

# Acoustic pMDI Patient Guidance Device: Impact on Delivery

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**INTRODUCTION:** Inhaler technique training initiatives tend to focus on instructions, device familiarity, and the differences between inhaler types. Clearly this should be part of healthcare provider (HCP) interaction but it does not necessarily lead to instinctive and correct use-habits, irrespective of type or multiplicity of devices within a treatment regimen [1,2]. A two-year development program of a new inhaler training device has focused on providing a tool to promote correct habits. The device (Clip-Tone®, Clement Clarke International) is an acoustic training tool which can be used stand-alone in combination with a pMDI, but is optionally mobile health (mHealth)linkable. The device is also usable during routine inhaler use, providing a ‘permanent’ reminder of correct technique. Clip-Tone attaches to the top of the pressurized metered dose inhaler (pMDI) actuator and emits a guiding whistle sound through the 20-48 L/min flow range but is silent outside this range. The sound is sustained during maintenance of a steady inflow. The first device (Clip-Tone E) is available for use with Ventolin® Evohaler® (GSK) pMDI. Development work with additional pMDIs and other inhaler types is ongoing [3]. We present a summary of in vitro characterization research and two user studies: the objectives were to understand the effect of the new device on drug delivery spanning the flow rates at which the guidance whistle sounds and on inhaler technique, focusing particularly on the duration of the inhalation maneuver.

**METHODS:** In all experimental groups, Ventolin pMDI plus Clip-Tone E (Figure 1) was compared with Ventolin pMDI alone as control. Aerosol characteristics (n=5, five actuations) were determined by i2c Pharmaceutical Services (Cardiff, UK) using a Next Generation Impactor (NGI, Copley Scientific, Nottingham, UK) operated at 20 and 48 L/min and, in separate experiment, at 30 L/min (n=5; n=3 for pMDI alone).



**Figure 1.** Clip-Tone E attached to Ventolin Evohaler, and separately (enlarged).

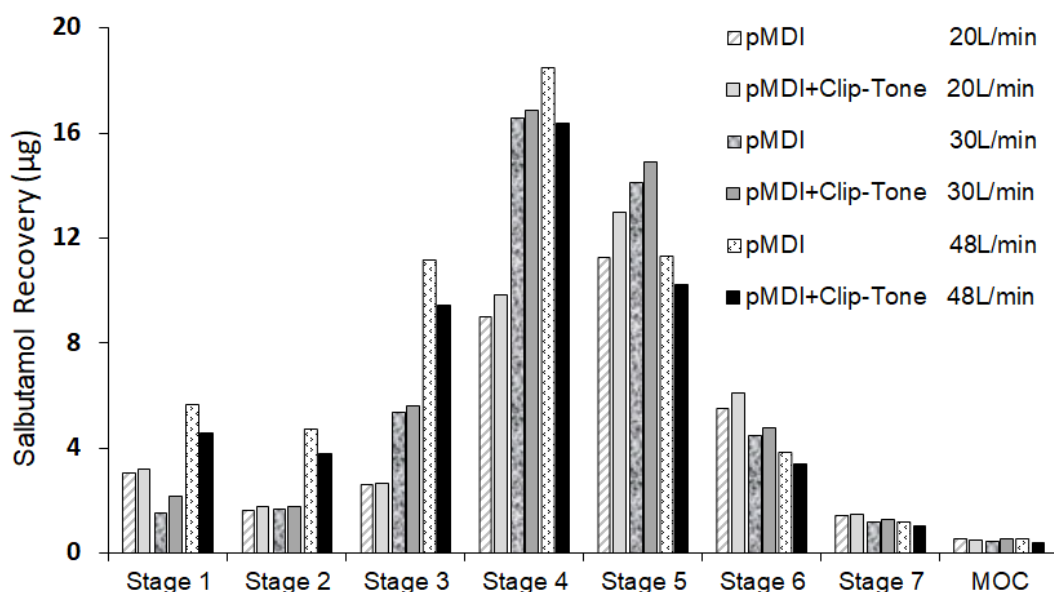
Standardized and validated preparation, chromatographic, and pharmacopeial procedures were followed [4]. Use of non-standard flow rates necessitated recalculation of NGI stage effective cut-off diameters. Within each flow rate the data were analysed using a two-sample Student's t-Test assuming unequal variances. Spray analysis sample images were taken and plume angle was assessed (Oz-UK Limited, Chippenham, UK, and Laboratory for Turbulence Research in Aerospace & Combustion, Monash University, Australia) using a Chronos 1.4 high speed camera (Kron Technologies, Inc.), Navitar, Inc MVL7000 zoom lens and a custom high-current pulsed LED module light source. pMDI mouthpiece air flow rate was measured 9mm downstream of the mouthpiece using a turbine rotameter. Plume angle tests (n=32 per group, 1,600 frames per second) comprised 800 width measurements for each of 2,400 images. Spray velocity tests (n=8 per group) comprised 12,500 images per test.

Two clinical investigations are on-going: pMDI inhalation duration (three efforts) in four groups of 25 volunteers (Beni-suef University, Egypt) [5] receiving: verbal use instructions (VI); VI plus a silent Clip-Tone; VI plus active Clip-Tone; or VI plus active Clip-Tone plus Clip-Tone Buddy development app (Clin-e-cal Limited, Manchester, UK), and a patient questionnaire following use of Clip-Tone with Clip-Tone Buddy which provides real-time visual feedback on coordination and duration.

**RESULTS:** For the in vitro studies, an audible whistle was detected at all flow rates. Comparing pMDI (control) with pMDI plus Clip-Tone E, within a flow rate, the addition of the device was without effect ( $p > 0.05$ ) on aerosol particle size distribution at 20, 30 and 48 L/min (Figure 2). Recovery of salbutamol from Clip-Tone was determined alongside other NGI recoveries and, not unexpectedly owing to the actuator-top location of the device, was either not applicable (control) or, when used, below the limit of detection. Similarly, metered (product label claim ex-valve 100 $\mu$ g salbutamol [120 $\mu$ g salbutamol sulfate]) and emitted doses, and fine particle fraction and fine particle dose were not significantly different (Table 1). Spray analysis images were not dissimilar. Mean plume angle and spray velocity for pMDI was  $10.2^\circ \pm 4.8$  and  $64.6 \pm 4.9$  m/s respectively; and for pMDI plus Clip-Tone  $11.5^\circ \pm 5.7$  and  $63.8 \pm 6.7$  m/s.

Mean inhalation duration of subjects receiving instruction-only was 6.79 seconds. 24 subjects achieved a duration of  $\geq 5$  seconds; one failed to achieve 3 seconds, with inter- and intra-subject variability (standard deviation) of 2.62 and 1.01, respectively. Inhalation duration of subjects receiving instruction plus use of Clip-Tone was 5.2

seconds. All 25 achieved  $\geq 5$  seconds with none falling below 3 seconds. Variability decreased to 1.45 and 0.39, respectively.



**Figure 2.** Salbutamol aerosol particle size distribution for NGI Stages 1-7

	20 L/min		30 L/min		48 L/min	
	pMDI	pMDI + Clip-Tone	pMDI	pMDI + Clip-Tone	pMDI	pMDI + Clip-Tone
Metered dose (µg)	118.6±6.7	120.2±4.8	93.9±4.7	98.0±5.1	119.4±16.1	103.6±4.0
Emitted dose (µg)	100.7±6.2	103.6±4.7	82.6±5.0	86.0±3.8	105.7±14.3	91.6±4.1
Fine particle fraction (%<5µm)	27.5±2.0	30.0±1.7	48.9±1.3	48.2±1.6	43.8±2.9	44.9±1.6
Fine particle dose (µg<5µg)	27.8±3.5	31.0±2.0	39.8±1.9	41.5±2.5	46.3±7.1	40.9±3.1

**Table 1.** Aerosol characteristics at 20, 30 and 48 L/min flow rate.

The questionnaire focused on use of digital solutions, not use of Clip-Tone plus app *per se*, and suggested that both HCP and peer recommendation are influential to acceptance of a digital solution. Use would need to be associated with feeling better, and negative comments were linked to the time it took to undertake the process.

Positive commentary included “It is good the way it tries to get you to breathe in for longer ...” and “... I can see the benefits in using this in order to show/teach someone how to use their inhalers correctly, particularly as it was able to show me how badly I was using mine”.

**CONCLUSIONS:** Although pMDI inspiratory advice and pharmacopeial measurement are standardized to 30 L/min, users rarely achieve such conformity. It was important to understand any Clip-Tone effects (despite being actuator-mounted) across a range of flow rates on aerosol distribution, characteristics, and the plume. In the current research, it was without effect. Differences in emitted dose of Ventolin control (target 100 $\mu$ g, actual range 82.6 – 105.7 $\mu$ g) were possibly due to Ventolin batch variability: the 30 L/min data originating from separate testing, nevertheless the data for Ventolin with Clip-Tone showed lower differences within this range (86.0 – 103.6 $\mu$ g). In addition pMDI emitted dose is not determined by flow rate unlike, for example, with a dry powder inhaler. Induction port recovery was also greatest at 20 L/min flow (data not shown), with comparatively lower fine particle dose and fraction. This was not thought clinically relevant; the dose being sufficient for clinical effect, which is understood to start from 20 $\mu$ g [6].

The early user data suggest that technique conformity was building, with adequate but less variable inhalation duration maintained when Clip-Tone use accompanied verbal instruction. Separately, patient experience was largely positive, but indicative of a required link between routine use and perceived patient benefit. These data support the role of Clip-Tone as a patient guidance tool that does not compromise dose delivery, and is therefore suitable for day-to-day use in situ on the pMDI. Future

research is exploring smartphone detection of the acoustic signal with a view to adherence monitoring.

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**REFERENCES:**

1. Lavorini F, Levy ML, Corrigan C, Crompton G, on behalf of the ADMIT Working Group: The ADMIT series – Issues in inhalation therapy. 6) Training tools for inhalation devices. *Prim Care Respir J* 2010, 19: 335-41
2. Hanania NA, Braman S, Adams SG, Adewuya R, Ari A, Brooks JA, Mahler DA, Ohar JA, Peters J, Sanjar S: The role of inhalation delivery devices in COPD: Perspectives of patients and health care providers. *J COPD Foundation* 2018, 5: 111-23
3. Sanders MJ: Whistles and apps: enabling low-cost objective feedback of inhaler use. In *Respiratory Drug Delivery Asia 2018. Volume 1*. Edited by Dalby RN, Peart J, Young PM, Traini D. DHI Publishing, River Grove IL: 2018: 155-66.
4. Sanders M, Johnson R, Young P, Duke DJ, Honnery D, Tran C: Understanding flow rate influence on Clip-Tone guided inhaler delivery. In *Drug Delivery to the Lungs 2019*. The Aerosol Society. Edinburgh, Scotland, UK: 2019: Poster #1. *J Aerosol Med Pulmon Drug Del* 2020; in press.
5. Wael W, Sanders MJ, Hussein RRS, Sarhan RM, Ramadan W, Abdelrahim ME: The effect of Clip-Tone® and its smartphone application on continuous optimization of inhalation technique of metered dose inhalers. Submitted to *Journal* 2019 (to be advised).

6. Fink JB: Metered-dose inhalers, dry powder inhalers, and transitions. *Respir Care* 2000, 45: 623-35.