# Defining a Reproducible Reference Condition for "Immediate" Actuation in Low-GWP HFA-152a Albuterol Sulphate Suspension pMDIs

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## INTRODUCTION

- Suspension pMDIs begin re-sedimentation immediately after shaking stops.
- Delivered dose depends on the timing between shake completion, valve actuation, and aerosol discharge.
- Dose metering occurs when the valve returns to rest after discharge, requiring actuation timing to be defined.
- Shake–fire timing is rarely specified in in-vitro test methodologies, despite known dose sensitivity[1,2].

**Aim:** to define "immediate" actuation operationally using automated shake–fire actuation with sub-second acoustic and gravimetric measurements for HFA-152a suspension

## Acoustic Monitoring & Shot Weights

- Acoustic monitoring of valve actuation and plume emission was performed using a microphone (GY-MAX4466) within the actuator body; signals were analyzed using an RMS-envelope approach to identify shake cessation, valve actuation, plume onset, and plume termination.

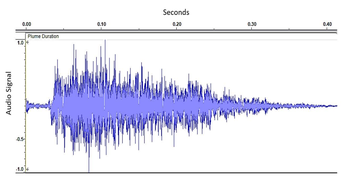


Figure 1; Example Plume Audio Signal from Test MDI; single actuation

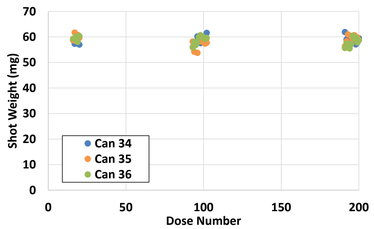


Figure 2; Through can-use life Shot weights for albuterol sulphate pMDIs

- Initial acoustic and shot-weight data were used to define a 500ms valve open time; all samples were quantified by validated HPLC.
- Shot weights were used to confirm complete metering-chamber evacuation as a function of valve open time.
- Combined acoustic, gravimetric, and delivered-dose measurements were used to define an operational "immediate" actuation condition (shots 1-10 from each MDI Tested).

## REFERENCES

[1] Hatley RHM, Parker J, Pritchard JN, von Hollen D. 'The effect of delay between shaking and firing on the delivered dose of suspension pressurised metered dose inhalers'. J Aerosol Med. Pulm. Drug Deliv. 2015;28(3):1–9.
[2] D'Angelo, D., Chierici, V., Quarta, E., Varacca, G., Cavalieri, L., Piraino, A., Melani, A.S., Sonvico, F. and Buttini, F. No-shaking and shake–fire delays affect respirable dose for suspension but not solution pMDIs. Int. J. Pharm. 2023, 631: 122478.
[3] Howlett, D. Determination and Improvement of patient's co-ordination with pMDI's. Drug Delivery to the Lung X, 1999, 104-106.

## METHODOLOGY

- Suspension pMDIs were actuated using the RockStar (OzUK Limited) fully automated shake–fire platform, providing precise control of shaking, actuation timing, actuation force, and dose collection (see Figure 4).
- Test MDIs delivering a nominal 120µg albuterol sulphate per actuation were manufactured at pilot scale (25Ltr vessel) and filled using Pamasol crimping and gassing equipment at H&T Presspart, UK.
- Devices comprised plasma-treated aluminium canisters filled with an albuterol sulphate suspension in HFA-152a, fitted with 63 µL Hybrid metering valves (Bespak, UK) and a standard actuator (0.50 mm orifice, 1.5 mm jet length, H&T Presspart).
- Samples were stored valve-down at 25°C / 60%RH for 18 months prior to testing.
- Prior to actuation, MDIs were shaken using a standardised protocol: ten continuous 180° inversion cycles (400ms inversion / 400ms return) with no dwell.
- Actuation was applied immediately after shaking, normal to the canister, using a pneumatic linear actuator (50N).
- Valve open time was independently controlled and set longer than the acoustically measured plume duration to avoid plume clipping.
- Delivered dose was measured using USP <601> dose uniformity sampling at beginning, middle, and end of can-use life.

## CONCLUSIONS

- "Immediate" actuation in low-GWP HFA-152a suspension pMDIs can be defined operationally using measurable physical criteria, rather than qualitative instruction alone.
- Automated shake–fire actuation combined with acoustic plume characterization establishes a reproducible temporal relationship between shake completion, valve opening, and aerosol emission.
- Plume duration provides a physical basis for selecting a valve open time sufficient to ensure complete dose emission without plume clipping.
- Under the defined conditions, aerosol emission and delivered dose were reproducible across can-use life.
- Explicit definition of shake–fire timing and actuation parameters is critical for robust in-vitro testing of suspension pMDIs and provides a practical, objective method for evaluating "immediate" actuation.

## RESULTS AND DISCUSSION

- Acoustic analysis showed that automated shake–fire actuation produced compact and highly repeatable aerosol plume emission immediately following completion of the final shake.
- Aerosol plume emission was fully contained within < 0.5 s following valve actuation (Figure 1).
- Plume duration was used to define the minimum valve open time required to ensure complete dose emission without plume clipping.
- A 0.5 s valve open time was selected as a conservative operational condition to ensure complete metering-chamber evacuation prior to capillary refill under the defined shake–fire conditions.
- Shot-weight measurements collected during delivered-dose testing were consistent across all three MDIs (Figure 2).
- Mean shot weight was 59 ± 1 mg (mean ± SD), confirming stable metered-mass discharge under the defined actuation conditions.
- Delivered dose measurements showed excellent consistency across can-use life (Figure 3).

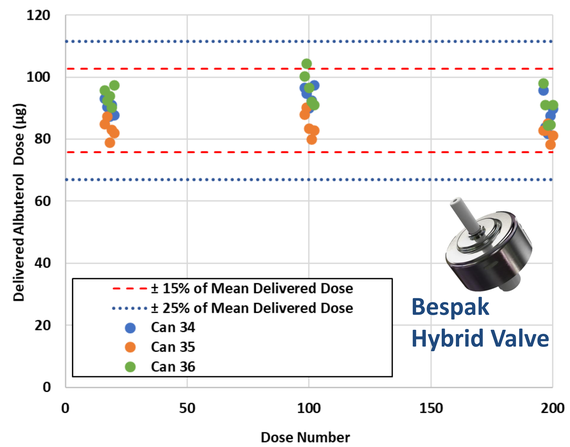


Figure 3; Albuterol delivered dose through can-use life actuated under defined "immediate" shake–fire conditions.

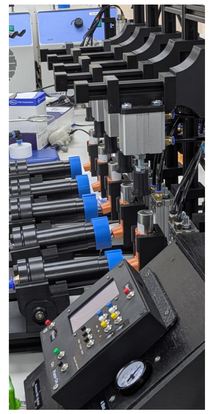

Figure 4; Rockstar Shake-Fire Hydra (5 Head System)

- Delivered dose was stable at beginning (BOL), middle (MOL), and end of life (EOL) for all three canisters.
- Mean delivered dose was 89 ± 6 µg (n = 45), with a range of 78–105 µg; all but one MOL measurement were within ±15% of the overall mean.
- Mean delivered dose at EOL was 97% of BOL, indicating minimal drift across can-use life.
- Mean metered dose was 98 ± 7 µg (n = 45), consistent with the nominal 100 µg dose.
- Together, acoustic plume timing, supported by gravimetric shot-weight and delivered-dose measurements, demonstrates that the defined shake–fire timing provides a reproducible reference condition for aerosol emission and consistent dose delivery across can-use life.