proveris®
LABORATORIES

Helping customers deliver quality orally inhaled and nasal drug products to patients around the world.

We're with you every step of the way.

Project Discussions > Technical Support > Implementation > Consultation

Why Proveris Laboratories?

100% Committment: uniquely positioned to help customers succeed in the OINDP market.

For over two decades, Proveris Scientific has been focused on helping customers deliver quality orally inhaled and nasal drug products (OINDPs) to patients globally.

We are a trusted partner to our customers and strive to deliver value to them in everything we do. We deliver complete solutions beginning with developing testing strategies, conducting method development studies, device formulation screening, and performing data comparisons.

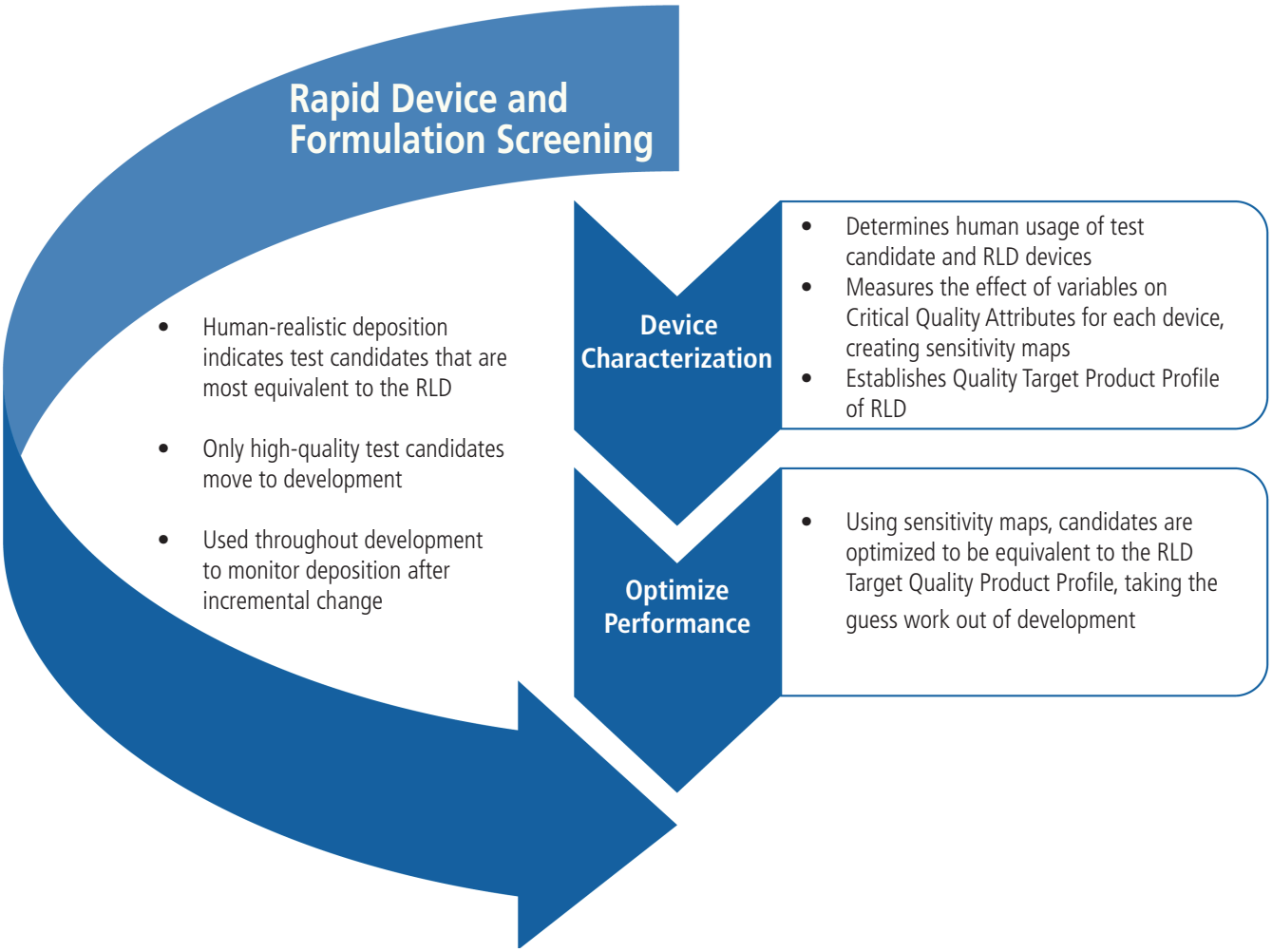
Our core objective is our focus and dedication to the OINDP market by working closely with generic and branded pharmaceutical companies, device suppliers, CDO/CMO/CROs, and global regulatory agencies.

We do extensive product testing with our own applications and laboratory teams to help us understand the challenges that our customers have in developing their products and successfully bringing them to market.

Proveris Laboratories provides expanded access to our core capabilities and expertise in ONIDP development and commercialization. Working closely with your team, we provide rapid insights into critical spray and aerosol parameters.

The Proveris by Design™ process: the key to unlocking a successful product submission!

Proveris by Design assesses the complex variables inherent in combination drug products to identify critical parameters that impact product performance. This allows optimization for successful product approvals. Based on the fundamentals of Quality by Design, Proveris by Design has been shown to minimize late-stage failures, shorten development times, simplify submissions, and reduce cost.



Understanding and Complying with Global Regulations

Understanding and complying with global regulations

Best practices at Proveris Laboratories are derived from working with global regulatory agencies. Our approach provides more reliable testing and fewer challenges from regulators, resulting in faster approvals. The Proveris by Design approach complies with major regulatory agencies incorporating all recommended *in vitro* testing as well as new, alternative methods, highlighted by regulators.

Weight of evidence for bioequivalence

Proveris by Design for bioequivalence is ideal for understanding the performance differences between a reference labeled drug and generic candidates. The Proveris by Design weight of evidence approach expands the toolbox for bioequivalence testing, employing all relevant tests, including new technologies, to build the most comprehensive demonstration of equivalence from start to finish. Extensive data generated during projects with Proveris Laboratories builds an overwhelming weight of *in vitro* evidence, helping you develop the most equivalent candidate for clinical endpoint studies, greatly reducing risk of late-stage failures.

Expertise from development to commercialization

For over 25 years Proveris Scientific has brought innovative testing solutions to the OINDP industry. Proveris Laboratories leverages this experience to get the most of your data in the shortest time possible. We also have the expertise to help you throughout commercialization, providing method transfer and validation, training, instrumentation, and access to comprehensive data generated during the project.

Development

- Human Usage Studies
- Device and Formulation Screening
- Methods Development

Alternative Bioequivalence Studies

- Spray Velocity (Plume Front Velocity)
- Regional Drug Deposition (Human-Realistic)
- Evaporation Fraction

CMC Services

- *In Vitro* Testing
- Drug Product Characterization
- Priming/Repriming
- Device Robustness

Commercial Support

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

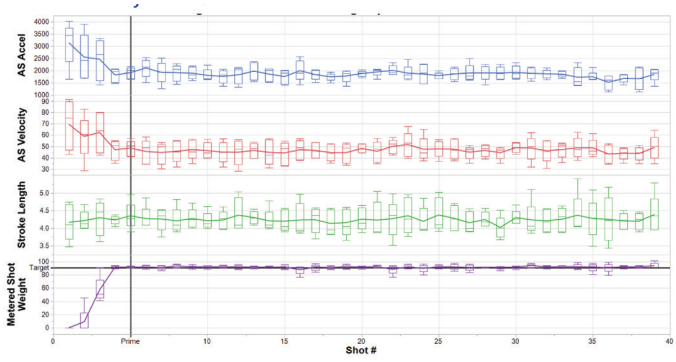
Proveris by Design Process

Human Actuation Study

A human actuation study is the essential starting point for an efficient product development and/or test method program. This study provides:

- Critical information in determining the performance data when comparing multiple devices or components
- A quantitative assessment of the product's pump delivery and priming specifications
- Identification of any patient usage issues early in the development process
- Documented evidence for regulatory submission on testing to replicate human usage

Human Actuation Studies are performed using Proveris Ergo™ technology to quantify how trained testers in the targeted population actuate the product. This information provides the parameters for Vereo® Automated Actuators to reproducibly execute. A range for the key actuation parameters (stroke length, velocity, acceleration, hold time, etc.) are obtained through the study, and can be applied for further optimization study, used to define the key characteristics of specific actuation of each device.

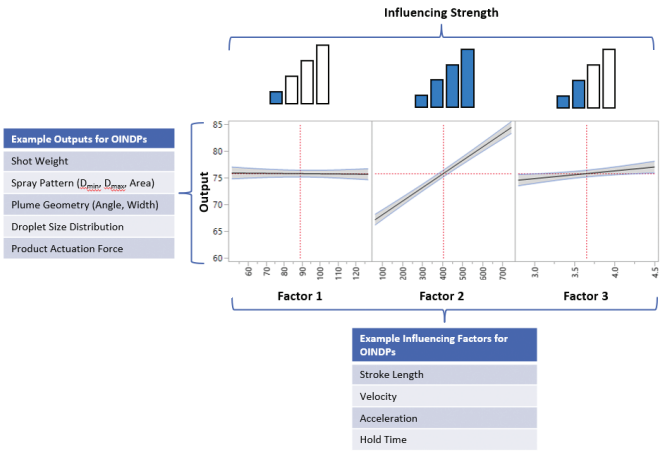


Example actuation parameters ranges obtained through human actuation study

Performance Screening and Prediction Models

This process helps you to understand the effect of each actuation parameter (e.g., stroke length, velocity, acceleration, hold time) on product performance (e.g., shot weight, Droplet Size Distribution, Spray Pattern, Plume Geometry) through sensitivity mapping. Optimized actuation parameters are then recommended based on comprehensive data analysis.

The Proveris by Design approach involves executing the screening experiments that are relevant for the product. These screening experiments are designed and executed using a controlled approach based on the Box-Behnken statistical method pioneered by FDA researchers. These experiments are intended to "screen" the parameters generated for their influence on the required test metrics (e.g., which parameter(s) influence shot weight, Droplet Size Distribution, and/or Spray Pattern and to what extent). The result of these experiments is a set of multivariate sensitivity/ performance curves for the product for each test metric (e.g., Plume Geometry, Spray Pattern, shot weight, etc.). These curves indicate regions of high and/or low sensitivity of the test metric to its corresponding input variables, providing valuable insights into which input parameter(s) drive product performance and which outputs need to be controlled and which ones do not.



Example of sensitivity mapping through performance screening and prediction models study

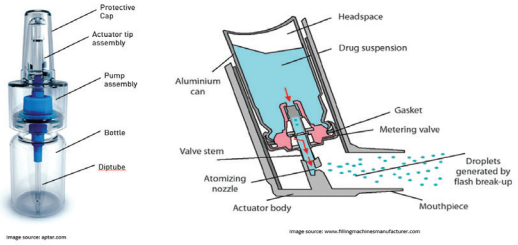
Proveris will use its time-synchronized, multivariant approach allowing the full power of failure mode and effects analysis (FMEA) to be leveraged. This results in a path for determination of root cause(s) of any problems that were encountered. Emphasis can be placed on the controlling parameters during validation and production, resulting in robust test methods that can be used for formal regulatory submissions.

Proveris by Design Process

Device-Formulation Screening

The performance of a drug-device combination product is influenced by both the formulation and the device constituent parts.

Proveris Laboratories will work with you to evaluate the actual spray performance on all the formulation and device combination candidates. With this process you can select the best device-formulation combination by evaluating all key characteristics. The Proveris by Design experimental model thoroughly evaluates and documents the effect of each attribute, providing the most comprehensive insight into product performance.

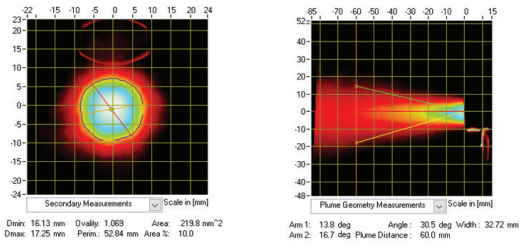


Example of device constituent parts of a nasal spray (left) and a pressured metered dose inhaler (pMDI, right)

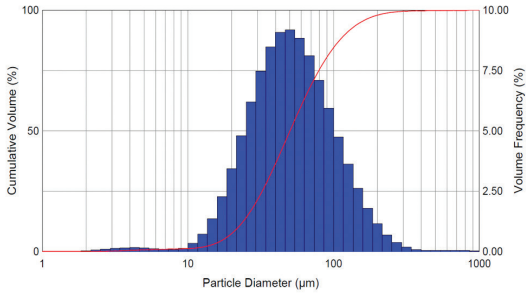
Product Characterization

Proveris Laboratories offers testing services in accordance with regulatory requirements for *in vitro* measurements:

- Shot Weight
  - Metered and delivered shot weight
- Droplet Size Distribution
  - Dv10, Dv50, Dv90, Span, v% < 10 µm
- Spray Pattern
  - Area, Ovality, Dmax, Dmin
- Plume Geometry
  - Plume angle and width
- Product Actuation Force
- Dose Content
- Priming/Repriming
- Tail Off Study
- New Product Evaluation



Example Spray Pattern (left) and Plume Geometry (right) measurement range



Example of Droplet Size Distribution (DSD)

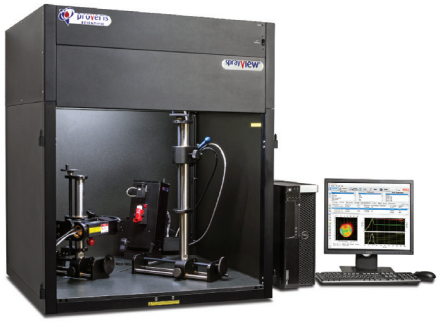
Study scope is customized based on different needs:

- Formulation development and/or device screening via qualitative characterization
- Confirmation studies for OOS and OOT results
- Comprehensive product characterization studies for reference product to set performance targets, and comparison to generic candidates
- Product characterization beyond regulatory requirements to provide insight for the aerosolization dynamics, skewed spray, and possible pre-pulmonary deposition for inhalation products which might cause unnecessary *in vivo* failure

Commercial Support

Method Development

Developing a robust method can be time consuming and requires experience and expertise. Proveris Labratories offers you a full method development with comprehensive reports within weeks. The final step is implementing the methods into your testing.



Method Validation and Verification

Method verification and validation demonstrates that the analytical methods are suitable for product characterization. Method validation will be performed using a single lot of the product to minimize the effect of lot variability. Validation parameters will be based on the ICH Quality Guidelines, Validation of Analytical Procedures, Q2 (R1) as a reference, and include:

- Method Precision
- Intermediate Precision
- Robustness

Additionally, the Proveris by Design approach involves executing the methods determined during development on multiple product samples from different lots.

Method Transfer

Method bridging at different sites and/or on different instrument generations can be challenging and time consuming. Proveris Laboratories assists you with identifying any possible differences on the instruments, achieving seamless method transfer within a short timeline. The final step is implementing the optimum methods into your testing.

Out-of-specification (OOS)

The occurrence of out-of-specification (OOS) and/or out-of-trend (OOT) causes serious delay in production. Thorough investigation involving additional time and resources is required. Proveris Laboratories assists you by reviewing and analyzing existing data, diagnosing possible root causes, making constructive suggestions on possible solutions, and potentially remeasuring samples for confirmation.

Custom Consulting Services

Our team of experts and industry thought leaders will assist you, from early development, method optimization, and validation, to release testing at manufacturing.

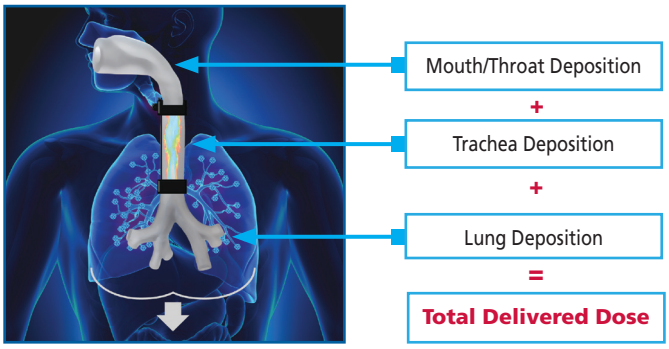
Commercial Support

Rapid Human-Realistic Testing

To reduce the risk associated with development of orally inhaled products, new tools are required to ensure the rapid evaluation of product performance throughout development. Proveris Laboratories' approach enables rapid development under human-realistic conditions that helps bridge the gap between traditional laboratory testing and real-world outcomes.

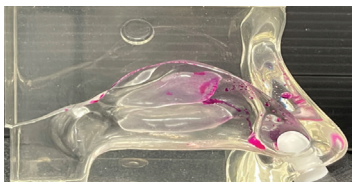
INVIDA® Services

In Vitro Inhaled Drug Analysis (INVIDA) services is a new paradigm for inhaled drug development that incorporates human-realistic breathing patterns and respiratory models to determine true product performance in a targeted demographic. Collecting multiple samples for regional deposition allows you to make informed decisions quickly. INVIDA testing enables a better understanding of the dynamics of inhaled substances in a human-realistic manner, allowing for rapid indications of *in vivo* performance. INVIDA services are ideal for evaluating and maintaining product performance throughout development.



Nasal Casts

Nasal Casts are powerful tools that can provide a cost effective and rapid means of evaluating nasal deposition in a human-realistic manner. Proveris Laboratories offers qualitative nasal deposition studies



using nasal cast model, that can be used to accelerate development by understanding where and how much product is deposited in the nasal cavity. Studying the effect of actuation profile, insertion angle, insertion depth and inspiratory flow rate on deposition can help optimize formulations, inform device selection, and create patient instructions to ensure a consistent targeted delivery in the nasal cavity.

Alternative Methods

Proveris is committed to supporting regulatory efforts by providing innovative testing solutions to the OINDP industry. In response to the FDA's inclusion of Spray Velocity, Spray Duration, and Evaporation Rate as alternative tests to support in vitro bioequivalence, Proveris Laboratories now provides Advanced Aerosol Characterization services for oral product development.

Plume Front Velocity

Plume Front Velocity provides insight into bulk aerosol behavior and can indicate changes in performance. It generates velocity profiles based on the leading edge of an aerosol plume.

Spray Duration

Spray Duration measures the therapeutic delivery time of a product and can be used to determine product compatibility with a patient demographic. Testing paired with INVIDA services enables breath coordination and misuse studies, using disease state specific breathing profiles.

Evaporation Fraction

Evaporation Fraction allows an understanding of what is the state of materials arriving to the lungs and can be used to monitor particle characteristics.

Advanced aerosol characterization services, for oral products, provide novel insight, additional demonstrations of equivalence, and the ability to rapidly predict changes in product performance throughout development.

Quality by Design System

The Proveris Quality by Design System controls all aspects of operations in Proveris Laboratories. The key elements of every process are evaluated and procedures with monitoring and review steps are designed into each protocol. Over 25 years of bringing gold standard testing solutions to the OINDP industry gives Proveris Laboratories a unique position to understand the best practices utilized at leading companies worldwide.

We work directly with regulatory agencies such as the FDA in the USA, EMA in Europe, NMPA in China, and other agencies such as ANVISA in Brazil. This provides a solid knowledge base to design experiments and create submission grade documents that are in line with current agency requirements and preferences.

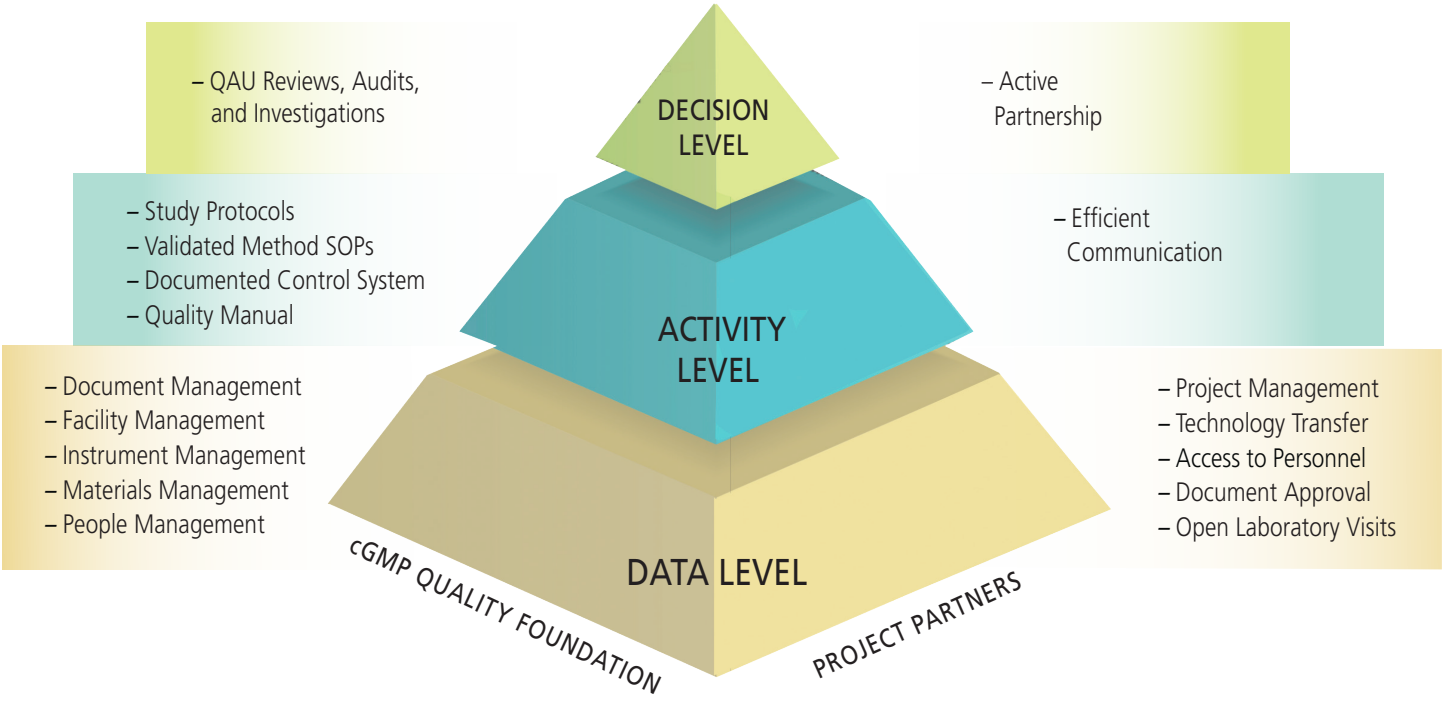
Quality Committment

The Quality by Design approach allows a logical progression from aggregating data on all key elements of a study. All fundamental aspects of the study are documented assuring a solid base of information. Data is collected on all project activities and organized for easy review. QAU monitoring and collaborative project updates ensure timely compliant decision making, justified by the data.

Consultative Project Management

We are a partner in all aspects from development to commercialization:

- An active partnership begins with efficient communication protocols, spelling out what information is transmitted, and the frequency
- All aspects of the project are open to review and evaluation throughout its entirety
- Project management protocols ensure all information required are discussed and exchanged up to the submission and technology transfer phases



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