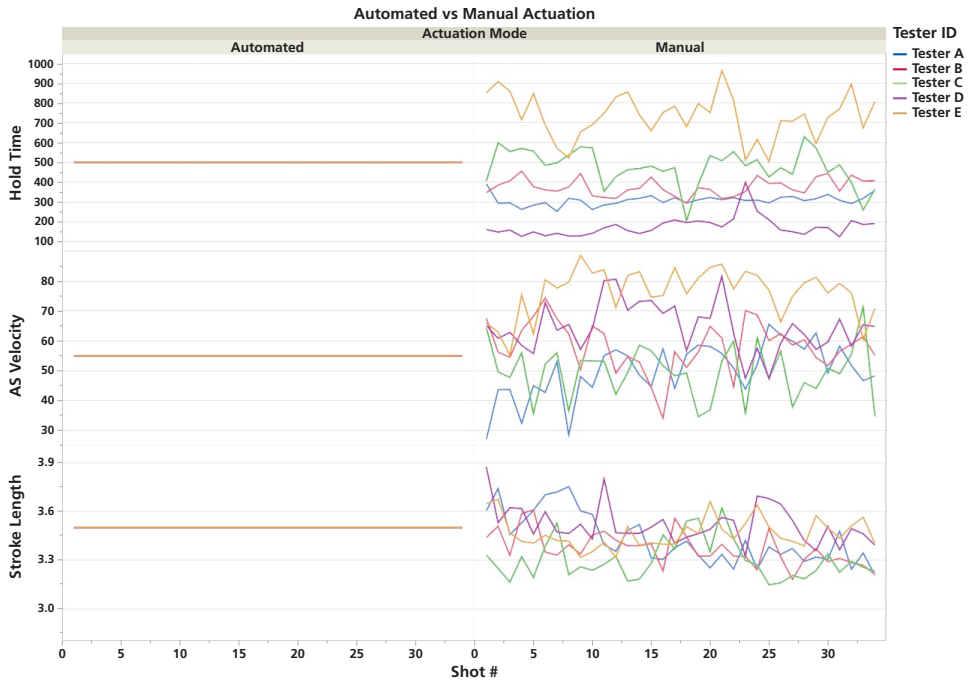

Figure 1. Consistent control over actuation parameters with automated actuation (left) and variation observed with human actuation for pMDI devices (right).

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particle size distribution (APSD). Therefore, it is critical to employ the precise control provided by electromechanical actuation, which enables use of exactly the same parameters across all of the different tests that need to be performed.

Controlling testing parameters with automated actuators can help maintain batch-to-batch reproducibility along with ease of regulatory submission. This is valuable when it comes to stability time points for quality control (QC) analysis, where it is important to keep the testing conditions identical over time, thereby minimizing the out of trend (OOT) results.

Moreover, the amount of dose delivered from the device can vary greatly depending on parameters such as shaking duration and the time between shaking and actuating the device.[1] Figure 2 shows the importance of shaking a pMDI product. Without adequate shaking, a high amount of drug will be delivered in the initial shots, followed by little to no drug at the end of device life.

Proveris Scientific's Vereo® automated actuators are designed to replicate human actuation of devices, whilst also providing precise control of the actuation parameters. Vereo® actuators fit seamlessly into different testing workflows (Figure 3). Furthermore, user-defined shaking parameters and a controlled delay between shaking and firing ensure consistent actuation of devices, especially for pMDI devices.

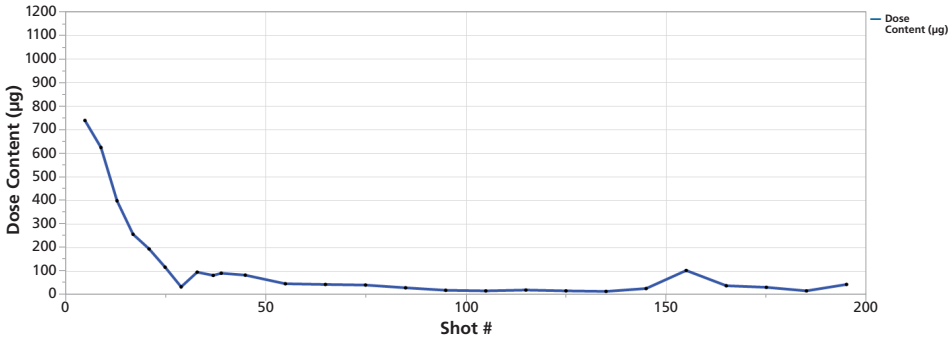

Figure 2. Variable dose delivery from a pMDI device due to lack of shaking.

Figure 3. Proveris Vereo® SFMDx actuator for pMDI products (left); SFMDx with DCU setup (top right) and Anderson Cascade Impactor (bottom right).

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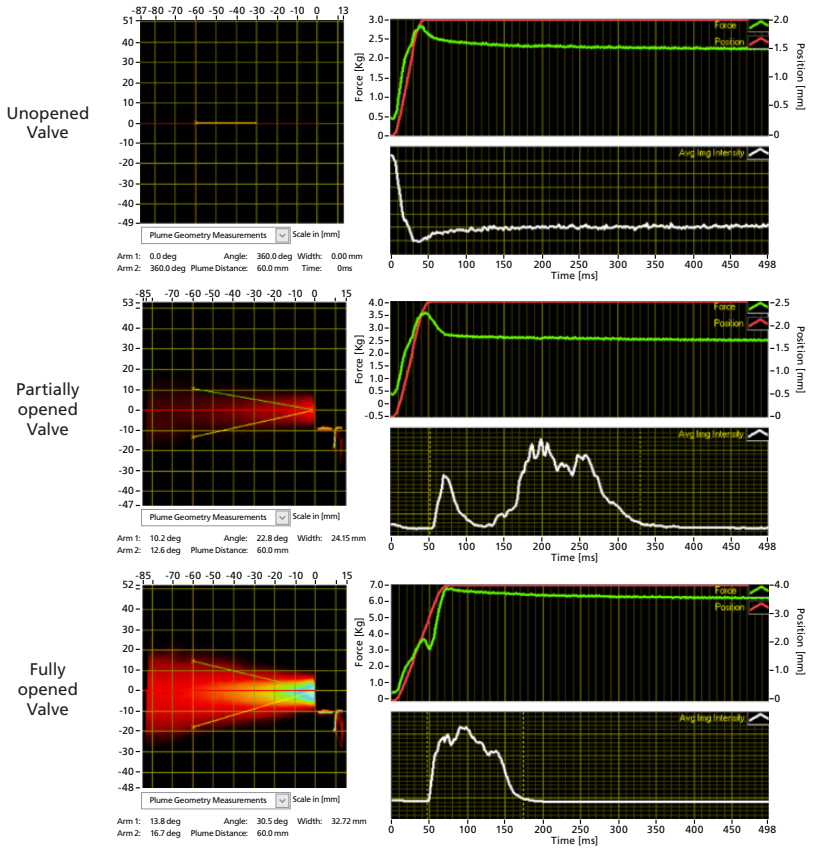

Figure 4. Comparison across plume geometry measurements between an unopened valve, partially opened and a fully opened valve.

All Vereo® actuators run on the Viota® software platform, which has technical controls to enable compliance with 21CFR Part 11 to allow the data created to be used in development submission documents and manufacturing-grade quality records. These controls include the use of electronic signatures, full audit trails, record protection, password controls, and multi-level permissions. Viota® uses a centralized database and tracks every actuation performed on the Vereo® actuator.

Importance of optimum actuation profile

For every device type, having an optimum set of actuation parameters is important for consistent actuation through testing. For example, to ensure complete dose delivery of a pMDI device, a fully opened valve is necessary. Figure 4 further highlights the importance of appropriate actuation parameters (actuation velocity, stroke length, hold time). The ideal approach would be to determine these parameters from a human actuation study to ensure the values are humanly achievable.

As seen in Figure 4, a subpar actuation profile leads to an incomplete opening of the valve, or complete failure to open the valve at all, as visualized by a plume geometry measurement. This may cause non-uniform dose delivery per spray. In contrast, an optimum actuation profile ensures a fully open valve and thus consistent actuation every time.

Vereo® automated actuators provide user-defined control over parameters such as actuation velocity, stroke length, and hold time, as well as return stroke velocity, which could influence the filling of the metering chamber for the next dose.

Critical quality attributes for pMDI devices, such as dose delivery and APSD, need to be tested throughout the life of a device (beginning, middle, end-of-life stages). To achieve this, the doses between life stages (e.g., beginning and middle) need to be fired down. Firing down represents about 90% of the actuations for each device and introduces the highest source of error in through-life testing if not performed in a consistent and reliable manner. Lack of controlled actuation during fire-down may lead to low end-of-life dose delivery. Using consistent actuation parameters throughout each test, as well as when firing down, ensures uniform testing conditions, resulting in accurate data.

Figure 5. Proveris' Kinaero™ High-throughput Fire-down System for pMDI devices ensures consistent fire down through device life.

Proveris' Kinaero™ (Figure 5) is a high-throughput, bench-top fire-down system that provides precise shaking and actuation control with a self-contained evacuation system. Vereo® automated actuators, coupled with the Kinaero™ system, seamlessly integrate consistent actuation parameters into the entire pMDI testing workflow.

Force profiles as key output from Vereo® actuators

Vereo® actuators come with time-sequenced force and position feedback that can be used to gain insight into the product, as well as being applied as a tool to monitor device performance in QC. All Vereo® actuators provide a force/position vs time graph for every actuation performed. The position profile is pre-defined and kept consistent throughout actuation (as determined by the user-defined stroke length). The force profile represents the device's resistive force during the actuation. Moreover, this signature force profile for each device type can be used to determine the product actuation force in Viota®. The differences in product actuation force across multiple products also help characterize the ease-of-use for specific patient populations (e.g., children and older patients).

Force Displacement Graph

Figure 6 shows the force displacement graph obtained from Viota® for two pMDIs. The change in force of the middle linear region of the graph indicates the compression of the spring in the device valve.[2] As seen from the figure, a higher force is required to open the valve and ensure complete delivery for Product B compared with Product A. Insight into the amount of force necessary to drive the valve a specific distance can be very useful during early product development, for characterization and to select the best valve during device screening. Moreover, evaluation of consistent force feedback from the device across different lots can be used to inspect incoming device components, as well as for further inspections at different points throughout the lifecycle of the product (e.g., during stability testing). The same metric can also be used to perform root-cause analysis in case of out of specification (OOS) results across the entire range of tests that use automated actuation (e.g., DCU, APSD, spray pattern, plume geometry, etc.).

Force Graph to Evaluate Metering Valve

Shot weight and dose content are critical performance indicators of the metering valve. However, errors could be introduced to such measurements through manual actuation. Alternatively, time-sequenced force/position feedback through automated actuation provides insight into how the valve interacts with the user during actuation.

As exemplified in Figure 7, three candidate valves for a generic product perform differently with the same actuation profile (stroke length, velocity, acceleration, and hold time). Each valve has a different actuation force, end-of-stroke force, and force profile. In this case, Valve #1 has the closest performance to the reference listed drug (RLD) product. Besides metering valve selection, the time-sequenced force feedback can be applied to ensure consistent valve performance across both the product's lifecycle and different lots and batches (release testing). Additionally, it can be used to identify whether the root cause for an OOS measurement is valve failure.

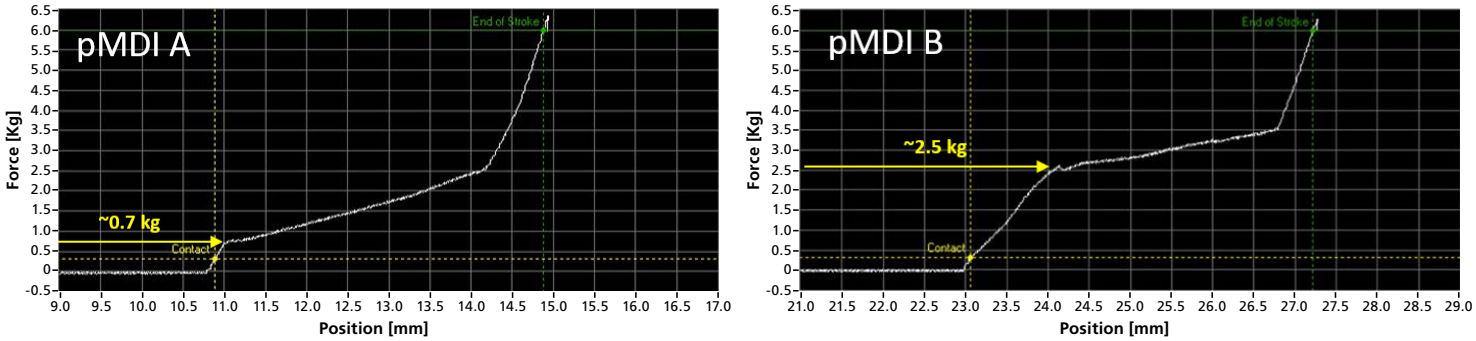

Figure 6. Force displacement graphs from two different pMDI products obtained from Viota® software.

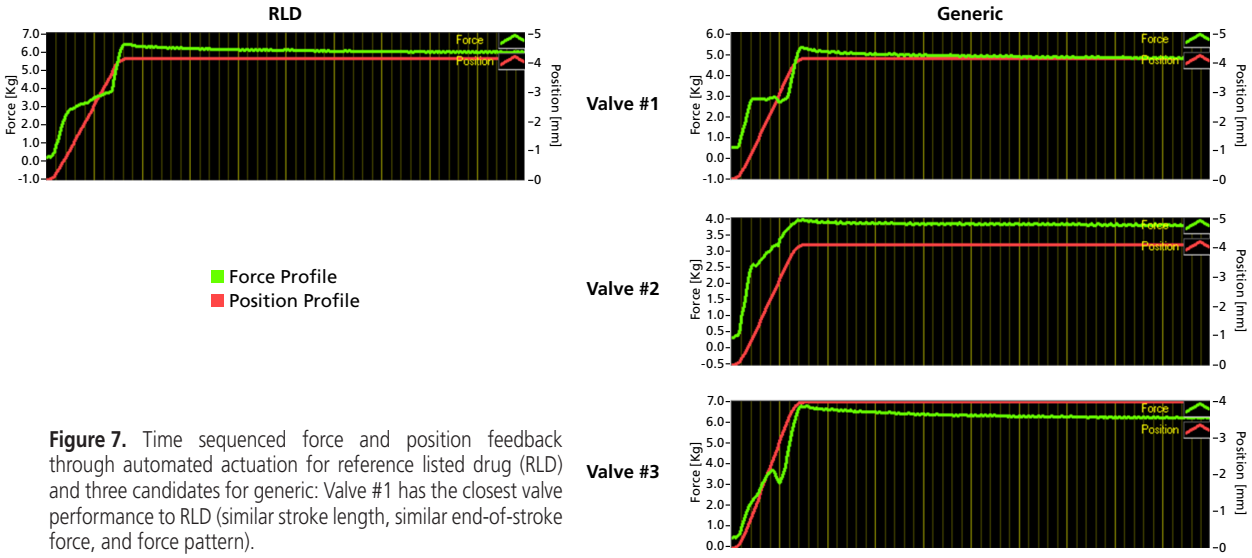

Figure 7. Time sequenced force and position feedback through automated actuation for reference listed drug (RLD) and three candidates for generic: Valve #1 has the closest valve performance to RLD (similar stroke length, similar end-of-stroke force, and force pattern).

Different devices need different modes of actuation

The critical quality attributes (i.e., performance metrics) of different device types are influenced by specific actuation parameters. Therefore, specific modes of actuation are needed for particular device types. For example, the shot weight of multi-dose nasal sprays is determined by the stroke length of the device. A lower-than-optimum stroke length will under-deliver the dose per spray and a higher stroke length might damage the pump components of the device. Therefore, using a consistent stroke length throughout the testing would be advisable. In contrast, unit dose devices have variable stroke length across multiple devices, even from the same lot (as seen in Figure 8). In this case, using a position-based actuation mode would not provide consistent dose delivery. For these devices, a force-limited actuation, whereby the device is actuated until the motor detects an end-of-stroke force, would be ideal, making sure the entire contents of the device are discharged.

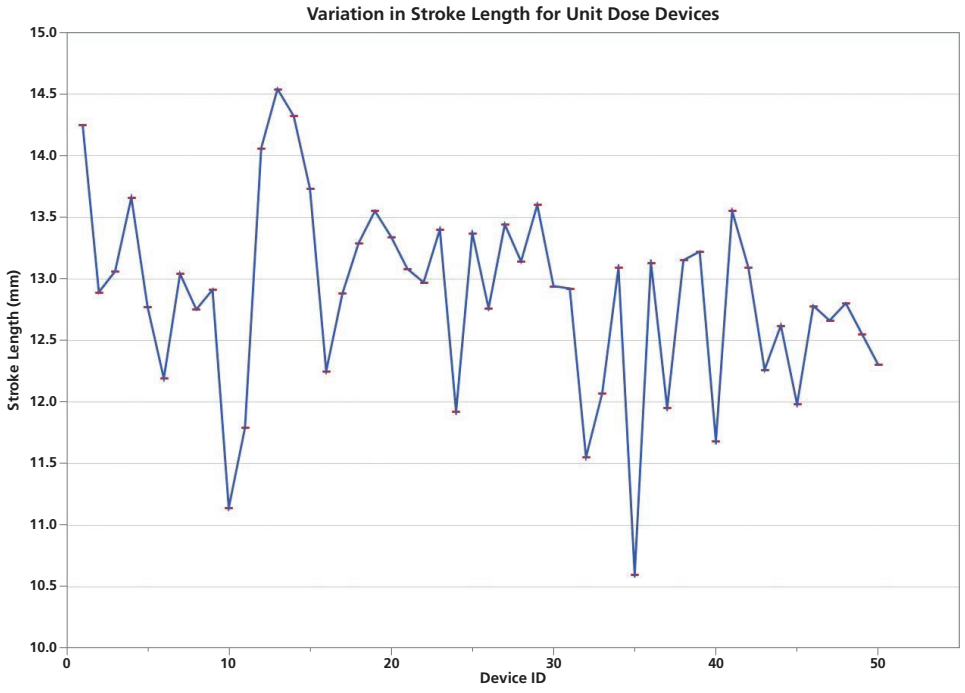

Figure 8. Stroke length differences in unit dose devices from the same lot.

Figure 9. Range of devices supported by Proveris' Vereo® actuators.

Figure 10. Different configurations of Vereo® actuators: (from left to right) NSx for nasal/oral sprays; SFMDx for pMDIs; DSx for dual-sided sprays and SSx for side-actuated nasal sprays.

Use with Novel Device Types

With the variety of new device types on the market in recent times, it is more important now to use consistent actuation parameters and to monitor performance throughout testing. Proveris' Vereo® actuators can be used with a multitude of device types (Figures 9 – 11, Table 1) and ensure accurate testing and traceability with Viota® software controls in place.

Applications of Vereo® actuators include:

- Pump/valve delivery (shot weight)
- Dose/spray content uniformity
- Through-life device testing
- Aerodynamic particle size distribution
- Droplet size distribution
- Spray pattern/plume geometry testing
- Priming/repriming studies

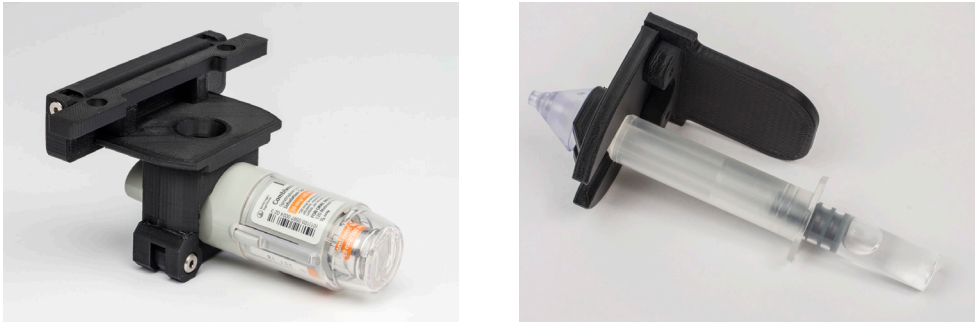

Figure 11. Device-specific holders for secure placement in Proveris' Vereo® actuators.

Actuator Configuration	Device Types
NSx	Vertically actuated unit dose, bi- and multi-dose nasal sprays
	Oral sprays
	Soft mist
	Syringe type nasal spray devices
SFMDx	pMDI products
DSx	Dual side-actuated nasal sprays
SSx	Side-actuated nasal sprays

Table 1. Device types suitable for each Vereo® actuator configuration.

Figure 12. Dose collection accessories for use with NSx actuator to support shot weight (left) and SCU (right) workflows.

Streamlining shot weight and SCU workflows

Even with automated actuation, some tasks, such as waste collection or sample collection for spray content uniformity (SCU), can be tedious and labor intensive. Proveris' dose collection holders streamline the process of sample or waste collection (Figure 12). The sample collection accessory eliminates the need for the error-prone method of manually inverting the flask for collection of doses for SCU.The hands-free method facilitated by the collection accessory makes it easier to accurately collect the entire dose without any loss or drip-down.

Conclusion

Testing with hand actuation introduces variability into crucial *in vitro* bioequivalence testing and QC results. Using a realistic, patient-relevant and optimized actuation profile is essential to accurate testing. Precise control of device performance via mechanical actuation eliminates manual variability and provides confidence in the quality of data. Proveris Scientific's family of Vereo® actuators and accessories increase testing efficiency by actuating consistently with user-defined actuation parameters, thereby expediting tedious manual tasks that can be prone to variability.

About the company

Proveris Scientific Corporation delivers innovative technologies, services, and deep product knowledge to a worldwide customer base of branded and generic pharmaceutical companies, device manufacturers, CDO/CRO/CMOs, and regulatory agencies working with orally inhaled and nasal drug products (OINDPs). Its team of engineers, scientists, and service professionals has developed a more complete understanding of the critical quality attributes affecting the performance of OINDPs, and effectively controlling them from a testing and patient usability perspective.

References

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2. Lacombe JP, Wilcox D, "Effect of force displacement profile on the spray pattern of pressurized metered dose inhalers using SprayVIEW®". *Respiratory Drug Delivery*, 2010, Vol 2, pp 477 – 480.

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