# Can a Mixing Inlet Interposed Between a Pressurized Metered Dose Inhaler-Spacer Combination and Cascade Impactor Enable Effective Performance Testing at Widely Different Inhalation Flow Rates?

Mark W. Nagel[1], Jason A Suggett[1], Rubina Ali[1], and Jolyon P. Mitchell[2]
1 Trudell Medical International, London, Ontario, Canada; 2 Jolyon Mitchell Inhaler Consulting Services Inc., London, Ontario, Canada

## SUMMARY

**The MI-NGI combination was in good agreement with the NGI at 30 L/min for almost all measures.**

## CLINICAL BACKGROUND

1. Multi-stage cascade impactors (CIs) are used to characterize of emitted aerosol aerodynamic particle size distribution (APSD) from orally inhaled products (OIPs).[1,2]
2. The Next Generation Impactor (NGI) [3] operates at 15 L/min [4] and between 30 and 100 L/min[5]
3. The low flow Marple-Miller impactor (MMI) was developed primarily to enable low flow rate characterizations at 4.9 and 12.0 L/min in support of delivery devices for infants and small children.[6]
4. The Miller design of mixing inlet (MI)[7] is located between the mouthpiece of the OIP-on-test connected to the induction port and the NGI.
   - The MI allows the CI to operate at an optimum flow rate for the inhaler on test.
   - The flow rate leaving the inhaler can be reduced for pediatric device testing by adding a fixed flow rate of clean make-up air less than that required by the CI via its sidearm.[8]

## STUDY PURPOSE

The primary purpose of our study was to discover whether a Miller MI used in conjunction with an NGI could be used to evaluate a pMDI with spacer add-on device at 30 L/min and at sampling flow rates comparable with those for the low flow MMI.

## MATERIALS AND METHODS

- A purpose-built tube spacer was used in conjunction with the albuterol pMDI as a common aerosol source to enable equal comparison of the different equipment configurations to be made with an add-on device present.
- Ventolin* (GSK, Canada) pMDIs delivering 100 µg albuterol base equivalent ex valve per actuation were fitted to the spacer exit (ca. 149 ml) as shown in Figure 1.
- Replicate measurements (n = 5) were made at each sampling condition
- We first made baseline APSD measurements with the spacer mouthpiece attached directly to the NGI via a USP/PhEur induction port, sampling from the inhaler-spacer at 30 L/min determined by mass flowmeter (model 4040, TSI Inc., St. Paul, MN).
- We then as sampled at 4.9 and 12 L/min via the low flow MMI connected directly to the spacer mouthpiece via a USP/PhEur induction port
- Finally, with the MI interposed between the inhaler-spacer and NGI whose flow rate was fixed at 60 L/min, we sampled from the spacer at 4.9, 12, and 30 L/min in separate measurements.
- A supply of compressed air was fed to the MI sidearm so that the nominal flow rate measured by a mass flowmeter located at the entry to the MI could be adjusted to the desired sampling flow rate
- The mass of albuterol recovered from the induction port and each Brij-35 surfactant-coated cup of the NGI or low flow MMI was subsequently determined by a validated UV-HPLC method.

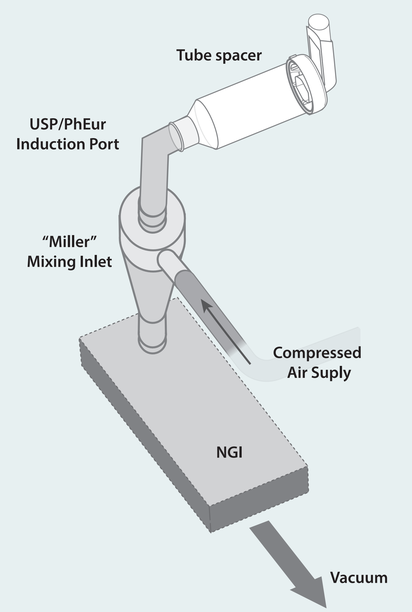


**Figure 1: pMDI-Tube Spacer Configuration Shown with MI-NGI Configuration**

## DISCUSSION

1. Mass balances at all sampling conditions were close to the expected value of 100 µg albuterol/actuation, indicating minimal losses had occurred within each of the sampling arrangements.
   - $TM_{exHC}$ sampling via the low flow MMI at 4.9 L/min (27.2 ± 5.1 µg/actuation) and 12 L/min (40.5 ± 8.2 µg/actuation) were lower than equivalent values using the NGI-MI combination (32.3 ± 4.8 and 50.9 ± 5.0 µg/actuation) [2-tailed, un-paired t-test at each flow rate, p ≥0.04).
     - Larger internal losses in the low flow MMI may explain the divergence.
   - $TM_{exHC}$ (MI-NGI combination, 53.7 ± 3.5 µg/actuation) agreed with the corresponding values using the NGI alone (56.0 ± 3.9 µg/actuation) [un-paired t-test, p = 0.35], confirming that losses in the MI were minimal.
2. $FPM_{<4.7\mu m}$ sampling via the low flow MMI at either 4.9 L/min (22.3 ± 4.3 µg/actuation) or 12 L/min (34.4 ± 7.8 µg/actuation), were equivalent to $FPM_{<4.5\mu m}$ using the MI-NGI (27.7 ± 3.8 (4.9 L/min) and 43.4 ± 4.3 (12 L/min) µg/actuation respectively) [p≥0.054].
3. Low-flow MMI-derived values of $FPF_{<4.7\mu m}$ at 4.9 L/min (91.9 ± 1.7%) were close to $FPF_{<4.5\mu m}$ using the MI-NGI combination at 12 L/min (91.2 ± 1.4%) [p = 0.31].
   - The cause of the small divergence observed at 12 L/min (88.9 ± 0.8 low-flow MMI), compared with the NGI-MI combination (92.4 ± 0.6%) [p <0.001], may be linked to the lower upper limit for fine particles in the low flow MMI data.
4. FPM<4.5 µm at 30 L/min using the MI-NGI (43.9 ± 3.3 µg/actuation) was comparable with FPM<4.0 µm obtained by the NGI alone (45.9 ± 4.1 µg/actuation), consistent with the findings for $TM_{exHC}$ (p = 0.42).
   - Likewise, FPF<4.5 µm (87.6 ± 0.7%) determined by MI-NGI concurred with FPF<4.0 µm) obtained directly by the NGI (85.9 ± 2.6%) [p = 0.14].
5. Importantly, estimated values of MMAD by interpolation of FPF values for the two stages either side of the median FPF associated with all the MI-NGI measurements ranged from 2.5 to 2.7 µm
   - This range was consistent with MMAD values from the low-flow MMI.
6. Spread factors determined for all sampling conditions were within 1.7 ± 0.05.

## RESULTS

- Total recovered mass of albuterol (n = 5 replicates/condition) are presented in Table 1.

**Table 1: Mass Balances for pMDI-Spacing Tube-Delivered Albuterol (mean ± SD) Sampling via Low Flow MMI, NGI alone and NGI-MI**

* Includes the mass recovered from the mouthpiece of the pMDI and the spacer interior

| Sampling Condition | Low Flow MMI | | MI+NGI | | | NGI |
|---|---|---|---|---|---|---|
| Flow rate through CI (L/min) | 4.9 | 12 | 60 | | | 30 |
| Entry flow rate (L/min) | | | 4.9 | 12 | 30 | |
| Total recovered* mass (µg/actuation) | 95.3 ± 4.8 | 102.7 ± 6.7 | 100.4 ± 4.7 | 104.4 ± 4.3 | 100.5 ± 1.1 | 101.6 ± 4.0 |

- CI-derived measures of total mass ex VHC ($TM_{exHC}$), fine particle mass (FPM), fine particle mass fraction (FPF) and the individual upper bound sizes for fine particles are summarized in Table 2.
- We did not interpolate FPM and FPF to a fixed upper bound size to preserve the statistical information available from the measured values at each sampling condition.
- However, the cut-point size of the CI stage for each condition was chosen to be as close as possible to 5 µm aerodynamic diameter, as specified in the European Pharmacopoeia.[2]
- We determined MMAD values by interpolation as the size corresponding to the 50th percentile of the cumulative mass-weighted APSDs.

**Table 2: CI-Derived Measures for pMDI-Spacing Tube-Delivered Albuterol (mean ± SD) Sampling Directly via Low Flow MMI, by NGI alone and NGI-MI**

| Sampling Condition | Low Flow MMI | | MI+NGI | | | NGI |
|---|---|---|---|---|---|---|
| Flow rate through CI (L/min) | 4.9 | 12 | 60 | | | 30 |
| Entry flow rate (L/min) | | | 4.9 | 12 | 30 | |
| TMexHC (µg/actuation) | 95.3 ± 4.8 | 102.7 ± 6.7 | 100.4 ± 4.7 | 104.4 ± 4.3 | 100.5 ± 1.1 | 101.6 ± 4.0 |
| Upper limit for FPM (µm) | 27.2 ± 5.1 | 40.5 ± 8.2 | 32.3 ± 4.8 | 50.9 ± 5.0 | 53.7 ± 3.5 | 56.0 ± 3.9 |
| FPM (µg/actuation) | 4.7 | 4.7 | 4.5 | 4.5 | 4.5 | 4.0 |
| FPF (%) | 91.9 ± 1.7 | 92.4 ± 0.6 | 91.2 ± 1.4 | 88.9 ± 0.8 | 87.6 ± 0.7 | 85.9 ± 2.6 |
| MMAD (µm) | 2.6 | 2.7 | 2.5 | 2.5 | 2.5 | 2.4 |
| Spread Factor | 1.7 | 1.7 | 1.7 | 1.7 | 1.7 | 1.7 |

- We found that all APSDs were unimodal but deviated sufficiently from lognormality, especially for the 4.9 L/min sampling flow rate conditions.
- We therefore calculated a spread factor from the square root of the 80th to 20th mass percentiles as an alternative measure to compare APSD spread.

## CONCLUSIONS

1. The MI-NGI combination was in good agreement with the NGI at 30 L/min for almost all measures.
2. FPM values using the NGI-MI sampling either at 4.9 or 12 L/min, were slightly greater than equivalent results via the low flow MMI,
   - This outcome is likely unimportant for predicting OIP performance
3. We conclude that the MI-NGI combination can be used as an alternative for the low flow NGI, as well as for measurements sampling from the inhaler at 30 L/min, with the NGI operating at 60 L/min.

TRUDELL MEDICAL INTERNATIONAL

[1] US Pharmacopeial Convention, United States Pharmacopeia/National Formulary, 2026. Chapter <601>: Aerosols, nasal sprays, metered-dose inhalers and dry powder inhalers, USP, Rockville, MD, USA. 2 European Directorate for Quality of Medicines & Healthcare (EDQM). Monograph 2.9.18: European Pharmacopeia, Preparations for inhalation: Aerodynamic assessment of fine particles. 2026, 12th Edition, Strassburg, France. 3 Marple VA, Roberts DL, Romay FJ, *et al.* Next generation pharmaceutical impactor. Part 1: Design. J. Aerosol Med. 2003; 16(3): 283-99. 4 Marple VA, Olson BA, Santhanakrishnan K, *et al.* Next generation pharmaceutical impactor: A new impactor for pharmaceutical inhaler testing. Part III. Extension of archival calibration to 15 L/min. J. Aerosol Med. 2004; 17(4): 335-43. 5 Marple VA, Olson BA, Santhanakrishnan K, *et al.* Next generation pharmaceutical impactor. Part II: Calibration. J. Aerosol Med. 2003; 16(3): 301-24. 6 Olson BA, Marple VA, Mitchell JP, *et al.* Development and calibration of a low-flow version of the Marple-Miller Impactor (MMI™). Aerosol Sci Technol. 1998; 29: 307-14. 7 Miller NC. Apparatus and process for aerosol size measurement at varying gas flow rates. US Patent 2002; 6435,004-B1. 8 Olsson B, Borgström L, Lundbäck H, *et al.* Validation of a general in vitro approach for prediction of total lung deposition in healthy adults for pharmaceutical inhalation products. J Aerosol Med Pulmon Drug Deliv 2013; 26(6): 355-69.
MD-744A-0426 * trade marks and registered trade marks of Trudell Medical International (TMI). † trade marks of their respective companies. ©TMI 2026. All rights reserved.