PEER REVIEWED

The Role of Ergonomic Studies and Automated Solutions in Nasal Drug Product Development

The development of orally inhaled and nasal drug products (OINDPs) presents significant challenges, with failure rates of 70% and higher.[1] This high failure rate stems from the complex interplay between formulation, device performance, and patient usage, compounded by limited *in vitro – in vivo* correlation. Since *in vivo* testing occurs later in development, integrating real-world conditions early, specifically through human-realistic actuation, can enhance regulatory approval chances and commercial success.

Regulatory agencies like the U.S. Food and Drug Administration (FDA) emphasise the importance of selecting actuation settings that reflect real-world patient use, stating that "selection of appropriate settings would be relevant to proper usage of the product by the trained patient."[2] Variability in actuation behaviour significantly impacts Critical Quality Attribute (CQA) testing, potentially leading to unexpected outcomes and regulatory delays. Conducting human actuation studies and establishing optimised actuation parameters for automated systems minimises variability, strengthens testing methodologies, and mitigates the risk of failure.

Proveris Scientific addresses these challenges through advanced methodologies, such as Proveris Laboratories' Ergo™ device for Human Actuation Studies and Proveris Scientific's Vereo® Automated Actuators for automated actuation. Capturing and implementing human-realistic parameters across required tests enhances reproducibility, reduces variability, and accelerates product approval.

Bridging the Gap Between Patient Use and Testing Standards

Despite FDA recommendations, human actuation studies remain underutilised in OINDP development. These studies provide critical insights into patient-device interactions, capturing key parameters such as stroke length, velocity, acceleration, and hold time, factors that directly influence drug delivery performance. Establishing a patient-relevant operational range not only optimises device and formulation design but also improves CQA testing reliability and regulatory compliance.

Selecting an appropriate study population is equally important. Proveris Laboratories follows industry best practices by recruiting participants based on target demographics, as studies show that actuation behaviour varies significantly between adult and pediatric users, affecting CQA performance.

The importance of human-realistic actuation continues to grow with evolving regulatory expectations, technological advancements, and patient needs. This is particularly critical for rescue medications like Narcan Nasal Spray, where reliable operation is vital for patient survival. Regulatory agencies, including the FDA, now require Actuation Force testing for emergency-use products to ensure real-world usability.

A thorough evaluation of actuation variables helps define proper specifications, balancing reproducible testing with real-world performance. For example, increasing actuation velocity while maintaining stroke length and acceleration can significantly alter the force required for full stroke actuation (see Figure 1).

Regulatory scrutiny over these factors has already influenced product approvals

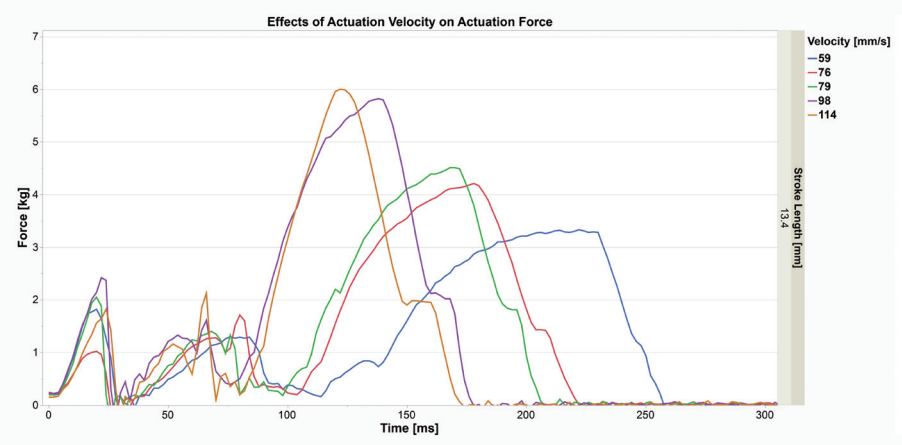

Figure 1. Effects of Actuation Velocity on Actuation force of a nasal spray product

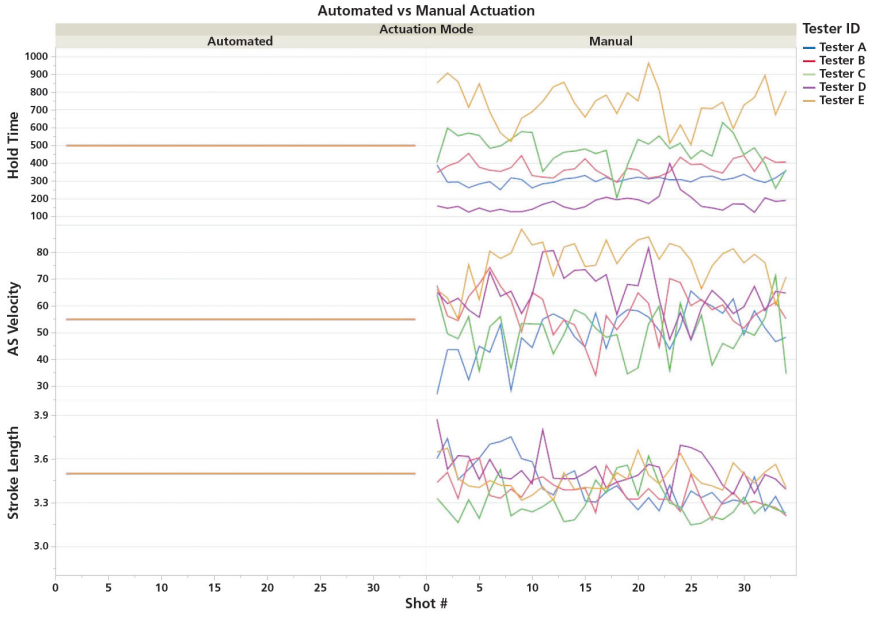

Figure 2. Comparison of Automated Actuation using a Vereo NSx system and manual actuation of various testers

– one sponsor's emergency-use product faced regulatory deficiencies due to missing Actuation Force specifications, but secured approval upon resubmission after defining and verifying these parameters.[3]

The Role of Automated Actuation in Nasal Product Development

Regulatory agencies such as the FDA and the European Medicines Agency (EMA) mandate rigorous testing methodologies to ensure product consistency and performance. To enhance reproducibility and eliminate human variability, agencies recommend automated actuator systems, which "are expected to decrease variability in drug delivery due to operator factors, thereby increasing the sensitivity for detecting potential differences between products." [2] Systems like Proveris Vereo Actuators provide precise and consistent control of device actuation during development testing.

Manual actuation, while not prohibited, introduces variability in critical parameters, leading to inconsistencies in product performance data. Figure 2 demonstrates the differences in variability between human actuation and the Vereo NSx actuator when used with the same device.

Although automation is essential, defining correct actuation parameters is equally critical for accurate product expulsion. Variations in stroke length, velocity, acceleration, and applied force can significantly impact CQAs, such as Aerodynamic Particle Size Distribution (APSD), Droplet Size Distribution (DSD), Spray Pattern, and Plume Geometry.[4,5] Even minor deviations in these parameters can lead to misleading characterisation results, creating misconceptions about product delivery and its effectiveness. Inconsistent drug delivery may affect whether patients receive the proper dose and whether the medication reaches its intended site of action.

For example, comparing Spray Pattern results from a device actuated at two different velocities across increasing formulation viscosities reveals substantial differences. A lower velocity may generate an optimal Spray Pattern for one formulation, while the same device actuated at a higher velocity fails to maintain consistency across all viscosities (Figure 3).

By implementing automated actuation with well-defined parameters, developers can enhance accuracy, reliability, and reproducibility in nasal product testing, ultimately leading to better patient outcomes.

Standardising Actuation Parameters for CQA Testing and Regulatory Success:

1. Establishing a Human-derived Actuation Profile

Human-realistic automated actuation is essential for both novel and generic drug products and is directly referenced in regulatory guidance documents, such as the FDA's Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action.[2]

A comprehensive human actuation study should serve as the foundation for nasal spray product development. Capturing real-world actuation parameters including stroke length, velocity, acceleration, and hold time, from a representative population informs the development of an operational range of actuation parameters. Once an optimal range of actuation parameters is established, an automated actuation method should be consistently applied across CQA testing to enhance reproducibility and *in vivo* correlation.

2. Implementation of Human-derived Automated Actuation in Regulatory Testing

Automated actuation based on human-derived parameters ensures consistency and reproducibility across all required performance tests. Automated actuators, such as Vereo Actuators, should be used with analytical tools like the Proveris SprayVIEW® measurement system, cascade impactors, and Malvern Spraytec instruments to improve accuracy and eliminate variability from manual testing.

Regulatory agencies require various spray characterisation and performance tests, all of which benefit from human derived automated actuation. They include:

- **Spray Pattern and Plume Geometry (Proveris SprayVIEW)** evaluates spray consistency and spatial drug dispersion.
- **Spray Velocity and Spray Duration (Proveris SprayVIEW)** determines drug dispersion over time.

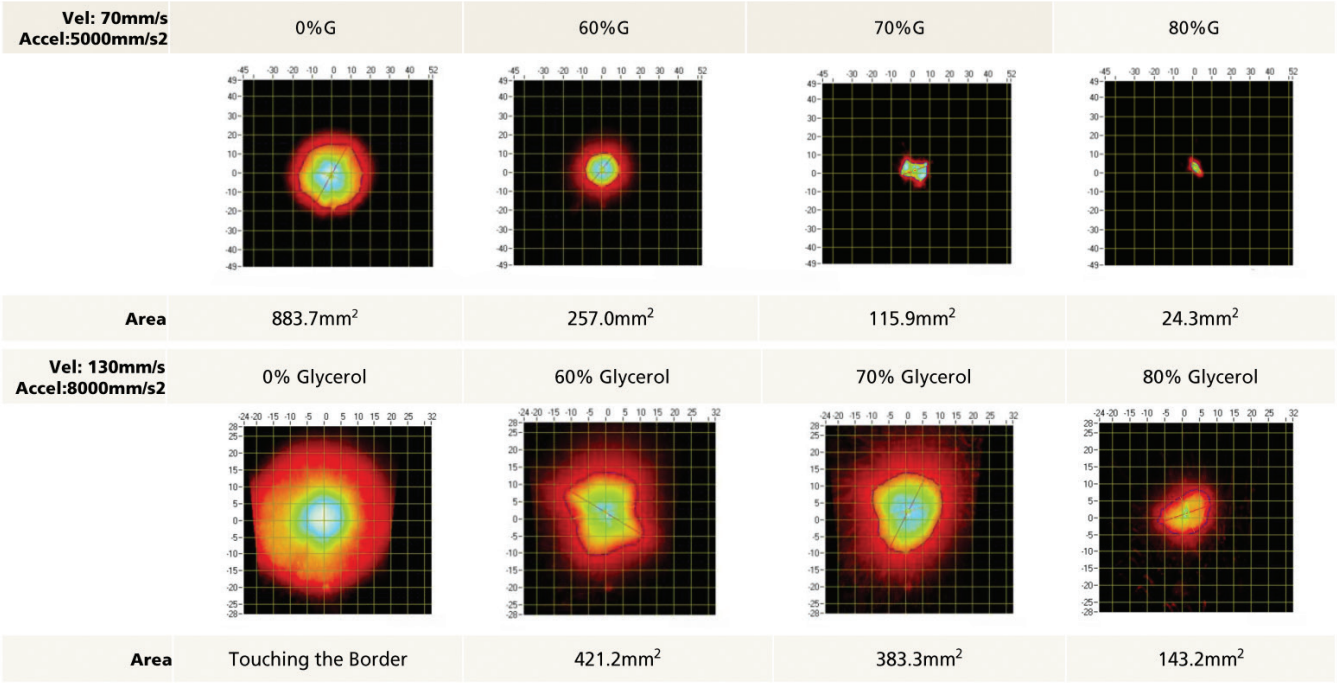

Figure 3. Spray Pattern results comparison from a device actuated at two different velocities across increasing formulation viscosities.

Proveris Vereo SWC (top, left) Vereo NSx (top right), Indizo (bottom)

- **APSD Testing (Cascade Impactors)** measures particle size distribution and deposition behaviour.
- **Droplet Size Distribution (DSD) Analysis (Malvern Spraytec System or similar)** assesses droplet size distribution in relation to formulation properties.
- **Priming and Repriming Studies** evaluate spray consistency after storage or multiple actuations.
- **Single Actuation Content** determines dose uniformity per actuation.
- **Actuation Force Testing** ensures usability compliance.

3. Scale-up for QC Testing

Automated systems such as the benchtop Vereo Spray, Weigh, Collect (SWC) System and Indizo® Nasal Spray Collection System enable rapid and consistent nasal device testing, optimising both research and development (R&D) and quality control (QC) workflows.

- **Vereo SWC:** An automated benchtop nasal workstation for efficient R&D and QC testing.
- **Indizo System:** Designed for high-throughput QC testing, automating through-life testing for up to 20 devices simultaneously.
- **Optimised Laboratory Workflow:** These automated systems enhance efficiency by eliminating the need for fume hoods and free analysts from repetitive and tedious tasks.

Ensuring Consistency and Regulatory Compliance Through Automated Actuation

As the industry moves toward greater standardisation and efficiency in OINDP development, automation has become essential for ensuring consistent and reliable testing. Manual actuation introduces variability that can impact dose content uniformity, aerodynamic particle size distribution, and spray characterisation, potentially affecting product performance and regulatory compliance.

By incorporating human-derived automated actuation, manufacturers can better align *in vitro* testing with real-world patient usage, improving the predictability and reproducibility of test results. Conducting ergonomic studies early allows for patient-relevant actuation parameters to be translated into automated systems, ensuring regulatory adherence and industry best practices from development through submission and batch release. Integrating these solutions throughout the testing process supports the development of safe, effective, and high-quality OINDPs.

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