

Beyond Propellant Replacement: A More Intelligent Development Pathway for Low-GWP pMDIs

The transition to low-global-warming-potential (low-GWP) propellants is one of the most significant changes to pressurised metered dose inhaler (pMDI) development in decades. The environmental driver is clear. The pharmaceutical challenge is considerably more complex.

A pMDI is not simply a drug formulation packaged with a propellant. It is a coupled formulation – container closure – device system in which the propellant contributes directly to metering, atomisation, plume formation, evaporation, and aerodynamic behaviour. Changing one of the fundamental physical components of that system can therefore affect formulation behaviour, device interactions, aerosol generation, dose delivery, regional deposition, and ultimately the evidence required to demonstrate acceptable product performance. The EMA's current low-GWP pMDI guidance reflects that breadth, covering quality, non-clinical, and clinical considerations rather than treating propellant replacement as a narrow formulation change.¹

The development objective is therefore not simply to demonstrate that a reformulated product produces acceptable analytical results. It is to understand whether the aerosol journey remains appropriate from device to patient. That requires a broader set of questions: How does it fly? Where does it land? What arrives? These are connected questions, but they are not answered by the same measurement. That three-part framework sits at the centre of the current Proveris low-GWP scientific strategy.

The low-GWP transition creates an opportunity to reconsider when those questions are asked. Rather than relying heavily on a full, expensive, compendial test package early in development when formulations, valves, actuators, and instructions for use may still be changing, a more efficient strategy is to generate a greater density of rapid, mechanistic, and comparative information first. More resource-intensive testing can then be concentrated on candidates that have already been characterised and understood. This is the principle behind Proveris by Design™ (PbD): generate actionable evidence early, follow the

mechanism, add realism where its required, and confirm the selected product rigorously.

Low-GWP Reformulation Changes a Connected System

The scientific challenge begins with aerosol generation. Following actuation, a metered volume of pressurised formulation passes through the valve and actuator and undergoes rapid pressure reduction, flash evaporation, and atomisation. The aerosol then continues to evolve after leaving the device as droplets or particles interact with surrounding air and volatile components evaporate.

Low-GWP propellants do not have identical thermophysical properties to the currently used HFA-134a. Reviews of HFA-152a and HFO-1234ze(E) have highlighted these differences and their potential consequences for formulation and atomisation.²

Recent experimental studies reinforce the point. Duke and colleagues compared solution pMDIs formulated with HFA-134a, HFA-152a, and HFO-1234ze(E) using APSD, laser diffraction, and high-speed imaging. In the systems studied, HFA-152a produced greater actuator and throat deposition and different plume behaviour, while HFO-1234ze(E) was more similar to HFA-134a in APSD but still showed differences in plume development.³ A subsequent suspension study demonstrated that the presence of suspended drug further modifies the relationship between propellant properties and spray structure, including flash-evaporation behaviour and plume width.⁴

Proveris and collaborators have examined related variables experimentally, including spray characteristics of P-134a and P-152a systems with and without ethanol, and

methods for quantifying evaporation fraction and evaporation rate in HFA-134a and HFA-152a formulations.^{5,6} These studies support the broader development premise that the propellant change can alter the physical processes that generate the aerosol. The Proveris framework treats formulation, device, aerosol, and patient-facing variables as an interconnected system.

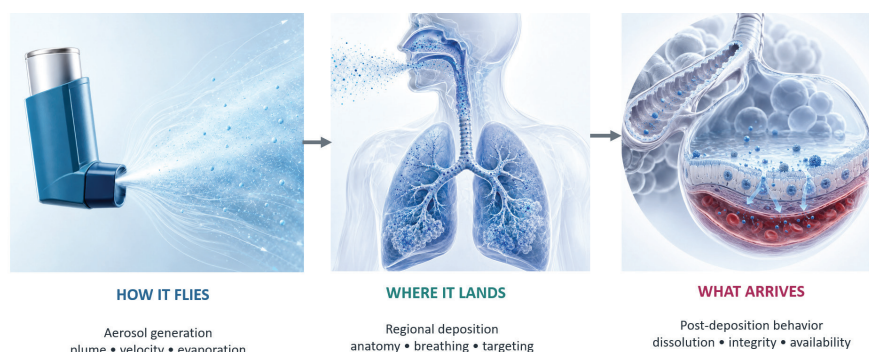
The Cost of Understanding Too Late

This problem has a long history in spray and aerosol development. In 2013, Proveris described the “Merry-Go-Round”: repeated cycles of testing, unexpected results, modification, and re-testing when data had not been converted into sufficient product knowledge to direct the next action.⁷

The concept remains relevant because low-GWP pMDI development creates exactly the conditions in which trial-and-error can become expensive. A single propellant change can cascade into uncertainties about formulation, valve, actuator, canister and closure materials, labelled shaking and firing instructions, analytical strategy, deposition behaviour, and the evidence needed for progression.

If a candidate differs from the reference in a compendial result, several explanations may be plausible. The formulation may not redisperse in the same way. Valve delivery may differ. The candidate may be more sensitive to shaking or shake-to-fire delay. There may also be other formulation, device, method, or handling related factors contributing to the observed difference. The result alone does not identify the cause.

This is also where timing becomes economically important. Early development



offers flexibility. Formulation composition, actuator geometry, valve choice, and preparation parameters can still be changed. Later, the same changes can affect stability, scale-up, analytical validation, PK, clinical work, or submission strategy, at greater consequence and cost.

Proveris by Design: More Learning Before More Commitment

Proveris by Design provides a framework for putting that principle into practice. The approach is consistent with Quality by Design thinking: understand the variables; build evidence around the development question with constant analysis; and use the results to guide the next experiment rather than executing a fixed battery of tests regardless of what the data show. Proveris formally describes PbD as a stepwise roadmap for in vitro characterisation of orally inhaled and nasal drug products.^{8,9}

The first step is to understand the product that is being changed or reproduced. For a reference product, that means more than establishing nominal DDU and APSD values. The baseline should include normal batch, device, and shot variability; sensitivity to shaking, delay, and orientation; dose delivery through canister life; aerosol formation and temporal behaviour; and, where relevant, upper-airway or regional deposition. The target is product performance, not meeting a single specification.

The second step is to generate rapid controlled evidence with enough statistical

power to distinguish real differences from noise. This is where more data earlier can be more cost-effective. Rapid screens can investigate multiple formulation and device variables before the programme commits large quantities of product, analyst time, and instrumentation to a full suite of expensive resource-intensive confirmatory methods.

This does not mean “do every possible test early.” It means selecting measurements according to the uncertainty. If the question is whether the device meters consistently, investigate valve delivery and DDU; if the question is whether the aerosol event has changed, interrogate spray pattern, plume geometry, velocity, duration, or evaporation; or if the question is whether the difference remains relevant when the product interacts with a patient, then add breathing, anatomy, or deposition.

Early mechanistic evidence also creates a defensible record of why development decisions were made and can support later root-cause investigation if stability, scale-up or manufacturing introduces a change.

How It Flies

The first scientific layer is how the aerosol is generated and evolves. For low-GWP pMDIs, this is especially important because changing the propellant changes the physical conditions under which atomisation and evaporation occur. “How it flies” includes plume formation, velocity, particle or droplet size, trajectory, duration, and evaporation. These variables are dynamic and interdependent.

Plume-Front Velocity, for example, provides information about how rapidly the aerosol moves away from the actuator. Evaporation measurements depicted help determine how the aerosol changes after emission. Spray Pattern and Plume Geometry provide spatial information about the developing aerosol. There are published methodologies addressing both emitted aerosol velocity and evaporation as additional characterisation variables.^{6,10}

The value is mechanistic. If two products have different deposition behaviour later, understanding how each aerosol was generated can help explain why. Conversely, if mechanistic differences are detected early, the development team can determine whether those differences persist or disappear as the evidence chain progresses.

Where It Lands

After leaving the device, the aerosol interacts with airflow, the mouth and throat, and the branching respiratory tract. At the same time, droplets may continue to evaporate and change size. The combination of velocity, particle or droplet size, trajectory, breathing profile, and anatomy influences where drug is likely to deposit. The Proveris framework makes this relationship explicit: an evolving aerosol is being inhaled into a complex airway, and the two processes together determine deposition.

Regional deposition therefore asks a different question from dose delivery or particle-size characterisation. A product may

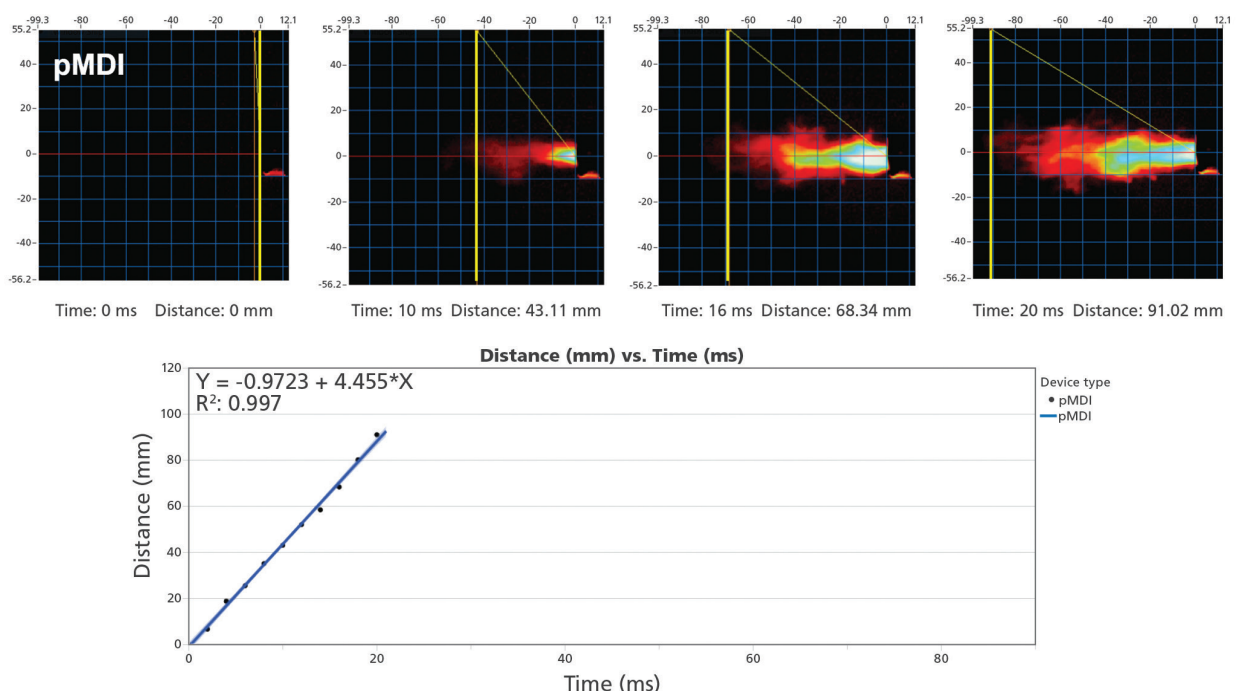


Figure 1: Plume Front Velocity (PFV) images and corresponding distance-versus-time plots.

deliver the expected amount of drug while distributing that dose differently through the respiratory tract under more representative conditions.

Human-relevant deposition models can provide additional context. For example, INVIDA® combines human-relevant oropharyngeal geometry with programmable breathing profiles and regional HPLC quantification to assess deposition across the mouth/throat, tracheal and lung regions. Olsson and colleagues used anatomically correct inlet throats with actual inhalation flow profiles and measured the fraction of drug passing beyond the throat. That ex-throat fraction was shown to predict typical total lung deposition across a range of inhaled products in healthy adults.¹¹

During development, the priority is to understand which formulation, device, administration, and physiological variables influence product performance, and to investigate those relationships while the product can still be changed.

Once those relationships are understood, standardised methods provide the controlled and reproducible framework needed for activities such as release, stability, and routine product control. Human-relevant experiments are therefore most useful during development when they help explain an observed difference or determine whether it is likely to matter under representative use conditions.

The principle is simple: add realism when it can affect the decision.

What Arrives

Once drug has reached a region of the respiratory tract, a further question remains: what has actually arrived, and in what state is it available to continue toward its intended local or systemic action? How is it absorbed?

For conventional small-molecule pMDIs, dissolution may be one important part of this question. For more complex products,

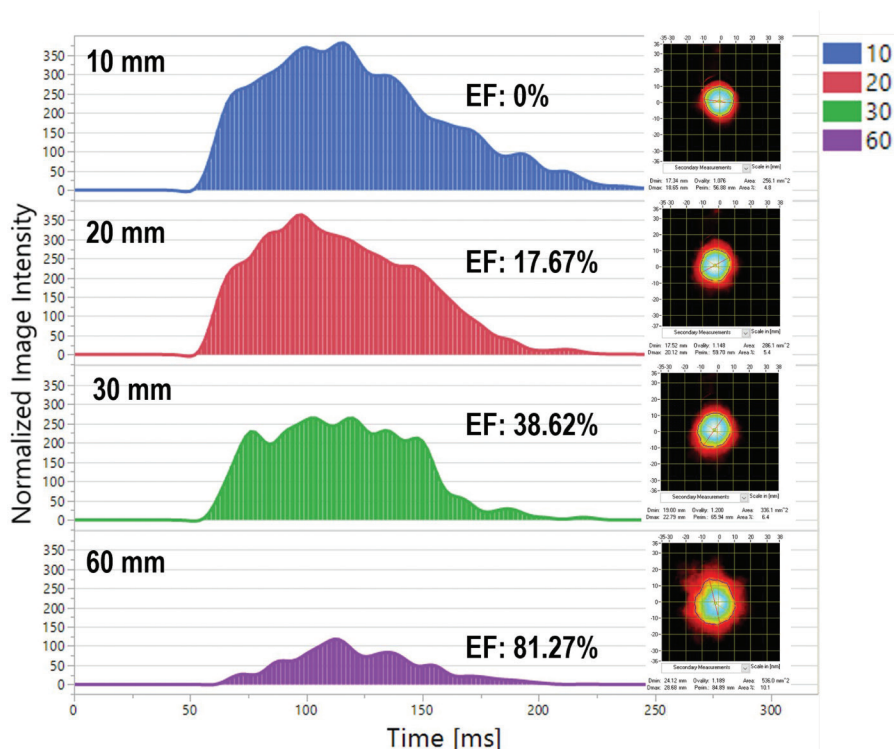
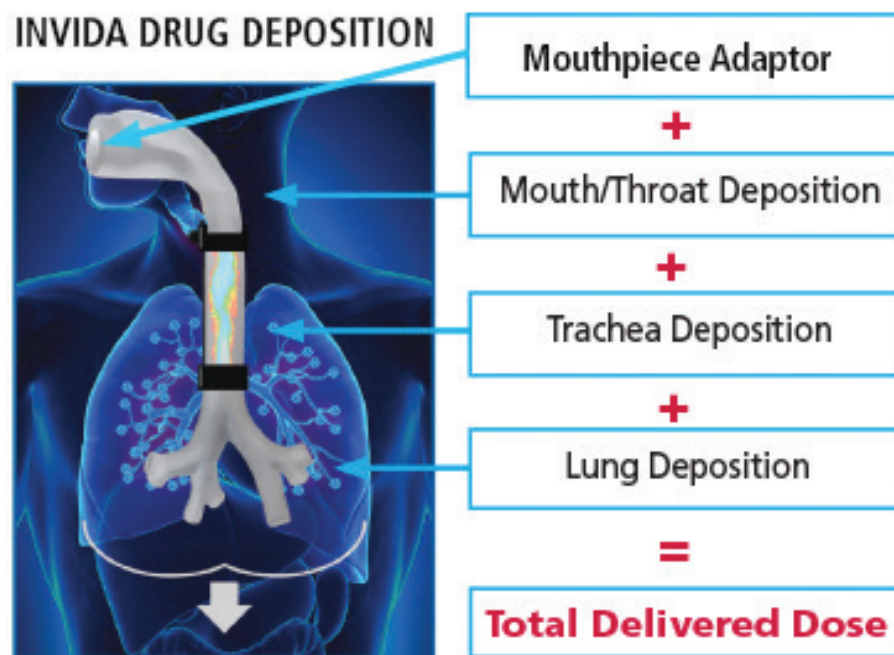
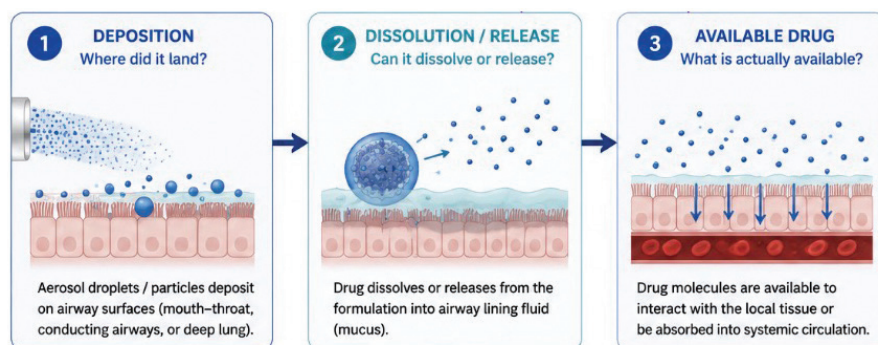


Figure 2: Evaporation measurements determined from Spray Pattern images taken at specified distances from a pMDI mouthpiece.



Schematic of Proveris Scientific's INVADA platform.



the relevant evidence may eventually include molecular integrity, aggregation state, payload association, or other measures of functional integrity. The framework therefore extends “where it lands” into “what arrives”: post-deposition behaviour, dissolution, integrity, and availability.

For low-GWP pMDIs, this does not mean every programme requires an extensive post-deposition package. It means that

the evidence strategy should be capable of following the drug further when deposition alone does not resolve the uncertainty.

Compendial Testing as Confirmation, Not Discovery

Established compendial and regulatory tests remain essential. DDU, APSD, and other required measurements provide controlled, standardised, and widely accepted evidence of product quality and performance. A full compendial package can be time, material, and analytically intensive. During early screening, when multiple formulations and device configurations remain in play, running the entire package repeatedly may be less efficient, and more costly, than first using faster measurements to establish which candidates are robust and which mechanisms need investigation.

PbD therefore places the larger compendial and confirmatory package later in the learning sequence, after formulation, device, and aerosol behaviour have been characterised and after human-relevant questions have been addressed. The proposed development strategy is therefore formulation screening, device-function screening, aerosol-formation screening, human-relevant evaluation, and finally compendial/confirmatory evidence. The objective is to avoid discovering fundamental product behaviour for the first time when the programme has already reached its most resource-intensive and expensive tests.

From the Laboratory Question to the Development Decision

The same philosophy explains the evolution of Proveris Laboratories. The laboratory was built because customers repeatedly asked for help beyond operating an instrument: method development, troubleshooting, reference-product characterisation, workflow automation, and interpretation of unexpected results.



Those questions often cross analytical boundaries. A problem first observed in a compendial result may originate in formulation, device function, actuation, aerosol formation, or deposition. A laboratory designed around the question rather than the test is therefore able to move through the evidence chain until the uncertainty is resolved. The output is not simply more data. It is a better development decision.

Low-GWP pMDIs as a Model for Better Development Science

The low-GWP transition is an environmental necessity, but it also exposes a broader weakness in conventional development thinking. Endpoint results can provide erroneous reassurance before the system that produced them is fully understood. The transition challenges the industry to preserve patient-facing performance while changing a fundamental component of the aerosol-generation process. That cannot be addressed efficiently by asking one test to answer every question.

A more rational pathway is to understand the reference product, generate high-information evidence early, manage formulation and device variables as a system, follow the aerosol as it is generated and evolves, determine where it lands, investigate what arrives, and then enter compendial and confirmatory testing with a product that is already substantially better understood.

This is the core proposition of Proveris by Design. More data earlier does not mean more indiscriminate testing. It means generating mechanistically useful evidence while change is still possible, escalating complexity when the evidence justifies it, and using confirmatory methods when they provide greatest value. The environmental objective and the patient objective must succeed together. The new propellant must reduce climate impact, but the product must still deliver the medicine appropriately.

The most effective way to de-risk that transition is to understand earlier, connect the evidence across the whole aerosol journey, and make each experiment earn its place in the next development decision.

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