Complete solution for pMDI products: From development to quality control testing

Proveris Scientific outlines the major challenges encountered in testing pressurized metered dose inhalers, and how Proveris' portfolio of instruments can be an invaluable addition to the testing workflow.

Introduction

Pressurized metered dose inhalers (pMDIs) are currently the largest revenue-generating segment in the asthma and chronic obstructive pulmonary disease (COPD) drug delivery devices market and are expected to maintain this position until 2020.[1] This results in extensive testing needs for pharmaceutical companies developing and manufacturing these products. The large volume of complex tests presents many challenges. With industry-leading instruments, support and lab services, Proveris provides a complete solution for pMDI testing throughout the life of the product.

Key challenges in pMDI testing

Today, the industry faces a number of challenges in testing pMDI products. Robust testing methods ensure the integrity of data over time. Consistent actuation parameters are important for accurate and reproducible actuation of devices. Actuating devices by hand is not consistent over time and can introduce variability from person to person. Figure 1 demonstrates the observed variation in results from manual actuation, showing the stroke length, actuation velocity and hold time as recorded from the manual actuation of a pMDI product by five testers. The variability in results exists from person to person as well as across different shots (x axis).

Automated actuation of devices eliminates the variability observed in manual actuation altogether. Vereo® actuators, controlled by Viota® software, ensure that the actuation parameters (velocity, stroke length, hold time) are controlled in a user-defined manner and are consistent across multiple actuations. Moreover, keeping the actuation parameters consistent throughout, across tests, results in high reproducibility of data. Proveris' software platform offers complete traceability of all actuation events along with force-position-time profiles to aid in root-cause analysis during an out-of-specification (OOS) analysis.

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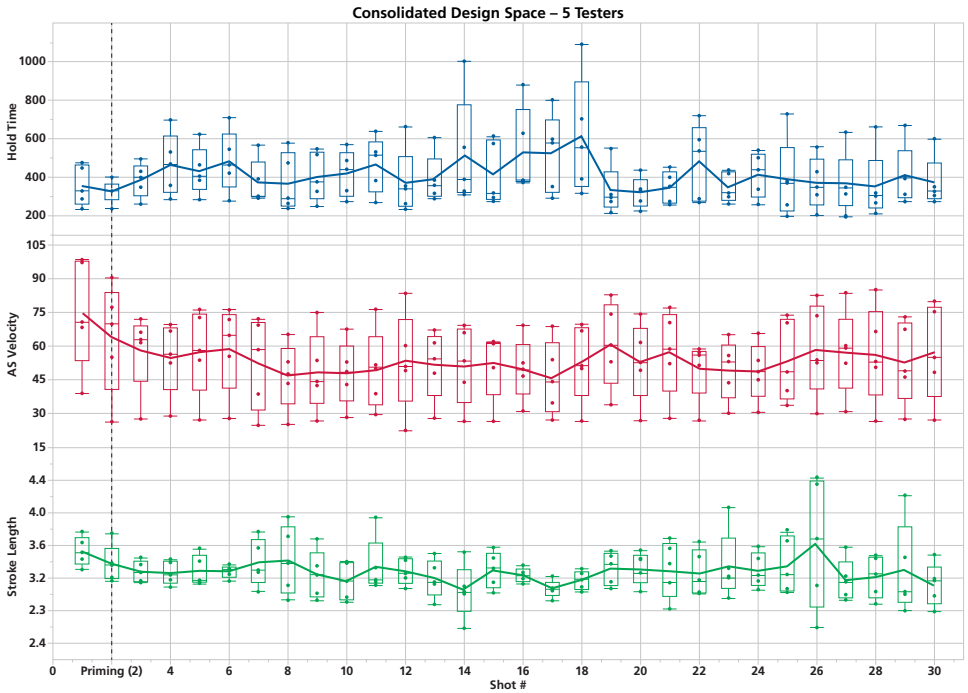

Figure 1. Range of actuation parameters recorded for a pMDI product from manual actuation by five testers.

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Since most pMDI products are suspensions, the shaking profile is crucial for accurate dose delivery. Lack of appropriate shaking delivers a high amount of the drug in the early doses followed by very little to no drug towards the end of product life. As can be seen in Figure 2, in non-shaking conditions (blue line), the amount of dose delivered is multiple times the intended target dose for the first few actuations and then drops over the life of the device. Since the drug formulation and the propellent are not mixed in this scenario, the emitted spray may have a very high concentration of drug formulation and less propellent. In comparison, the doses delivered after five-second shaking profiles were more uniform throughout product life. This lack of shaking could be fatal for some patients, should they get huge amount of drug in the initial shots from the device and mostly just propellant afterwards.

The shake-to-fire delay time (i.e., time between shaking the device and its actuation) of a pMDI device is known to play a role in dose content variability.[2] Furthermore, specific shaking profiles are required for certain products depending on the type and number of excipients present.[3] This underlines the importance of determining and performing the proper shaking profile to ensure the correct dose is delivered every time.

The same effect as described above was observed when spray pattern (SP) area was measured using Proveris' SprayVIEW® Measurement System over the entire life of the device (Figure 3). Initial high SP area followed by a steep drop was observed for the "no shaking" condition. In comparison, a more uniform SP area was seen for the five-second shake duration.

These observations highlight the importance of shaking properly and reproducibly when testing pMDI devices both during development and as a quality control measure. Proveris instruments provide the user with the flexibility of programming the shaking angle, frequency, shaking duration and shake-to-fire delay so that all the devices have a uniform shaking profile for all the required tests. This will also eliminate shaking as a cause for inconsistencies in dose content and spray performance results.

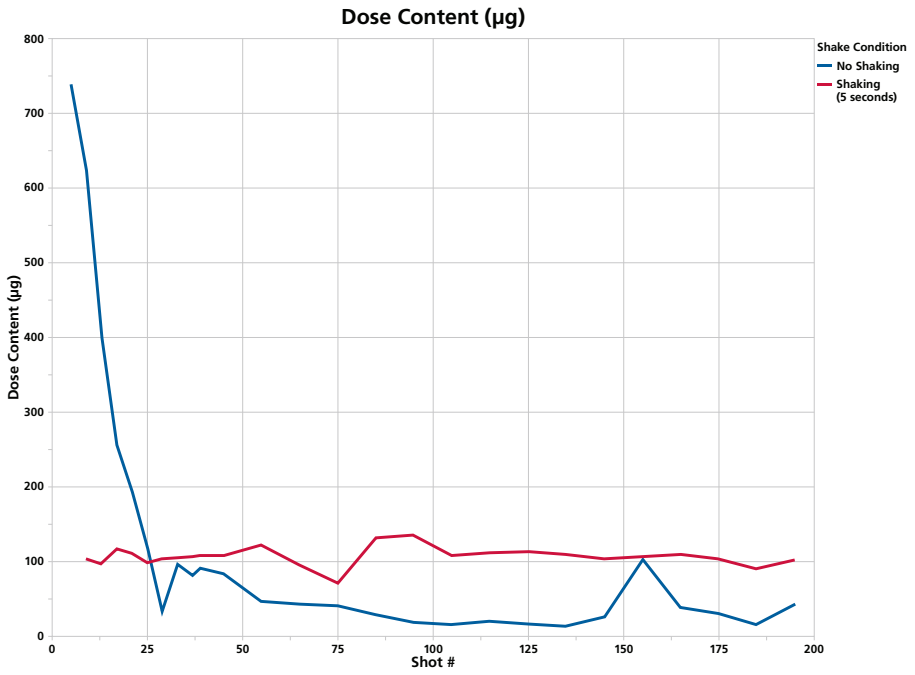

Figure 2. Effect of shaking on the dose content of drug over the life of the product.

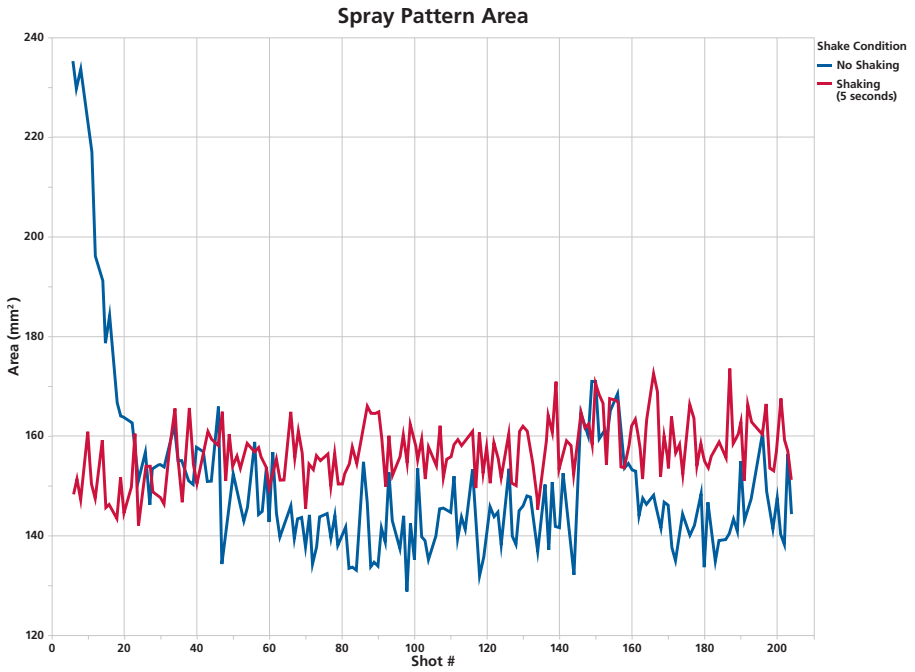

Figure 3. Effect of shaking on spray pattern area over the life of the product.

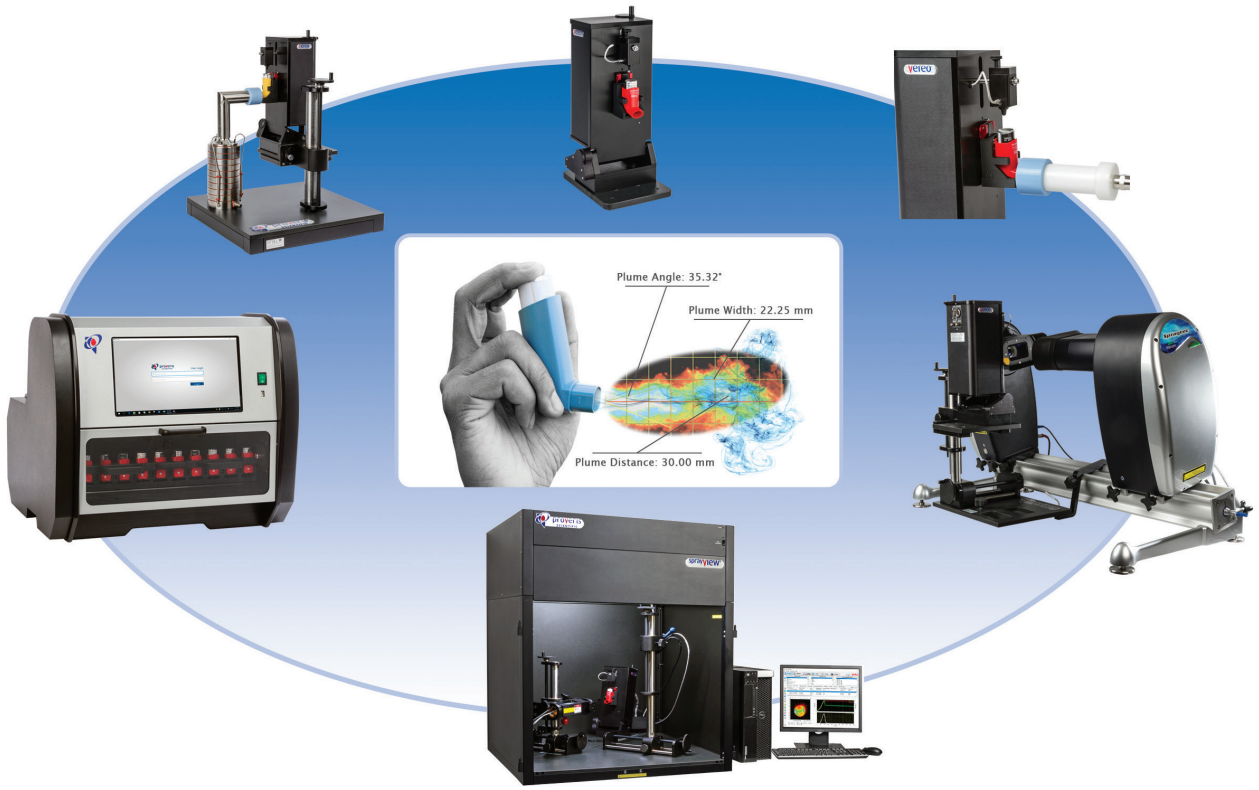

Figure 4. Proveris Scientific precision instruments for testing of pMDI products

Proveris as a pMDI testing solution provider

Proveris aims to provide a complete solution for testing pMDI products with its precision instruments (Figure 4). The Vereo® SFMDx Automated Actuators are flexible and fit seamlessly into multiple testing workflows, such as:

- Shot weight measurement
- Dose content uniformity
- Aerodynamic particle size distribution (cascade impaction)
- Particle size distribution (laser diffraction)
- Spray pattern and plume geometry
- Fire-down of sprays between testing

Spray Pattern and Plume Geometry as a Prescreening Tool for Clinical Trials

Spray pattern measurements from the SprayVIEW® Measurement System are a valuable screening tool during early development. The spray pattern is sensitive to changes in individual parameters, such as orifice length, orifice diameter, and chamber depth—which are crucial design characteristics of the pMDI actuator.[4] Gaining the ability to see the effects of these parameters on spray performance can have a significant impact on successful product development and prevent costly late-stage development failures.

Spray pattern and plume geometry measurements give a substantial amount of valuable information, irrespective of being a regulatory requirement by the US FDA. To illustrate this, take the measured spray pattern for two pMDI devices using the same canister and only a slight difference in the actuator. As displayed by Figure 5, the spray duration for the two are significantly different (60 ms versus 140 ms).

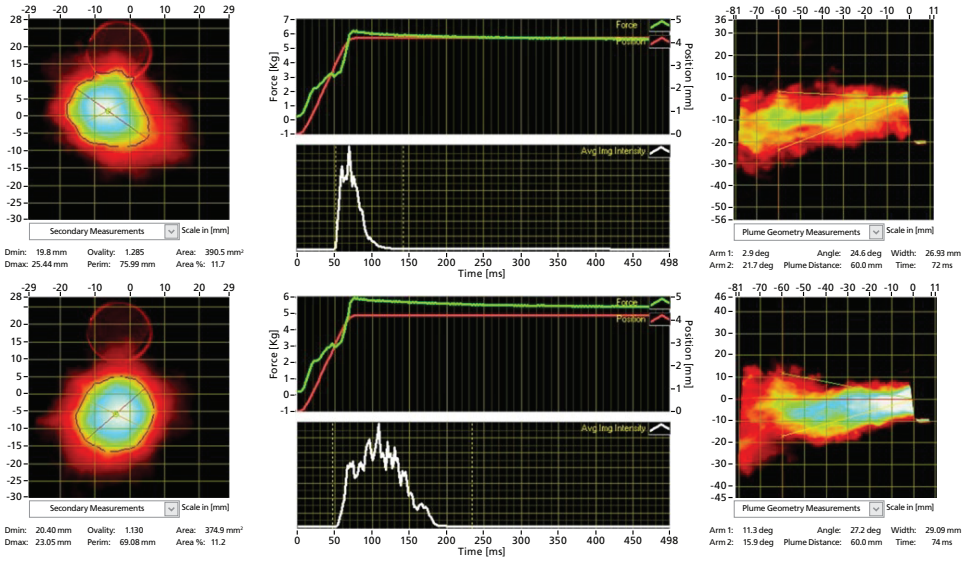

Figure 5. Changes in the spray duration between two identical pMDI devices with slight differences in the actuator.

Figure 6. Kinaero™ High-throughput Fire-down System and Universal Cassettes designed to address a wide variety of devices and canisters.

Further, the plume geometry data and the playback video of the plume from these devices gives a qualitative insight about the direction of the spray. Direction of spray is important to determine during development, as any skew can lead to higher deposition on the sides of the mouthpiece and low availability to the patient during clinical study, ultimately leading to failure *in vivo*. This quantitative and qualitative set of data can be invaluable for decision making prior to running an expensive clinical study. Proveris also offers lab services that include patient usage studies, device characterization, formulation/device screening as well as qualitative/quantitative analysis of product performance. These studies can be especially helpful for companies who do not plan on testing in-house but nevertheless want to evaluate the product performance on a small scale or require consulting during early development.

Kinaero™ High-throughput Fire-down System

The newest addition to Proveris' family of instruments is the Kinaero High-throughput Fire-down System for pMDIs. Firing down pMDI devices can be tedious and time consuming. Proveris' Kinaero™ system addresses this issue, capable of firing down either canisters only or entire devices with actuators using specific easy-to-insert cassettes (Figure 6).

By replicating human use of inhalers, the Kinaero™ system provides reproducible actuation throughout product life. The software platform, with database storage and retrieval is compliant with 21CFR Part 11. Programmable shaking angle, frequency, duration, and inter-actuation delay along with multiple modes of actuation (force, position, or time-based) provides greater flexibility during automated fire down.

The compact benchtop model with a large touchscreen display offers the following key features and benefits:

- Automated fire down for up to 10 pMDI devices
- Multiple modes of actuation based on force, position, and time
- Programmable shaking angle, frequency, and duration
- Self-contained evacuation system that eliminates tedious waste disposal methods
- Updated operation and data management software with database storage and retrieval
- US 21 CFR Part 11 compliance

Since the entire system is self-contained and requires only AC power, no vacuum or pressurized air connections are necessary. The multi-level filtration system containing high efficiency particulate air (HEPA) and activated carbon filters can withstand tens of thousands of shots before replacement is required. Moreover, no additional cleaning steps are required along with easy replacement of filters and system alerts to remind the user that a filter is due for replacement. The software platform also offers multiple operator levels with differences in privileges depending on whether the user is in an R&D or QC setting. Additional features such as the Break/Resume mode allows the user to pause a method, walk away from the instrument, and resume it easily.

The Kinaero™ system fits into the pMDI testing workflow with ease, allowing users more control over their testing parameters. It also reduces the ergonomic burden on the analyst of firing down multiple devices. The time saved increases the operational efficiency of the lab and reduces testing backlog.

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.

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3. Newcomb A, Farina D, "Understanding the Importance and effects of shaking on pMDI performance". Proveris Scientific Poster, DDL Conference (Edinburgh, UK) Dec 2015.
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