AUTOMATING MDI ACTUATION: PRECISION DATA WITH LESS EFFORT

COPLEY

Paul Martin of **Copley Scientific** considers how automation can enhance testing for metered dose inhalers by removing the variability in actuation technique introduced by manual operation, presenting two case studies that demonstrate this potential improvement in data quality.

The susceptibility of metered dose inhaler (MDI) performance to vary depending on actuation technique is an important source of variability in both testing and use. Patient-related variability is unavoidable, but analyst-related variability during testing need not be. Automating actuation reduces a significant and avoidable source of analyst-to-analyst variability in MDI testing, resulting in tighter, more precise data and clearer differentiation between handling effects and true product performance.

In practice, automated actuation reduces the risk of apparent out-of-specification (OOS) results and the need for repeat testing driven by handling variability rather than product performance. Furthermore, with more precise and repeatable data, it becomes easier to investigate the specific effects of actuation parameters and to distinguish those effects from changes in formulation or device design. The net impact is faster progress towards robust performance under conditions that are representative of patient use.

Current efforts to reformulate MDIs with low-global warming potential (GWP) propellants have increased the need for repeatable MDI testing. Changes in formulation properties, such as density and vapour pressure, can increase their sensitivity to variations in actuation technique, reinforcing the importance of tightly controlled testing when assessing comparability or interchangeability. Identifying and controlling such effects is crucial for making confident decisions on accelerated timelines.

Copley Scientific's Vertus® III is an automated shake, fire and flow control platform offering controlled and repeatable delivery for MDIs and nasal drug products. By setting, executing and recording specific actuation parameters, such as shake frequency, shake-to-fire delay and actuation hold time, Vertus III supports controlled studies that isolate which aspects of technique drive variability. The following case studies illustrate how this structured approach can support the investigation and optimisation of actuation technique and the development of more robust test methods, helping to ensure that observed variability reflects product performance rather than differences in operator technique.

HOW ACTUATION PARAMETERS INFLUENCE DOSE DISPERSION AND DELIVERY

To understand how actuation parameters influence MDI performance, it is useful to review their principles of operation. MDI formulations contain an API dissolved or suspended in a propellant or propellant-solvent mixture. The main components of an MDI device are:

- The cannister, which holds the formulation under pressure
- The metering valve, which measures out each dose
- The actuator mouthpiece, which delivers the aerosolised dose to the patient.

Pressing down on the cannister releases a defined metered volume through the actuator mouthpiece. The associated drop in pressure triggers rapid propellant expansion driving aerosol formation and delivery. When downward pressure on the cannister is released, the metering valve refills to prepare the next dose for delivery. This refill, and any associated "priming" behaviour, can be influenced by timing and storage orientation.

Actuation-related variability is generally greater for suspensions than solutions; solutions are inherently homogeneous, whereas suspensions may settle or cream depending on the physicochemical properties of the drug and formulation. Although users are instructed to shake an MDI prior to use, there is typically no specific guidance on how to achieve consistent API dispersion. Key sources of variability include:

1. Shaking, and the time between shaking and firing
   - Shake speed, angle and duration
   - Delay between shaking and firing.

2. Metering valve refill and priming behaviour
   - Actuation force profile (force/time) applied to release the dose
   - Time between repeat actuations and whether it is sufficient to refill the metering chamber
   - Storage orientation during testing, which can influence drainage and loss of prime.

These mechanisms can affect critical quality attributes (CQAs), including:

- Total emitted dose (TED)
- API concentration in the TED relative to the intended homogeneous dispersion
- Aerosolisation dynamics and particle size distribution, influencing the respirable fraction.

Since these CQAs underpin product comparability assessments, controlling actuation conditions is central to robust MDI testing.

HOW AUTOMATED ACTUATION IMPROVES THE QUALITY AND VALUE OF TEST DATA

Published studies demonstrate that actuation-related variability can be significant. For example, a study of five commercially available MDIs reported that, for some products, delays of just 60 s between shaking and firing resulted in delivered doses ≥ 300% relative to the label claim (LC),[1] but only for some – not all – of the MDIs tested. Three produced excessively high delivered doses, one a sub-LC dose and the fifth, a solution-based MDI, showed no discernible change. Actuation-related variability can be both significant and difficult to predict.

In a controlled laboratory setting, training and aids such as timers and metronomes can improve repeatability. However, given the complex interacting mechanisms at play, manual actuation can introduce sufficient variability to obscure subtle but important product-related effects. Reduced sensitivity compromises the value of test data for:

- Understanding its susceptibility to individual aspects of the actuation technique
- Identifying strategies that reduce variability for different patient populations
- Confirming parity between test and reference products when interchangeability is the objective.

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"AUTOMATING ACTUATION REDUCES UNCONTROLLED VARIABILITY IN DOSE DELIVERY, ENABLING RIGOROUS DoE STUDIES. THE RESULTING DATA CAN SUPPORT OPERATOR TRAINING, INFORM INSTRUCTIONS FOR USE AND STRENGTHEN THE QUALITY OF REGULATORY SUBMISSIONS."

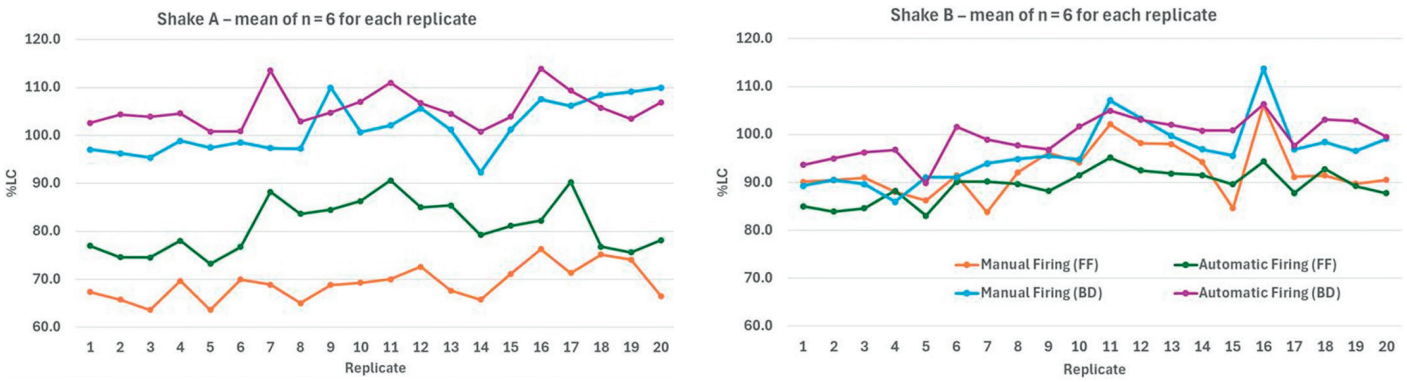

Figure 1: Through-life delivered dose data show that FF delivery is more susceptible than BD to shake, hold and fire variability (Shake A – left, Shake B – right). Shake B produces more consistent FF dose delivery closer to LC. (Originally presented at DDL 2025 and reproduced with kind permission of the authors.)

Automating actuation reduces uncontrolled variability in dose delivery, enabling rigorous design of experiment (DoE) studies. The resulting data can support operator training, inform instructions for use and strengthen the quality of regulatory submissions. The following case studies illustrate these benefits.

CASE STUDIES

Isolating the Impact of Human Factors in MDI Testing

This case study demonstrates how automated actuation improves MDI data quality – especially for suspension-based products – and differentiates shake profiles with respect to dose consistency, establishing a secure basis for operator training and test method development. Figure 1 summarises delivered dose uniformity results for Symbicort (AstraZeneca), a dual API MDI containing budesonide (BD) in solution and formoterol fumarate (FF) in suspension.[2] Tests were carried out using two different shake, hold and fire profiles – Shake A and Shake B (Table 1) – with both manual actuation and automated actuation using Copley Scientific's Vertus III+. Six MDIs were tested for each shake method (24 in total). Shots were collected at beginning (10), middle (5) and end of life (5) for each test.

These results show that the delivered dose of the BD solution was relatively insensitive to the applied shake, hold and fire profile. In contrast, the FF suspension was sensitive, with Shake B clearly preferable for delivering the LC. A proposed rationale for this is that the formulation is prone to creaming or foaming, with the susceptibility minimised by the shorter shake time and longer delay of the Shake B profile.

	Shake A	Shake B
Shake time	5 seconds	1 second
Wait time	None	3 seconds
Actuation time	2 seconds	2 seconds

Table 1: Shake, hold and fire profiles for Shake A and Shake B. (Originally presented at DDL 2025 and reproduced with kind permission of the authors.)

For FF using Shake A, manual actuation produces greater variability and a shift in mean relative to automated actuation (Figure 2). This suggests that the Shake A parameters are not robust for this product. With the Shake B parameters, the manual and automated data were more closely aligned, but automation still produced tighter and more consistent data. Automation also reduced variability in the

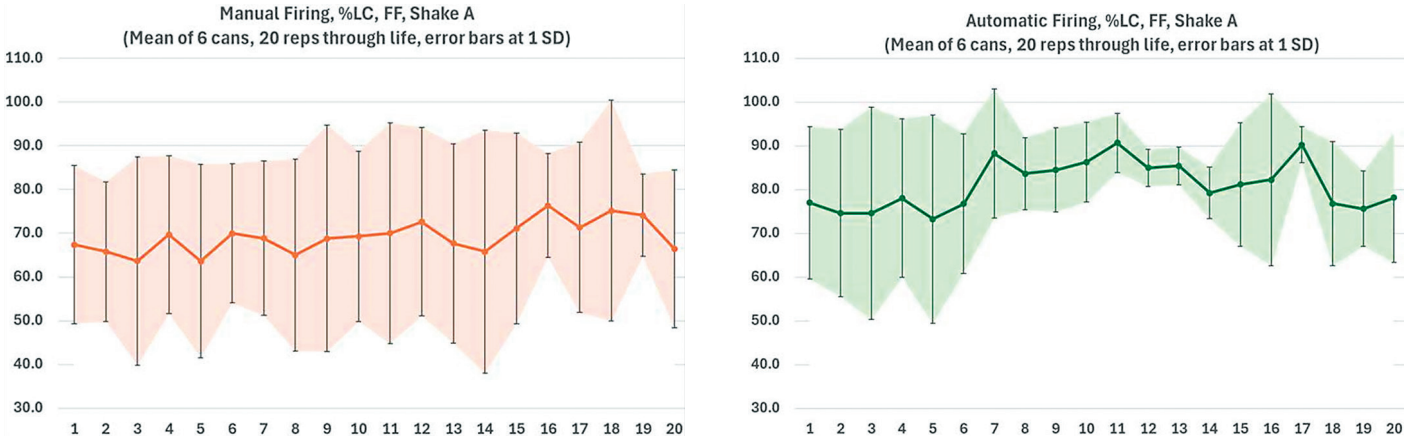

Figure 2: Under Shake A, automated actuation reduces the variability of the FF delivered dose relative to manual actuation, with tighter clustering around the mean. (Originally presented at DDL 2025 and reproduced with kind permission of the authors.)

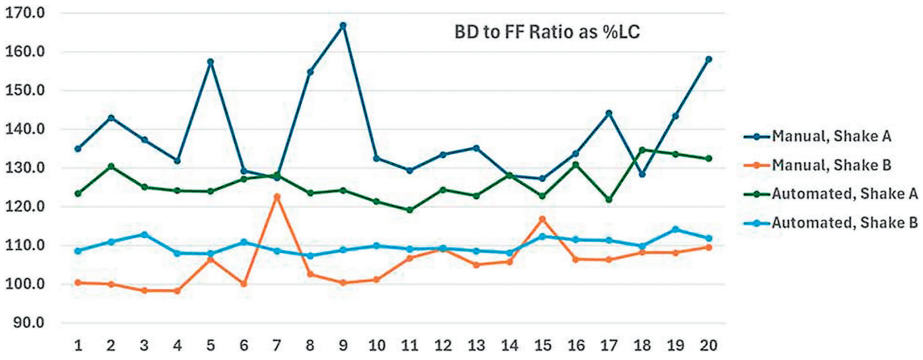

Figure 3: Automated actuation improves the consistency of BD:FF delivered dose ratio. (Originally presented at DDL 2025 and reproduced with kind permission of the authors.)

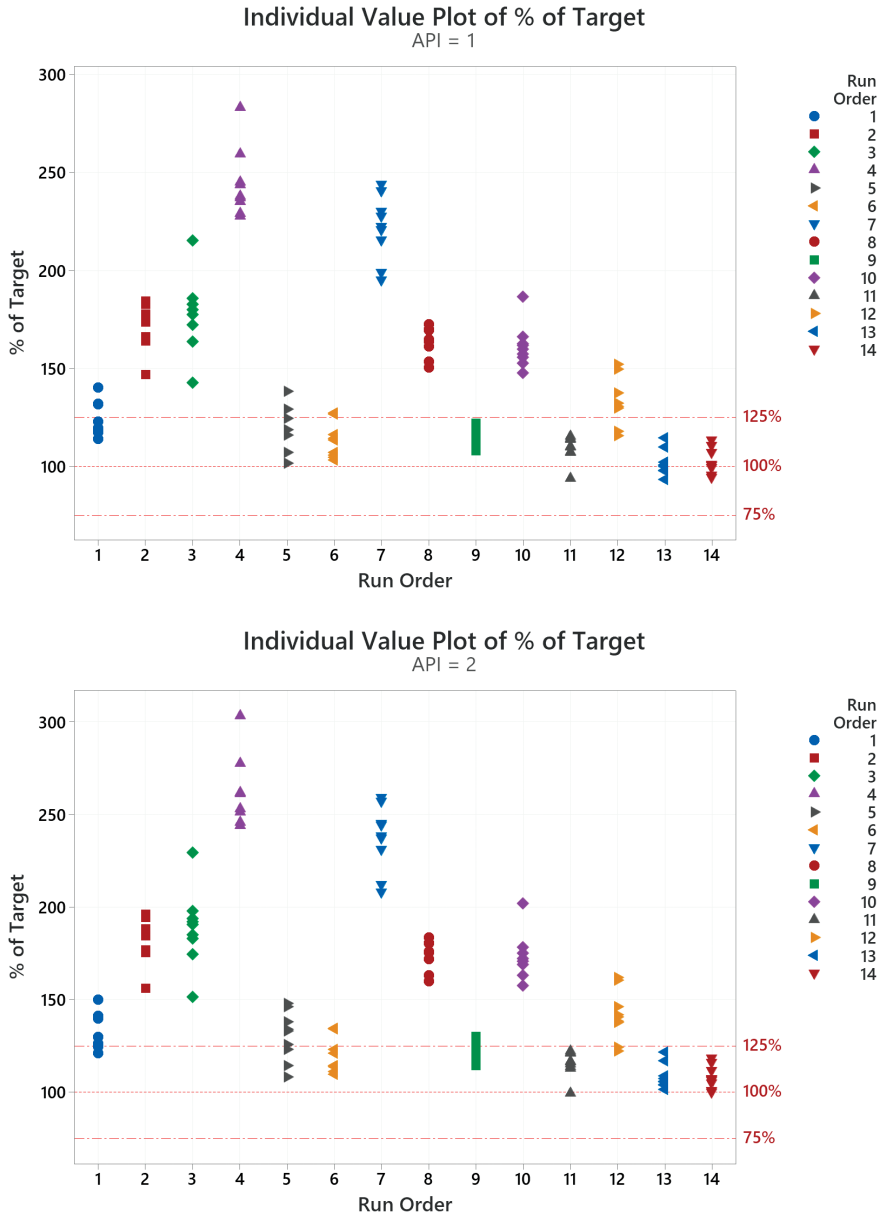

Figure 4: DoE results identify actuation conditions (runs 13 and 14) that produce delivered doses closest to LC for a novel low-GWP dual-active MDI (API 1 – top, API 2 – bottom). (Originally presented at DDL 2025 and reproduced with kind permission of the authors.)

BD data (data not shown), although to a lesser extent, which is consistent with the lower susceptibility of solution-based MDIs to actuation variability.

For this dual API product, the BD:FF ratio (Figure 3) can be a sensitive indicator of dispersion consistency. Under Shake B parameters, ratio consistency was strong, with a relative standard deviation (RSD) of 1.7%, while individual API RSDs were higher (7.2% RSD for FF, 6.8% RSD for BD). This suggests that, with Shake B, metered doses are close to homogeneous in composition, with both APIs trending together.

A key conclusion from this study is that automated actuation in combination with an optimal actuation profile (Shake B) is an effective way of reducing variability to ensure robust testing and enable the study of inherent variability relating to device metering and product performance.

Assessing the Influence of Actuation Technique on Dose Delivery for a Low-GWP MDI

This case study demonstrates how automated actuation can be used to quantify the susceptibility of an HFA 152a-based MDI to variability in specific actuation parameters and to identify robust analytical methodologies to support early-stage product development. Figure 4 and Table 2 show data from a DoE study evaluating the impact of actuation parameters on dose content uniformity for each API from a dual-API, ethanol-free MDI formulated with HFA152a (a low-GWP propellant).[3]

Four parameters were investigated:

- Shake speed (1 or 2 Hz)
- Shake duration (5 or 10 s)
- Shake to fire delay (1, 2 or 3 s)
- Actuation hold time (0 or 1 s).

For each condition, three doses were collected from each of three devices at the beginning of unit life. Samples were collected into a standard dose uniformity sampling apparatus in accordance with relevant pharmacopoeial guidelines, using automated actuation for dose delivery (Vertus® +).

Runs 4 and 7 produced the highest delivered doses, exceeding 200% of LC

Standard Order	Run Order	Shake Speed (Hz)	Shake Duration (s)	Shake-to-Fire Delay (s)	Actuation Hold Time (s)
5	1	2	10	~2	1
7	2	2	5	~3	1
13	3	1	5	~2	1
12	4	1	5	~3	1
3	5	2	5	~3	0
9	6	2	5	~1	1
1	7	1	10	~3	1
10	8	1	10	~3	0
8	9	1	10	~1	0
4	10	1	10	~1	1
14	11	2	10	~2	0
6	12	1	5	~2	0
2	13	2	5	~1	0
11	14	2	10	~1	0

Table 2: DoE settings used to evaluate the impact of actuation parameters on dose content uniformity. (Originally presented at DDL 2025 and reproduced with kind permission of the authors.)

for both APIs. In contrast, runs 13 and 14 produced delivered doses closest to target at ~102% and ~108% of LC for API 1 and 2, respectively. Runs 13 and 14 shared a higher shake speed (2 Hz) and the shortest combined time for shake-to-fire delay (1 s) and actuation hold time (0 s). Differences relative to LC between the two APIs were consistent with differences in their density and, by extension, settling rate.

More generally, the study identified shake speed, shake-to-fire delay and actuation hold time as statistically significant factors for delivered dose, while shaking duration was not significant within the tested range. These findings are consistent with the practical expectation that vigorous shaking followed by immediate firing minimises the risk of settling in sedimenting formulations. Minimising hold time further improves dosing consistency by increasing the probability of sampling a more homogenous formulation prior to the next actuation.

A key observation is that the trends are driven by small timing differences, on the order of just 1 s. Executing this run order with that level of precision would be challenging using manual actuation; automated actuation therefore enables generation of method-development data that would be difficult to obtain reliably using manual actuation. For development programmes in which bioequivalence and comparability decisions depend on sensitive measurements, this can materially reduce risk.

STEP-BY-STEP TO THE BENEFITS OF AUTOMATION

For laboratory managers, the value of automation is usually measured in two ways: data quality and throughput. This article focuses on a single task – actuation – and shows how controlling actuation parameters reduces an avoidable cause of variability. However, with automation, the broader opportunity is cumulative; when repeatable actuation is combined with automation across additional steps and supported by connected data handling, laboratories can strengthen:

- Data integrity and traceability of test conditions
- Method robustness and transferability
- Speed and defensibility of OOS investigations.

In laboratories where dose variability leads to repeat testing or difficult investigations, controlling actuation is

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a logical first step. Establishing defined and documented actuation conditions removes a significant cause of variability and strengthens confidence in every result generated.

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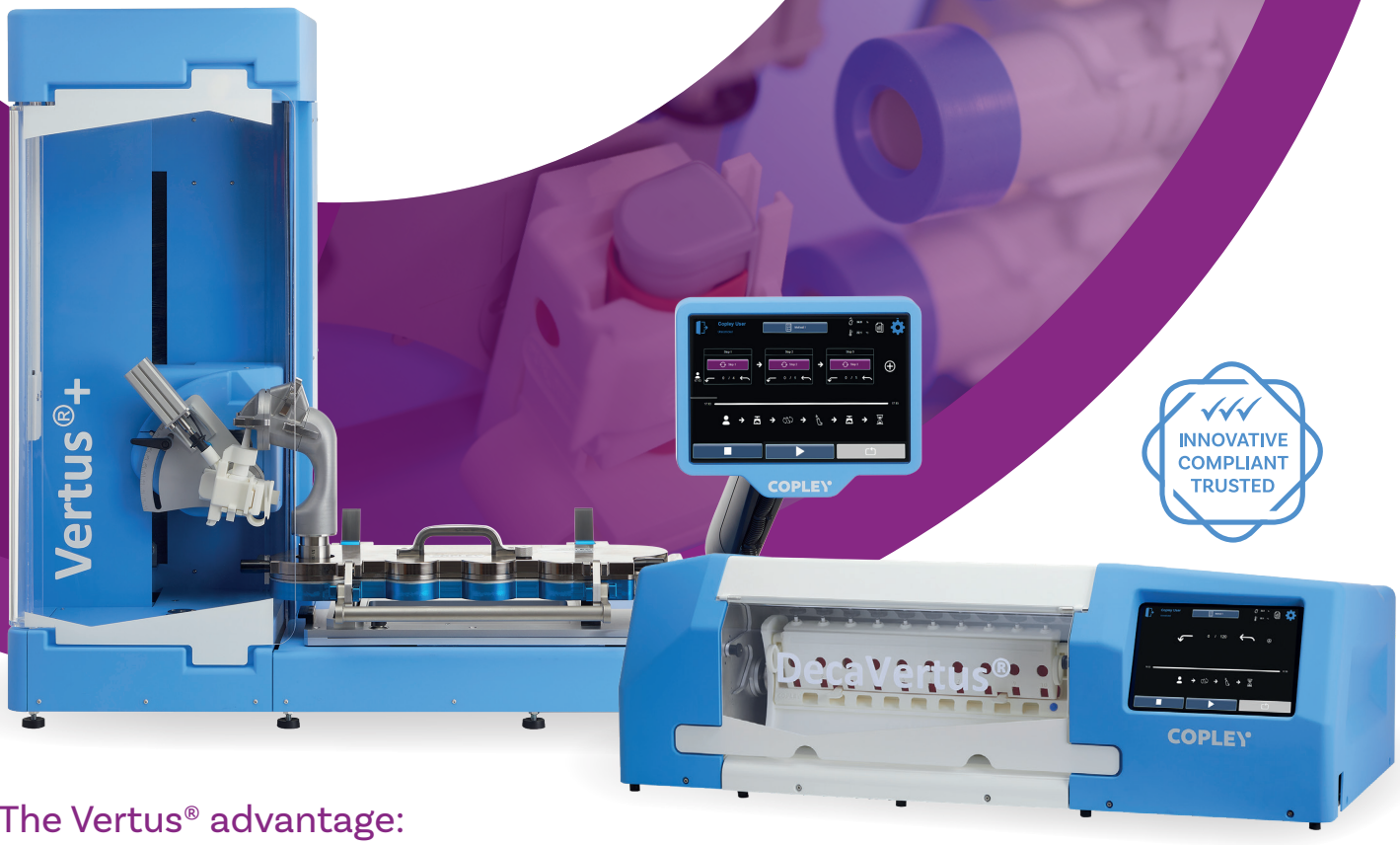

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