Addressing the challenges in nasal device testing: Evaluation of pump performance

Proveris Scientific addresses the challenges faced by the OINDP industry, with a particular emphasis on nasal spray devices. Solutions are offered in the form of the fully automated Indizo® system and Vereo® actuators. These instruments expedite the analysis by effectively streamlining the workflow and eliminating manual processes. They can be used to conduct a variety of the required regulatory tests in a reproducible manner while simulating human use of the product.

Introduction

The orally inhaled and nasal drug product (OINDP) market is growing rapidly and the number of nasal spray products on the market, as well as in development, has been significantly increasing in recent years. More than 150 million units of fluticasone propionate nasal spray alone are sold in the US every year.[1] Production of this magnitude generates a vital need for robust, reproducible release testing of nasal spray products.

The OINDP industry currently faces a plethora of challenges when it comes to product testing. Of the utmost importance is the need to generate accurate data consistently. This is problematic at present because reproducibility is compromised by hand actuation of pumps during testing; the forces and precise methods involved naturally vary from analyst to analyst.

The second major problem is that, due to the increasing number of samples involved, testing can be a labour intensive, time consuming, and error-prone process. Another challenge is posed by the absence of adequate diagnostic tools to evaluate the mechanics of a nasal spray device in case of an aberrant result. A serious issue when it comes to product release in a quality control (QC) setting is an inability to perform a proper investigation and root cause analysis of out of specification (OOS) results. With the aforementioned ramp up in manufacturing, both transitioning to more efficient workflows and maximising throughput whilst minimising analyst time required will be critical aspects of success.

Proveris Scientific's Indizo® System (Figure 1) addresses all of these challenges. The fully automated Indizo can be used to conduct a variety of the required regulatory tests in a reproducible manner while simulating human use of the product. It expedites the analysis by effectively streamlining the workflow and eliminating manual processes.

This white paper focuses on addressing the three main challenges faced by the OINDP industry:

1. Reproducibility of data
2. Lack of investigative tools to evaluate pump performance during OOS
3. Increasing productivity whilst maintaining high quality of data.

Manual versus automated actuations

Testing using hand actuation is neither consistent over time nor between analysts. Stroke length and velocity are known to influence nasal drug delivery, therefore any variation in the actuation profiles—for example, due to manual actuation by different analysts—will influence the accuracy and reproducibility of the data. Automated, mechanical actuation using a testing profile derived from patient-use data is the ideal way to conduct OINDP testing, ensuring there is no variation in the results over time while using a humanly achievable actuation profile. It also makes it possible to avoid human error—an occurance made probable by a high volume of samples, operator fatigue, and other sources (Table 1). This results in 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 actuations can be seen in Figure 2. The data is derived from a Proveris by Design® ergonometric study using Proveris' Ergo®, a device that measures and records human usage parameters. The figure shows the high variability in stroke length and actuation velocity as recorded from a hand study (left) compared to consistent parameters with automated actuation (right) for a multi-dose nasal spray. This could lead to variability in test results for delivered shot weight, spray pattern and droplet size distribution.

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

Diagnostic measures of pump performance

With manual actuation, there is no traceable data for an investigation. Root cause analysis becomes tedious which prolongs resolving a lab investigation, potentially delaying product release. This challenge can be addressed with the multitude of tools made available by automated actuation, such as force and intensity profiles that help analyse changes in the device over the duration of the spray, as well as life of the product. Quantitative real-time force and position feedback, obtained from the Indizo software platform Viota®, provides insight into device performance. This information, along with a fully traceable audit trail, can help resolve investigations/OOS faster in compliance with 21CFR Part 11. The result is significant savings in time and resources. Some of these applications are further discussed below.

Confirmation of Priming

It is extremely important to prime a multi-dose nasal spray pump prior to using the product. Inconsistencies in shot weights and other spray results, like spray pattern and spray content uniformity (SCU), in the beginning of life (BOL) actuations can be avoided by sufficiently priming the device. The force graphs from Indizo can provide information about the priming of the device. Figure 3 shows the force profiles (measured in kgF) of a commercial multi-dose nasal spray device over the course of the six labelled priming actuations (Shots 1 to 6). As seen from the graph, the force value (y-axis) increases consistently from Shots 1 through 6. Initially, air is pumped out of the dip tube, leading to a lack of resistance which, in turn, results in a lower maximum force (≈2.4 kg for Shot 1). Following this a mixture of air and formulation is discharged, increasing the resistance to the pump (5 kg maximum force in Shot 4). Once the device is primed, a consistent force is observed (≈6 kg for Shots 5 and 6). This force profile analysis can be used to compare the required number of priming shots for test and reference products and detect any systematic differences between the two.

Figure 1. The Indizo system (left) available in two separate configurations (right).

Description	Manual	Indizo
Shaking the device before analysis	Lack of consistent shaking for suspension products manually	Consistent shaking for every bottle
Recording tare weight/dose weight (metered or delivered)	Inadvertantly miss to record the tare/dose weight	No issue
Dose Collection	Incorrect number of doses in the dose collector; improper positioning of collector causing loss of entire or part of dose	No issue
	Variation in dose content due to person-to-person differences	No issue
Actuation into waste collector	Ergonomic burden on the operator during larger devices (firing down 200 shots)	No issue

Table 1. Source of error comparison between manual analysis versus Indizo for pump delivery (PD) and spray content uniformity (SCU) testing.

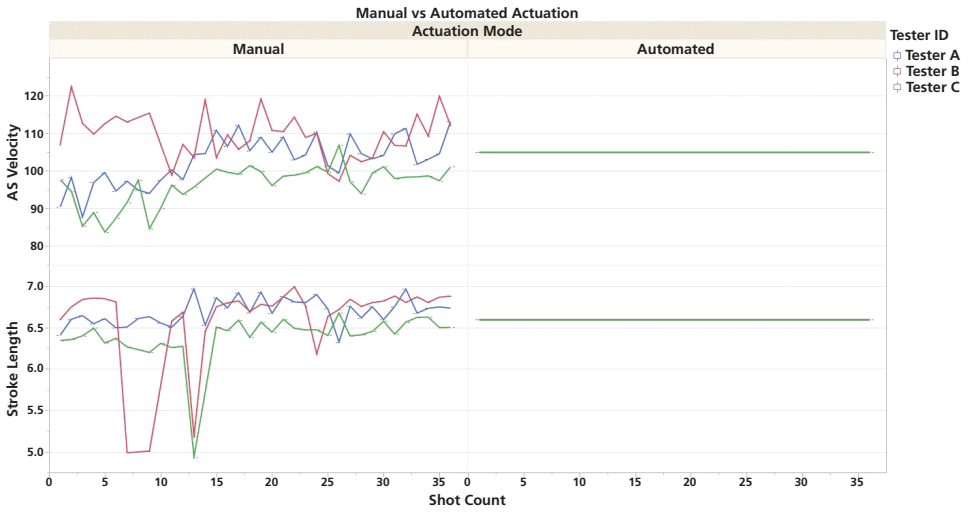

Figure 2. An example graph of data from a hand study (left) that shows the variation in actuation velocity (mm/s) and stroke length (mm) of a commercial nasal spray from three analysts, compared with the reproducibility of automated actuation (right).

Priming/Re-priming in Various Orientations

A priming/re-priming study is required by the US FDA for multi-dose nasal spray drug products.[2,3] The CMC guidance recommends to "Characterise the priming and re-priming required for the product after storage in multiple orientations (upright and inverted or upright and horizontal) and after different periods of non-use". SCU and other pertinent parameters should be evaluated, and the following information should be established:

- The approximate interval that can pass before the drug product should be re-primed to deliver the labelled amount of medication.
- The number of sprays recommended to prime or re-prime the unit. "Multiple orientation studies should be performed with initial sprays and with sprays near the label claim number."

Indizo can be a useful tool during this study. It not only makes it possible to test multiple conditions in a single run, but provides confirmation for priming as well. The lower force to actuate (FTA) can indicate whether or not the device requires re-priming and the force profile can confirm whether priming was achieved.

Loss of Prime (OOS Root Causes)

Root cause analysis is crucial during an out of specification (OOS) event for QC samples. When the device is actuated manually, there are no measurable metrics to distinguish between a normal and an aberrant result. The FTA data as well as the force position profile from Indizo enables the user to investigate the cause of an atypical result by comparing it to a standard force profile example. The FTA is the resistive force exhibited by a device when it begins to emit the spray. A typical force profile can be the starting point for investigation in case of an OOS shot weight or spray result. Depending on which region of the force profile is different from the typical profile, it can be determined what could be a probable reason for the failure (e.g., defect in pump, actuation or delivery). As a proof of concept study, a commercially available multi-dose nasal spray device was used partially and then stored for 30 days (Figure 4). The label on the product states re-priming is required after 48 hours of non-use. In this way, the 30 day storage ensured the device lost prime. Following this, FTA was measured for the first five actuations. The bottom image of Figure 4 shows the first actuation after non-use with a force to actuate

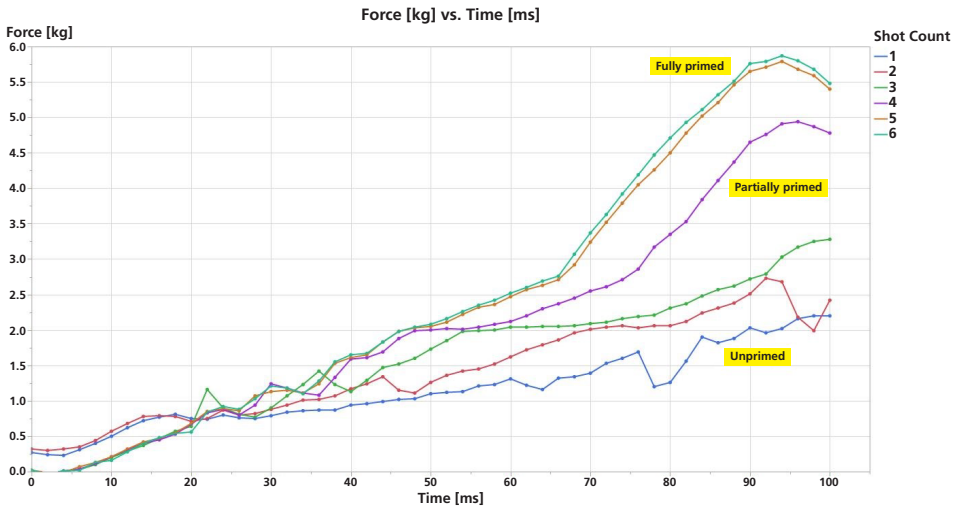

Figure 3. Changes in force profiles over the six priming shots for a commercially available multi-dose nasal spray.

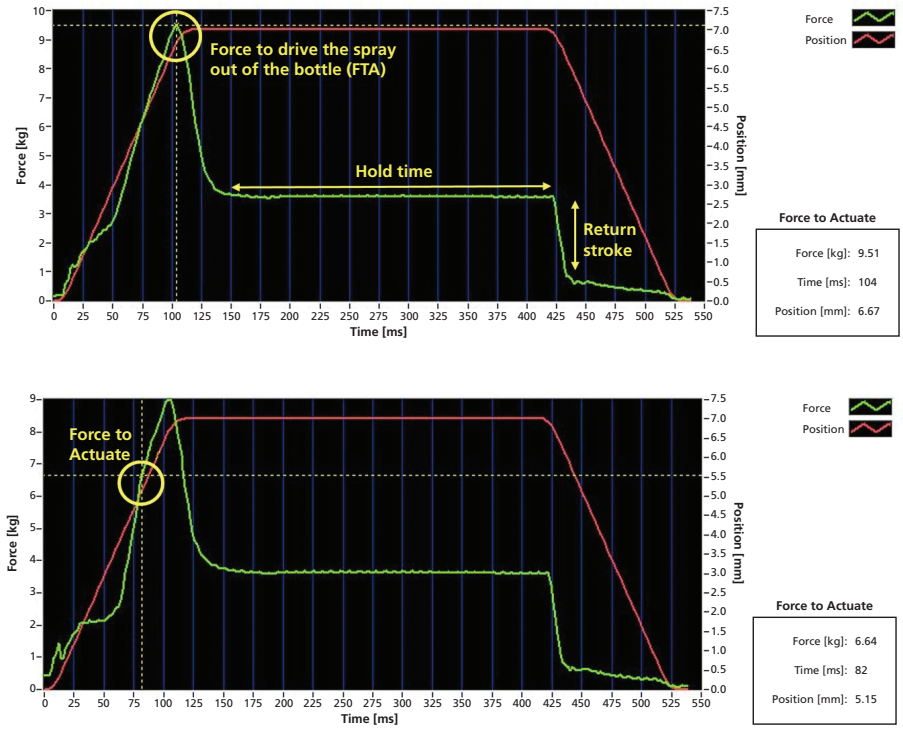

Figure 4. Example of a typical force profile of a commercial multi-dose product with a FTA of 9.51 kg (top), compared with a result with a much lower force to actuate (6.64 kg) indicating loss of prime in the device (bottom).

of 6.64 kg. The top image is the actuation following the re-priming of the device with FTA of 9.51 kg. The lower force in the bottom image is due to loss of prime in the device. This can also be confirmed from the decrease in maximum force and distance travelled for the lower image as seen from the force versus time (green) and position versus time (red) graphs.

Tail-off Determination

The tail-off study is part of drug product characterisation of nasal sprays. "These studies help determine if the target fill and any proposed overfill of the containers are justified, since the tail-off characteristics can vary as a function of pump design, container geometry, and formulation".[2] Pump delivery needs to be performed for each individual spray after the last labelled dose until no more sprays are discharged from the container, a tedious and time consuming process. Indizo can carry out this analysis on multiple devices without operator intervention.

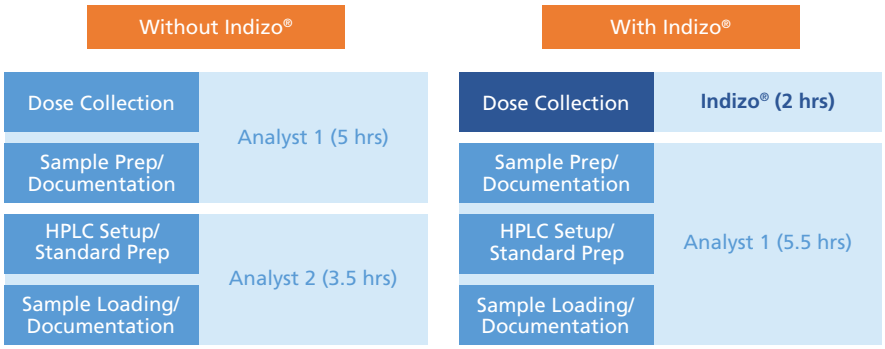

Figure 5. Workflow comparison for SCU analysis with and without Indizo.

Workflow improvement

The importance of continuous improvement in workflow to increase productivity is often overlooked. A typical OINDP testing lab faces a lot of issues, such as batch release schedules, minimising errors, and increasing throughput. These issues can be resolved by small improvements in the workflow. Introducing complete automation can be a major step forward when a large volume of samples need to be tested on a strict timeline. This is extremely useful during stability testing when there is a high number of samples, due to controlled room versus accelerated temperature storage testing and multiple orientations (i.e., upright, inverted), and a tight deadline.

Operator Hands-on Time

In a QC setting, hundreds of batches need to be tested per year owing to the high rate of manufacturing for commercial products.[1] Indizo greatly reduces the amount of operator time required for testing. To perform pump delivery for 1 batch (10 devices), with a method that includes 4 priming, 5 BOL, 86 fire-down and 5 end-of-life (EOL) actuations, the operator time for Indizo was found to be under fifteen minutes, whreas it was over four hours if done manually. Time saved increases with more rated doses in the product. Although the overall testing time might be similar for manual/semi-automated workflows and those supported by Indizo for nasal spray bottles with a lower number of rated doses (i.e., 30 or 60), a significant amount of analyst time can be saved, and ergonomic burden reduced, when testing products with higher number of doses (e.g., 200 or 240). For example, pump delivery (PD) testing for one batch of a nasal spray bottle with 240 doses takes over six hours when performed manually, compared to under fifteen minutes of operator time with Indizo. This also generates an opportunity to continue testing outside of business hours, by running Indizo overnight without any analyst oversight. For SCU, as per the current workflow, it takes almost an entire day for dose collection and sample preparation and up to two analysts to complete the analysis for a single batch. Using Indizo can greatly reduce the dose collection time to only a couple of hours. Indizo improves the workflow and reduces the required labour from two analysts per batch to one analyst (Figure 5). Furthermore, shot weight can be combined with SCU to complete both the tests in the same run with the completely automated Indizo.

Cost Analysis

One of the main concerns when it comes to adopting automated instruments is the initial cost of investment. However, when analysed in detail, automation increases the overall efficiency and productivity of the lab and saves time and labour on individual analyses. Based on Proveris' time comparison analysis between Indizo versus manual/semi-automated analysis, for high-volume manufacturing environments, tens of thousands of dollars can be saved per year whilst generating time savings equivalent to one full-time analyst. The return on investment also lies in the high-quality data gathered, reduced OOS results, and increased ease of regulatory submission.

Conclusion

This article has outlined some of the many challenges in OINDP testing. The Indizo system addresses these issues, providing valuable data for troubleshooting purposes, reliably consistent testing and increased efficiency through automation. The applications described here are not just limited to QC and can be applied to product development as well. By integrating automation as part of the workflow, Indizo increases the productivity and safety of the operators, whilst maximising use of resources. The end results are high quality data, high throughput and a better understanding of the overall performance of device.

About the company

Proveris Scientific 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 in effectively controlling them from a testing and patient usability perspective.

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