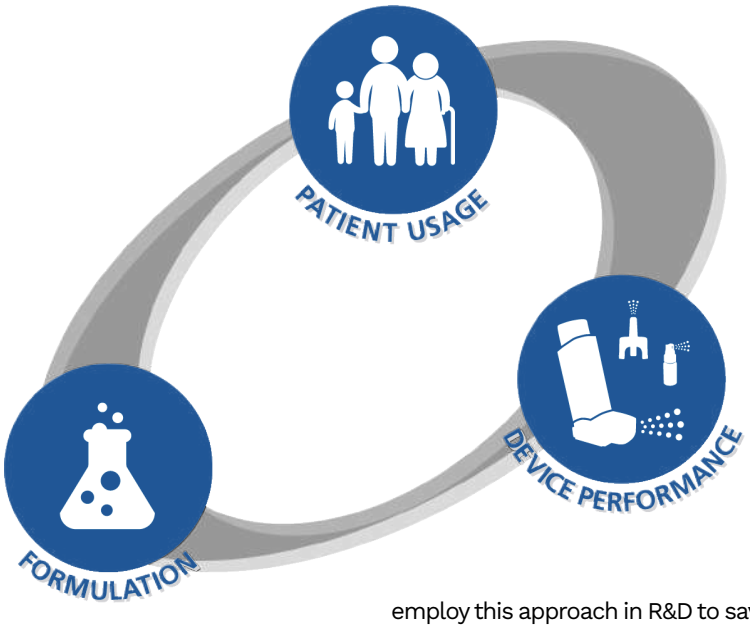
Proveris by Design: A Roadmap for *In Vitro* Characterisation of Combination Products

Combination products are complex by definition and the product development cycles can be both time- and resource-intensive. Recently, Novartis discontinued the generic Advair Diskus programme after investing $442M and years of efforts[1]. There are several other companies struggling with generic drug development for orally inhaled and nasal drug products (OINDPs). The common theme of challenges has been formulation device incompatibility, lack of *in vitro* bioequivalence, analytical methods that fail to replicate patient usage, lack of understanding of critical quality attributes (CQAs), and the expensive *in vivo* failures.



This article offers a stepwise guide to develop nasal spray and pressurised metered dose inhaler (pMDI) products for both innovator and generic drug products, using a quality by design approach. Also, novel characterisation tools are introduced which can be used to demonstrate better correlation to clinical performance.

Pressurised metered dose inhalers (pMDIs) and nasal sprays are available in a range of device shapes, sizes, and actuation mechanisms.

Part 1: Stepwise guide to development of nasal sprays and pMDIs – a Proveris by Design™ approach

The quality by design (QbD) approach was first endorsed by the United States Food and Drug Administration (USFDA) in a report titled, "Pharmaceutical Quality for the 21st Century: A Risk-Based Approach"[2]. The approach was characterised by a focus on science and quality risk management. Today, many companies employ this approach in R&D to save time and money during product development and preparation of regulatory submissions. The results show an overall reduction in approval timeline and minimised queries from regulatory agencies, such as the USFDA. Moreover, the insight gained into product performance can be used long after product approval to investigate and resolve any out-of-specification (OOS) or out-of-trend (OOT) disruptions to manufacturing.

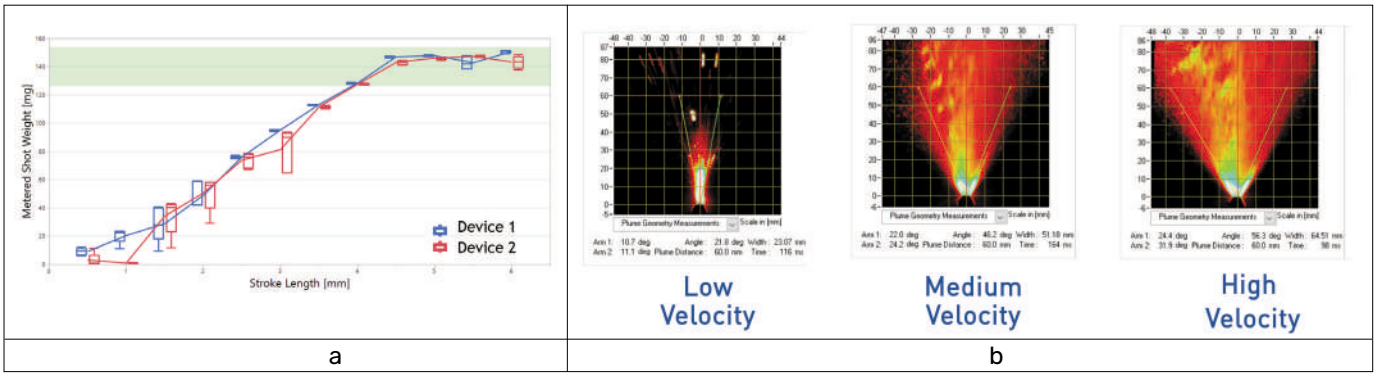


Figure 1 a) Shot weight results for a nasal spray product with different stroke length settings; b) Example PG results for different velocity settings

As for any pharmaceutical product, it is important to perform *in vitro* tests with repeatable, reproducible and robust methods for smoother OINDP development. However, unlike other dosage forms (tablet or capsules), combination products are affected not only by the formulation, but also by the delivery system (device) and patient usage. Variations in analyst technique have long been a source of errors in accurately evaluating product performance. For OINDPs, actuation of the product by hand can contribute to variation in data. Due to this, automated actuation based on human realistic usage has been recommended for OINDP testing for decades. The purpose for this is to eliminate the variability of human usage and translate the complicated biomechanics of patient actuation into a controllable mechanism through multiple key parameters. Proveris Scientific's Vereo® Automated Actuators allow control for up to six actuation parameters for nasal sprays and pMDIs and four additional parameters related to shaking for pMDI devices. To ensure data integrity and accuracy, it is crucial that an identical actuation mechanism is implemented across all the *in vitro* testing, including fire-down during through-life tests.

Several critical quality attributes have been identified to assess the performance of nasal sprays and pMDI products including shot weight, spray pattern (SP), plume geometry (PG), and droplet size distribution (DSD). It has been reported that for most nasal sprays, the stroke length is a major influencing factor for shot weight, and that the velocity/acceleration drives spray performance (including spray pattern, plume geometry, and droplet size distributions[3]. For pMDI products, the use of suspension formulations adds additional complexity to analytical testing and requires adequate shaking and minimum shake-to-fire delay in order to maintain the uniformity of the delivered dose[4]. Other important influencing factors on pMDI performance include product actuation force and hold time to ensure that the metering valve is open long enough to deliver a complete dose.

For example, Figure 1a shows that shot weight increases with the stroke length increase, until a stroke length threshold is reached to deliver the full dose. It is worth noting that the trend of curve (shot weight vs. stroke length) will vary by device types. Figure 1b shows example PG image at different actuation velocities: the PG image shows that at low velocity setting, the spray is not fully atomised; as the velocity increases, the plume gets wider, which usually results in smaller droplet size distributions.

Figure 2a describes the effect of shaking on the dose content for a suspension pMDI sample. With improper shaking, initial doses at beginning of life are up to six times the label claim, which drops to one-tenth of the label claim by the end of life stage. Conversely, proper shaking provides a consistent and complete dose. Proper shaking and shake-to-fire delay ensures uniform dose delivery throughout the life of a pMDI device. Figure 2b shows the plume geometry results with time-synchronised intensity graph to

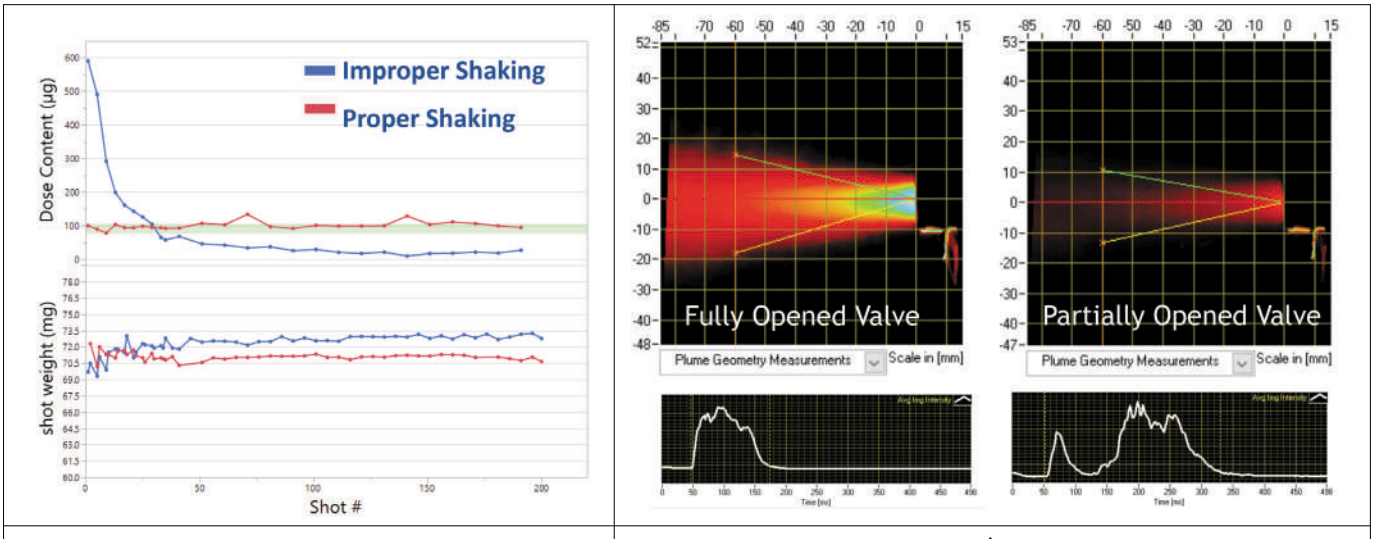


Figure 2 a) Dose content and shot weight for a suspension pMDI product with improper and proper shaking; b) Example PG results for a fully and partially opened valve

demonstrate the differences between fully and partially opened valve: the fully opened valve delivered a continuous and relatively strong intensity PG, compared to discontinuous and weak intensity PG for the partially opened valve.

With that said, the first step to establish *in vitro* methods is to record the range of human usage of OINDP products through a human actuation

	Nasal sprays	pMDI
Formulation	Morphology of API (size and shape) Viscosity Excipients	Morphology of API (size and shape) Formulation form (suspension/solution) Propellant Excipients
Device	Pump Actuator (swirl chamber) Dip tube	Metering valve Actuator (sump geometry) Assembly process
Patient Usage	Stroke length Product actuation force Velocity/ acceleration Return stroke	Shaking and shake to fire delay Hold time Product actuation force Inspiratory profiles

Table 1 Influencing factors for nasal sprays and pMDI performance

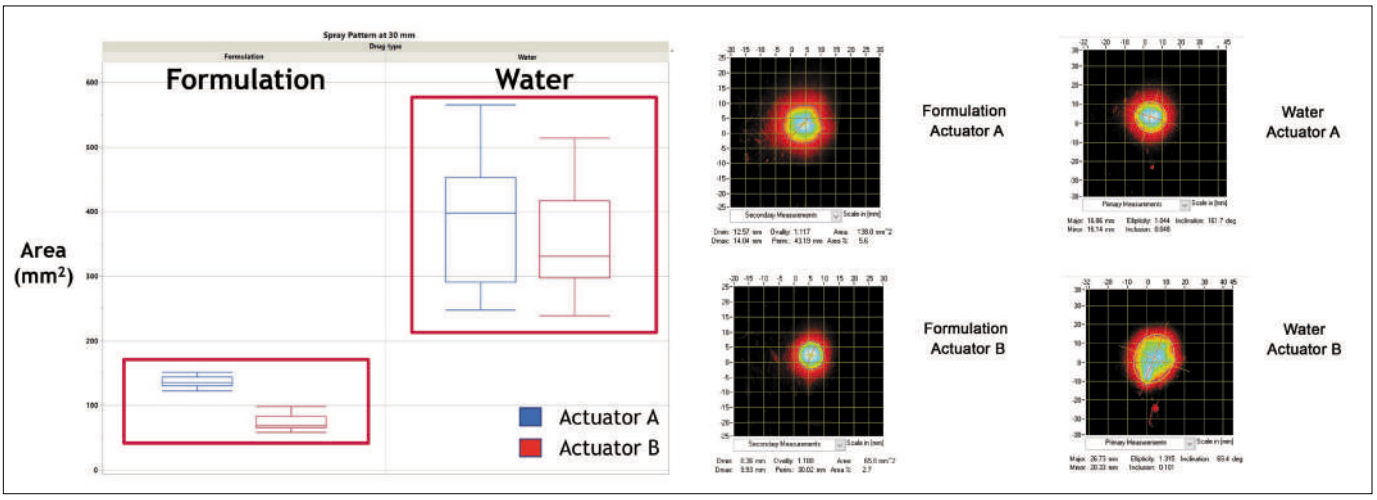


Figure 3 The SP area results for four different formulation/actuator combinations

study. A controlled strategy in product development starts with defining the design space for different factors influencing product performance. This involves considering all the possible formulation and device factors, and to understand how the product performs in the hands of a patient. Example factors are listed in Table 1. Each factor could contribute to a different performance aspect of the product, and certain factors have more of an impact than others. The goal of the first step is to determine the human achievable range for the actuation (and shaking) parameters for all the device/formulation combinations within specific demographic groups. It is likely that the product performs differently within and outside this human achievable range.

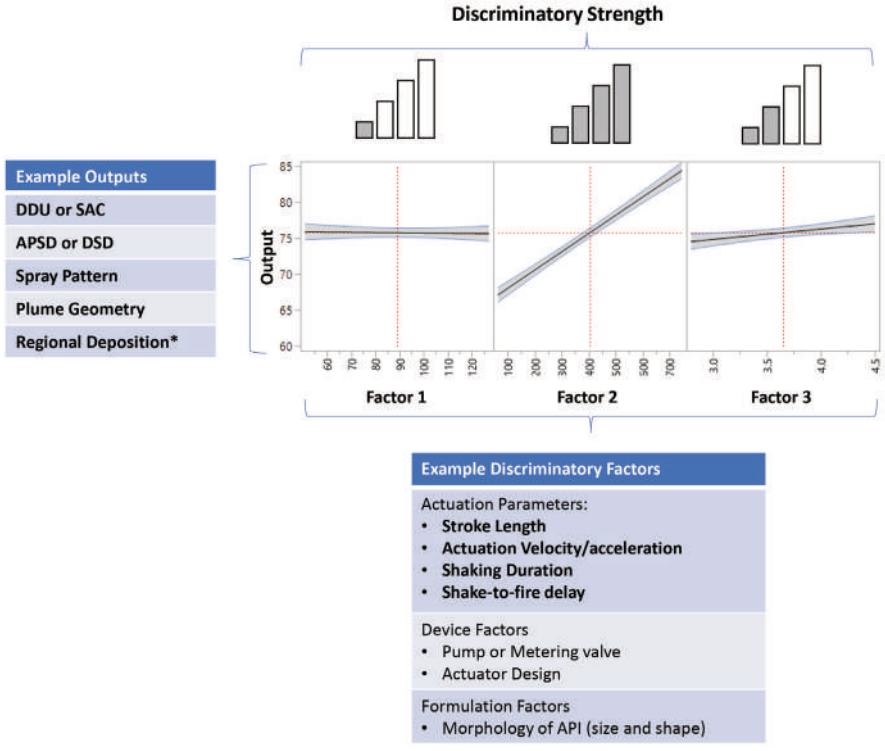


Figure 4. Performance sensitivity mapping with example discriminatory factors and outputs

The second step is to test the range of design spaces and gain an understanding of the control space: which factors have the most impact on product performance? This step will immediately rule out some device/ formulation candidates due to poor performance or incompatibility. It is recommended to start with shot weight (nasal sprays) or valve delivery (pMDI) as a key *in vitro* test to determine the effect of different factors in the control space.

For generic product development in general, it is important to begin your project with a thorough benchmarking of the reference product. Having a full understanding of the performance target and the variations across different devices and lots will help guide the initial design work for the generic device and formulation. For an innovator product, more emphasis should be put on the possible correlation to the *in vivo*

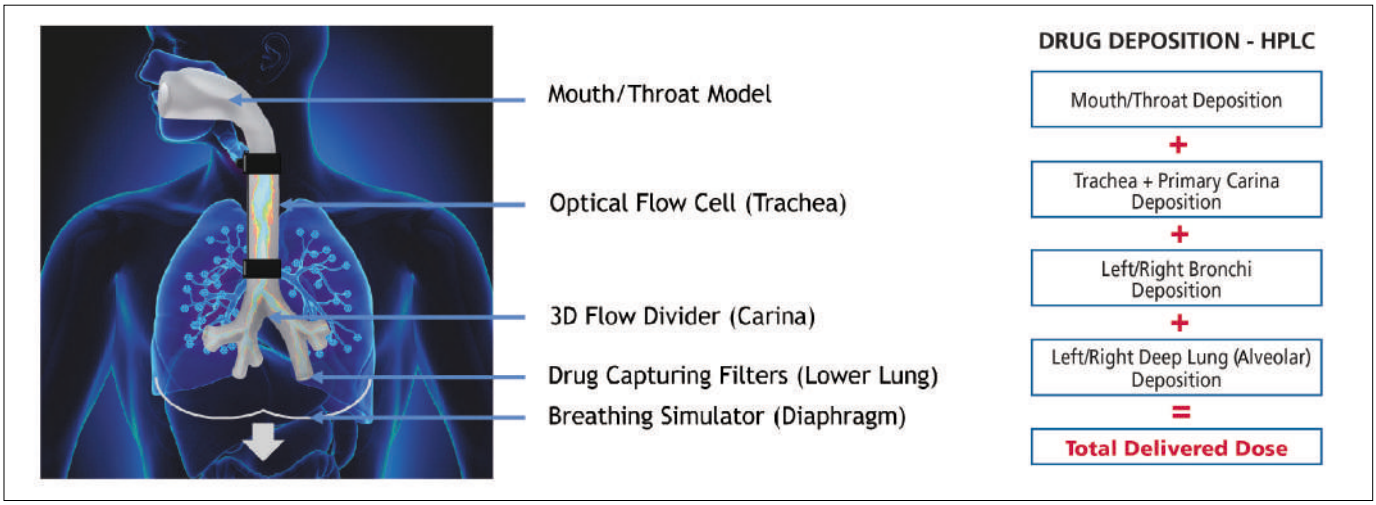


Figure 5. The apparatus of in vitro inhaled drug analysis (INVIDA) platform

performance, as well as aspects like product stability and consistency.

It is likely that two or more factors will influence each other systematically. Figure 3 shows the spray pattern area results from four different formulation/device combinations (formulation/actuator A; formulation/actuator B; water/actuator A; water/actuator B). Spray pattern area results were found to be similar for both actuator types (A and B) and highly variable when tested with water as the formulation; spray pattern areas for formulation showed distinct differences between the two actuator types (A and B) and were significantly different from water. This stresses the combination effect of both device and formulation, and the importance of evaluating the device with actual formulation instead of water.

The final step is to identify the target operating space and control key influencing factors in a tight range during manufacturing and testing. The results seen in the second step, and insights gained regarding the key actuation parameters, key formulation elements, and key device components must be used to formulate a plan for closely monitoring these critical quality attributes (CQAs).

The Proveris by Design™ approach generates a sensitivity map based on design of experiments and evaluates these results. As exemplified in Figure 4, the possible discriminatory factors will be listed on the x axis, against the outputs (usually *in vitro* test results) on the y axis. The discriminatory strength will be analysed statistically and used to systematically determine the most influencing factors driving the output.

For other dosage forms, including side actuated nasal sprays, syringe type nasal sprays, unit dose nasal sprays (aqueous or powder formulation), unit dose oral sprays, breath actuated metered dose inhaler, soft mist inhaler (SMI), dry powder inhaler (DPI), as well as over-the-counter (OTC) aerosol sprays (e.g., topical/dermal spray), the designing approach and the final controlling strategy can vary, but the overall principles remain unchanged.

Part 2: Using a Novel Human-Realistic Approach for *In Vitro* Characterisation to Better Predict *In Vivo* Performance of Inhaled Aerosols

The issue of poor correlation between the current *in vitro* testing and the clinical performance (*in vivo*) is widely acknowledged in the industry, and the high failure rate for generic drug approval in the inhalation space testifies to this.

In 2012, the USFDA started the Generic Drug User Fee Amendments (GDUFA) program, aimed at expediting the delivery of safe and effective generic drugs to the public and improving upon the predictability of the review process[6]. In the interim, numerous product-specific guidance documents have been released for orally-inhaled and nasal drug products (OINDPs). In May 2019, the FDA released a product specific guidance for beclomethasone dipropionate[7] that introduced approaches using new, alternative *in vitro* characterisation studies that are more representative and/or predictive of the clinical effect at the local sites of action in the human respiratory

tract. Characterisation of the emitted aerosol spray velocity profiles and evaporation rate were proposed as alternative tools for use in comparative clinical endpoint bioequivalence (BE) studies. Also, it was encouraged to apply human-realistic mouth/throat models as well as breathing profiles to existing *in vitro* testing.

A method to measure plume front velocity based on the well-established Proveris SprayVIEW® technique (which produces calibrated, time-synchronised image sequences of the entire aerosol plume and duration) was proposed by Proveris scientists[8]. The study shows a straightforward data analysis method based on the current PG measurements to generate a plot of distance travelled by the aerosol plume front versus time and thereby calculate the velocity. This method has the sensitivity to distinguish plume front velocity differences between different types of products, propellants, and formulations.

Moreover, an evaporation fraction approach was also developed based on the SprayVIEW® technique (to be published in the upcoming RDD 2020 conference). This method integrates the dynamic spray pattern (SP) data and correlates the cumulative image intensity results with the drug product mass (formulation + propellant). The technique then allows for a comparison of the drug product mass loss to the baseline in order to demonstrate the percentage loss of mass due to evaporation (evaporation fraction) at various distances from the mouthpiece edge.

In addition, Proveris has developed a novel platform called INVIDA™ (*in vitro* inhaled drug analysis) with emphasis on quantifying the regional deposition of aerosol drug products within different regions of the human respiratory tract. The deposition of drug in the deep lung drives bioavailability and *in vivo* performance of inhaled therapies. Many computational fluid dynamic (CFD) models of the respiratory system show that achieving the desired regional deposition in the deep lung is more complicated than just the aerodynamic particle size distribution. The unique geometries involved (variations in diameter create

pressure drop changes), as well as the respiratory environment (high humidity, constant temperature, and mucus layer) play an important role and cannot be ignored. Moreover, the mucociliary escalator clearance mechanism can greatly influence regional deposition.

The INVIDA platform includes a specially designed model of the upper respiratory tract which can be easily disassembled and assayed separately. The components are designed to mimic human respiratory physiology (mouth/throat, trachea, carina – left/right lung imbalance, lower lung) as shown in Figure 5, and the filter designed for drug capture is inserted following tracheobronchial and carina simulated model to measure the amount of drug that reaches the lung. A breathing simulator is connected to the apparatus to simulate realistic breathing profiles (inhalation, hold, exhalation). Further, a temperature and humidity chamber is attached to the airstream in order to simulate the human respiratory environment; and the inner surfaces of the airway models are coated with appropriate coating solutions to mimic the viscosity of the mucus. The API concentration can be analysed in the four major respiratory sections to understand the deposition across different regions. Finally, the mass balance of all the regions provides the total delivered dose from the device.

The INVIDA platform enables applying various breathing profiles that represent different demographics and disease states. It can be programmed with device resistance to replicate specific devices as some devices can be more difficult to breathe through than others. For breath-actuated inhalers (DPI, breath-actuated pMDI, and SMI), the minimum airflow to actuate the device can be obtained. In addition to inhalation, hold and exhalation parameters are available to study the effect of the full breathing cycle on the drug delivery and efficiency.

Conclusion

The performance of OINDPs is affected by a combination of formulation, device, and patient usage. Utilising automated actuation that replicates human usage with high precision is key to reveal the true product quality throughout life stages, for both testing and fire-down. Shaking is critical to suspension products and should be controlled. The Proveris by Design approach closely follows the quality by design approach recommended by the FDA and can save both time and resources while accelerating the time to market of these products.

Alternative *in vitro* approaches that are human-realistic can enable companies to make data-driven decisions and expedite product development and approval while saving time and resources. Proveris's *in vitro* testing platform (INVIDA) is built to replicate human usage of the product (in terms of breathing profile, respiratory geometry and environment) while minimising the gap between *in vitro* and *in vivo* performance to predict true product performance.

REFERENCES

1. https://www.fiercepharma.com/pharma/after-years-development-and-fda-rejection-novartis-calls-it-quits-advair-generic-and-takes
2. https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/pharmaceutical-quality-21st-century-risk-based-approach-progress-report
3. Guo, C. & Doub, W. H. (2006). The influence of actuation parameters on *in vitro* testing of nasal spray products. Journal of Pharmaceutical Sciences, 95, 2029–2040. https://doi.org/10.1002/jps.20678
4. Hatley, R. H. M., Parker, J., Pritchard, J. N. & von Hollen, D. (2017). Variability in Delivered Dose from Pressurized Metered-Dose Inhaler Formulations Due to a Delay Between Shake and Fire. Journal of Aerosol Medicine and Pulmonary Drug Delivery, 30(1), 71–79. https://doi.org/10.1089/jamp.2015.1284
5. Chauhan, H., Liu-Cordero, S. N., Liao, L. & Werbeck, J. (2018). Impact of Actuator Design on Multi-dose Nasal Spray Characteristics. In RDD 2018 (pp. 497–502).
6. FDA: Generic Drug User Fee Amendments [https://www fda.gov/industry/fda-user-fee-programs/generic-drug-user-fee-amendments]. Accessed October 31, 2019
7. FDA Beclomethasone dipropionate Inhalation Aerosol Metered NDA 207921 PSG Page RC May 2019
8. Liao, L. L., Ramos, K. & Farina, D. (2019). A Novel Characterization of Emitted Aerosol Velocity Profiles from Metered Dose and Soft Mist Inhalers (pMDI and SMI). In DDL 2019 (Vol. 30, pp. 287–290). Edinburgh, UK: Aerosol Society.

Starting a new OINDP project can be intimidating. A partner with the right expertise and extensive experience in the field can significantly streamline the development effort. To learn how Proveris laboratories can be your partner from early development to commercial scale testing, please visit https://www.proveris.com/why-proveris/

Linda Liao

Linda Liao is a senior application scientist who has focused her career on spray characterization, particle size, and shape characterization, and fluid dynamics as it pertains to the development and release of orally inhaled and nasal drug products (OINDPs). She has a strong technical understanding of *in vitro* testing requirements as defined by global regulatory agencies and is experienced in method development and quality by design (QbD) methodologies. Linda has authored numerous publications and spoken globally on the use of spray characterization technologies. Linda holds an M.S. in Chemical Engineering from the University of Florida and a B.S. in Chemical Engineering and Technology from Central South University, P.R. China.

YOUR PARTNER...

FROM DEVELOPMENT TO COMMERCIALIZATION

Scientific expertise and testing strategies for innovator and generic OINDPs

- Human Usage Studies
- Device Selection
- Formulation Screening

Alternative BE Studies

- Regional Drug Deposition
- Plume Velocity
- Evaporation Fraction

- In Vitro Testing
- Drug Product Characterization Studies
- Priming/Repriming
- Temperature Cycling
- Device Robustness
- Stability Studies

- Batch Release Testing
- Long-term Stability Testing
- Root Cause Analysis
- OOS/OOT Investigation

NOW FEATURING cGMP COMPLIANT LABORATORY

LEARN MORE:

www.proveris.com
contactus@proveris.com
+1 508 460-8822

proveris SCIENTIFIC