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.

Put our team to work for you.

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, testing devices, and performing data comparisons.

Our core objective is dedication to the OINDP market and 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 team and laboratory to help us understand exactly 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 you team, we provide rapid insights into critical spray and aerosol parameters

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

Our unique, patented process is a launch point because it identifies the human usage performance of an OINDP according to current FDA and ICH guidelines for in vitro testing. This process is highly interactive between our scientists and you, and normally results in our customers making comments like, *"Now I know why we were experiencing such erratic performance from our product. We were in the dark for so long – thanks for opening our eyes!"* And, *"Now I know what changes we need to make to our OINDP to achieve bioequivalence and why!"* Some key benefits of the Proveris by Design process are:

Accelerate Development with Proveris Laboratories

Device Selection and Screening | **Method Development** | **Method Verification**

In less than two months

Achieve the following in less than two months with Proveris Laboratories:

- Device-formulation Selection
- Robust Method Development based on FDA recommended Quality by Design (QbD) approach
- Product understanding based on sound science
- Identify input variabilities influencing critical quality attributes (CQAs)

Typical Project Workflow

- Initial calls to understand project needs and requirements
- Develop Study Plan Proposal with deliverables, cost, and timelines
- Sample testing, data analysis, and web based progress meetings
- Data Review
- Submission grade final report

Services Offered

Customized Studies

- Human Actuation Study
- Method Development for Spray Pattern and Plume Geometry
- Determining Optimum Actuation Profile
- Device Screening
- Reference Product Characterization
  - Shot Weight
  - Droplet Size Distribution
  - Spray Pattern
  - Plume Geometry
  - Actuation Force
  - Dose Content
  - Aerodynamic Particle Size Distribution
- Formulation Screening
- Actuation Force Evaluation
- Technology and Method Transfer
- INVIDA™ Human Realistic Deposition Studies
  - Nasal Deposition Studies
  - Plume Front Velocity
  - Plume Evaporation
- Stability
- Method Optimization
- OOS Investigations
- Viscosity
- Spray Content Uniformity
- Weight Loss
- Customized Training
  - Quality Control
  - Development
  - Methods Development

Device Types

- pMDI (pressurized metered dose inhalers)
- Nasal sprays
  - Multi-dose, bi-dose, unit dose
  - Aqueous, powder, propellant driven
  - Vertical actuated, side actuated, dual side actuated, syringe type
- Oral sprays
- Soft mist
- Breath actuated inhalers
  - DPI (dry powder inhalers)
  - pMDI
  - Soft mist
- Topical/dermal sprays
- New spray product types

Stability Testing

Stability provides documented evidence on how time effects the quality of either the active pharmaceutical ingredient and / or the combination device. This data can be used to determine or support shelf-life claims.

Each device can be studied under various conditions and environmental factors which include: temperature, humidity, and light over a period of time, degradation products, and any specific conditions related to the API or device.

Accelerated time studies performed at higher temperature or more extreme conditions can serve as an indicator of stability but cannot replace real time evaluations.

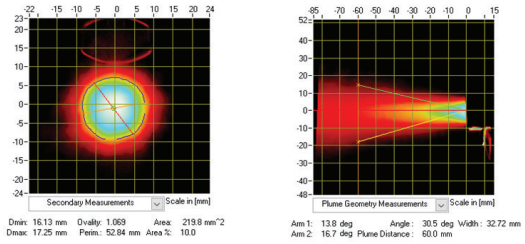
Typical stability studies are set up to evaluate and document performance using key indicators such as temperature, humidity and light. Some of the key aspects of a study protocol that are documented include: each of the storage conditions, timing intervals, strength and acceptance criterion of purity levels, batch size for testing, orientation versus baseline results, specific degradation products, and any specific conditions related to the API or device.

Proveris Laboratory Offerings

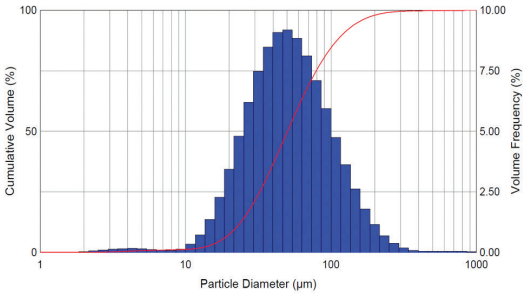
Product Characterization

Proveris Laboratories offers the regulatory service required for *in vitro* measurements:

- Shot weight
  - Metered and delivered shot weight
- Droplet size distribution (DSD)
  - 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



Example spray pattern (left) and plume geometry (right) measurement range



Example of droplet size distribution (DSD)

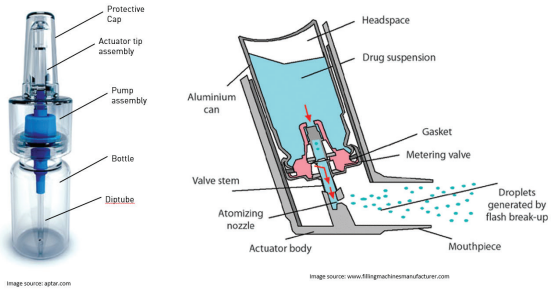
Study scope is customized based on different needs:

- Formulation development and/or device screening via qualitative characterization
- Confirmation studies for out-of-specification (OOS) and out-of-trend (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

Device-Formulation Screening

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

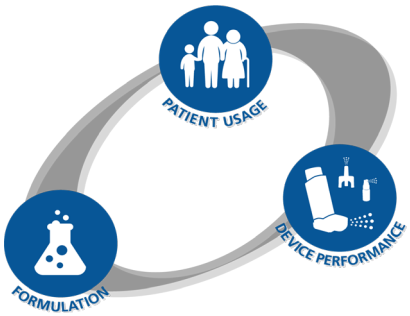
Proveris Laboratories will work with you to evaluate the actual spray performance on all the formulation and device combination candidates. With this process you can select the best device-formulation combination by evaluating all key characteristics. The Proveris by Design experimental model thoroughly 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)

Proveris Laboratory Offerings

Proveris by Design approach results in robust methods development.

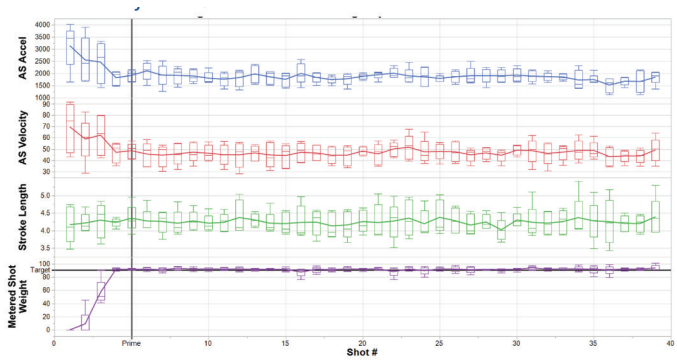


Human Actuation Study

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 people in the targeted age and gender group (Trained Testers) actuate the product in a way that is transferrable to statistical analysis. This information can be translated into parameters for Vereo® automated actuators to reproduce. 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 your design space.

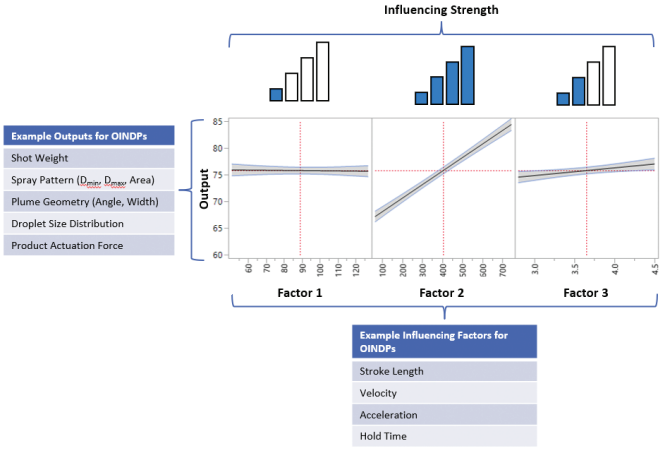


Example actuation parameters ranges obtained through human actuation study

Performance Screening and Prediction Models

This step helps you to understand the effect of each actuation parameter (e.g., stroke length, velocity, acceleration, hold time) on the product performance (e.g., shot weight, DSD, SP, PG) through sensitivity mapping. An optimized actuation parameter combination is recommended based on comprehensive data collection and 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.



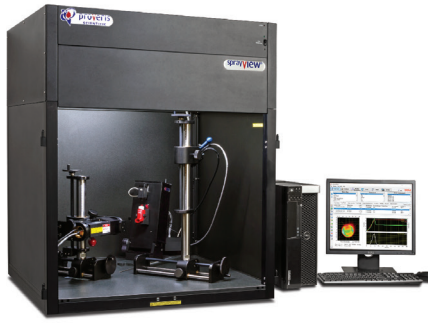
Example of sensitivity mapping through performance screening and prediction models study

Proveris will use its time-synchronized, multivariant approach that allows the full power of failure mode and effects analysis (FMEA) to be leveraged, resulting in a suggested route 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 Laboratory Offerings

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.

Technology and 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.

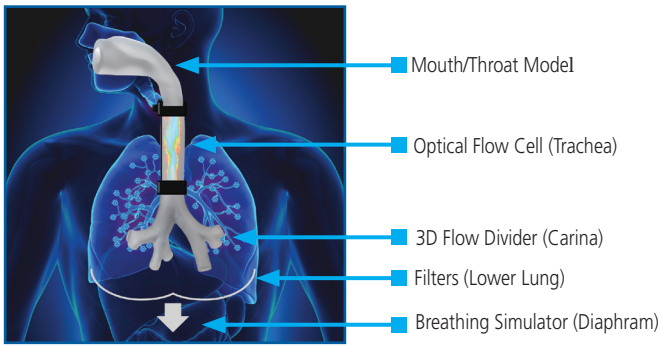
Novel *in vitro in vivo* Correlation Approaches

Inhalation drug development is a complex relationship between device design, particle engineering, formulation and inspiratory flow. The lack of successful *In vivo* correlation to *in vitro* experiments demonstrates that the existing technologies used do not provide enough information to accurately evaluate these relationships. Lack of this information has delayed product development by delaying clinical studies and not providing information on *in vitro* to *in vivo* correlation (IVIVC). The result is increased development costs and extended timelines.

INVIDA In Vitro Inhalation Drug Analysis

Proveris Scientific's innovative INVIDA system provides data that can better predict *in vivo* performance due to *in vitro* testing being performed with human-realistic conditions.

This innovative technology measures the aerosol dispersion and regional deposition of inhaled drugs. Use of a programmable breathing module allows breathing profiles for normal and diseased states to be evaluated. Being fully programmable allows patterns published in the literature to serve as a baseline, as well as patterns created de-novo to optimize studies. Visual mapping along with quantitative measurements enables researchers to better understand their product's performance. Trending critical factors and measurements enable scientists to better predict *In vivo* performance.



- Simulates drug dispersion and deposition under human-realistic respiratory conditions
- Visually maps drug flow through the respiratory tract
- Quantifies regional deposition in mouth/throat, trachea, and lower lung
- Unrivaled approach to IVIVC

Also employed by Proveris Laboratories are new innovative *in vitro* techniques outlined by the US FDA. These include measuring spray velocity, evaporate rate, and quantifying deposition of nasal drug products using human realistic models. For generic drug developers these tests can serve as an alternative *in vitro* approach to evaluate bioequivalence between Test and Reference products. Innovator drug developers can utilize the data generated to help guide key decisions early on regarding device selection, formulation development, and IVIVC.

Plume Front Velocity

Plume Front Velocity is a measurement tool that was developed on the well-established Proveris SprayVIEW® system technique (which produces calibrated, time-synchronized image sequences of the entire aerosol plume and duration) to create a plot of the distance travelled by the leading edge of the aerosol plume versus time. In a recent draft guidance, the FDA includes analysis of spray velocity as one of the alternative tools for use in comparative clinical endpoint bioequivalence (BE) studies. This test is available as a service for all inhalation products (pMDI & Soft Mist inhalers).

Evaporation Fraction

Evaporation Fraction is a measurement tool that was developed on the SprayVIEW system. 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. This test is also available as a service for all inhalation products (pMDI & Soft Mist inhalers).

Nasal Deposition Studies

Nasal Deposition is a new offering from Proveris Laboratories. The modular design is based on the Koken nasal cavity model using the Sargel technique and provides a quick screening tool to analyze nasal drug product deposition. The system allows the study with open and closed pharynx to accommodate all types of nasal devices. A breathing simulator may be added to provide human-realistic conditions.

GLP/cGMP Quality Operations

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.

Twenty five years of being the leader in providing measuring tools to the OINDP industry places Proveris in a unique position to understand the best practices utilized at leading companies worldwide.

We have been working 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 preferences.

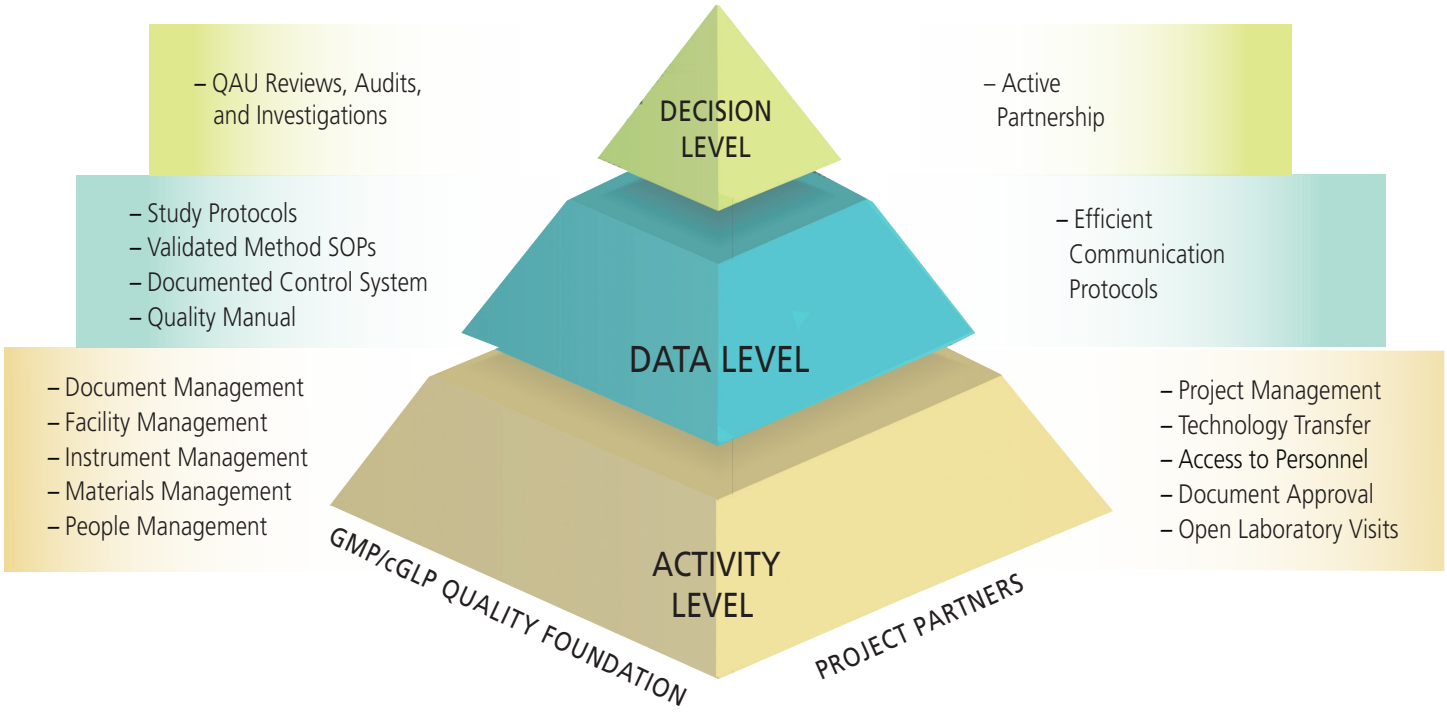
Quality Commitment

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 reviews allow informed decisions.

Dedicated Project Management

We are 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 parts of the project are open to review and evaluation throughout its entirety
- Project management protocols assure all information required are discussed and exchanged up to the submission and technology transfer phases
- Critical Success Factors are in place to assure a successful project being completed ahead of time and under budget



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LABSRV0620