In vitro bioequivalence evaluation of pMDI spacer devices

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Methods to Assess BioEquivalence of pMDI spacers

A series of aerosol size experiments using the NGI cascade impactor were undertaken to collect data on 2 MDI spacers (Space Chamber Plus and Compact Space Chamber Plus) along with the predicate spacer device (Trudell AeroChamber Plus Flow-Vu Anti-Static Valved Holding Chamber) in order to evaluate spacer equivalence and inter- and intra- variation of the test spacers in comparison to the predicate device. In addition, the pMDI used was also tested by itself without spacer device. The method used to prime spacers before the onset of testing followed manufacturers' guidance. The MDI spacers are each primed by washing in mild detergent followed by air-drying. The AeroChamber Plus Flow-Vu Anti-static Valved Holding chambers did not require priming, as per manufacturer's instructions.

A summary of pMDI aerosol testing using the NGI cascade impactor includes:

1. pMDIs primed according to manufacturer's recommendations prior to initial aerosol sizing experiments.
2. Aerosol was emitted from pMDIs and directed into the a NGI cascade either directly alone or directly through a test spacer.
3. Aerosol passing through the NGI impactor impacts on the impactor 'throat' – a right angled tube simulating the human throat – and subsequently passes through the throat into the body of the NGI impactor where aerosol deposits on the various stages on the basis of its aerodynamic size. There are a total of 7 impaction stages in the NGI, as well as an MOC (micro-orifice collector) stage and a final filter. Each of the stages has a 'cut-point' which describes the aerosol size collected for a given flow rate (both 15 or 30 L/min used in this work).
4. After collection, aerosol residue deposited in the throat, cascade stages, MOC and final filter were quantitatively desorbed using known volumes of appropriate HPLC mobile phase solution.
5. Quantification of the drug from each sample was undertaken by HPLC against known USP drug standards.
6. Results were processed into aerosol size distributions using proprietary SolAero Ltd software, from which relevant aerosol size parameters were extracted.

Regulatory guidance from the FDA and Canada teach that analysis and reporting of relevant aerosol size parameters should not include the residue found in the NGI impactor throat. The size fractions calculated and described in this report consider the aerosol collected within the NGI (i.e. stages 1-7, MOC and filter), but excluding the throat, as per FDA guidance. Size fractions and aerosol size parameters included:

a) Mass Median Aerodynamic Diameter (MMAD) for all size distributions interpolated from the Cumulative Undersize Distribution plot
b) Calculated Geometric Standard Deviation (GSD) for all MMADs interpolated from the cumulative undersize distribution GSD = $(d84.13/d15.87)^{0.5}$
c) Particle size fraction, %, greater than 4.7 µm
d) Particle Fraction (FPF, %) as cumulative size less than 4.7 µm
e) Particle Size Fraction % as cumulative size less than 1.0 µm
f) Particle Size Fraction % as cumulative size less than 0.5 µm

Calculated mean, SD, SEM and 95%CI for each set of 3 results for each pMDI as well as on each pMDI and spacer sample, and similarly for each set of n=9 composite results for each pMDI with all 3 spacer samples of the same design. In addition the 'total' amount of drug collected in the cascade impactor was calculated which *included* the amount collected in the throat.

An example of an aerosol size distribution is shown below

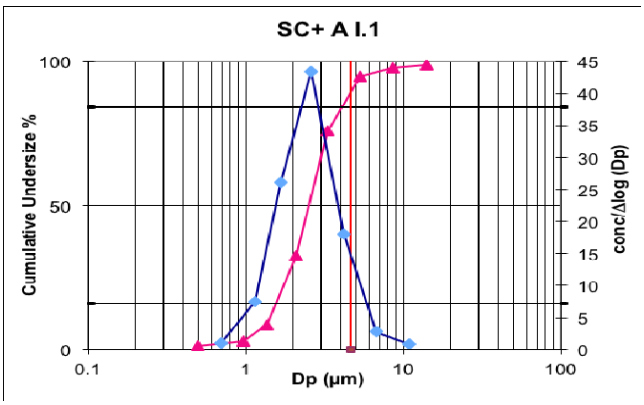

Figure 1 Aerosol Size Distribution. Data set obtained from a Salbutamol pMDI aerosol delivered through a primed MDI Spacer Chamber Plus device through an NGI cascade impactor at a 15 L/min flow rate.

Results of BioEquivalence of pMDI spacers

Comparative pMDI aerosol Size and Output Results obtained from repeat testing using the NGI cascade impactor at 15 L/min.

Device	Mean MMAD, um (95% CI)	Mean GSD of MMAD (95% CI)	Mean total delivered dose, ug (95% CI)	Mean total respirable (0.5-4.7 um) dose, ug (95% CI)	Mean respirable fraction PF% (95% CI)	mean total delivered dose as % of dose actuated from valve	mean total respirable dose as % of dose actuated from valve
Ipratropium Bromide							
Ipratropium Bromide pMDI	0.7 (0.1)	NA*	93.55 (2.26)	51.14 (2.8)	54.7 (1.7)	45.86%	25.07%
Space Chamber Plus	0.9 (0.1)	NA*	130.50 (4.06)	85.26 (3.3)	65.3 (0.9)	63.97%	41.79%
Compact Space Chamber Plus	0.8 (0.0)	NA*	105.34 (2.60)	65.19 (2.1)	61.9 (0.7)	51.64%	31.96%
Aerochamber Plus Flow Vu Anti-static	0.8 (0.1)	NA*	92.14 (3.34)	55.28 (3.0)	60.0 (1.8)	45.17%	27.10%
Albuterol							
Albuterol pMDI	2.6 (0.11)	1.8 (0.08)	435.50 (70.82)	347.1 (43.3)	79.7 (3.3)	80.56%	64.28%
Space Chamber Plus	2.5 (0.04)	1.7 (0.02)	333.28 (39.31)	286.9 (36.3)	86.1 (0.9)	61.72%	53.13%
Compact Space Chamber Plus	2.3 (0.05)	1.6 (0.02)	287.82 (43.45)	253.4 (38.7)	88.0 (0.6)	53.30%	46.93%
Aerochamber Plus Flow Vu Anti-static	2.4 (0.03)	1.6 (0.01)	333.74 (23.80)	292.2 (19.2)	87.6 (0.7)	61.80%	54.11%
Beclomethasone Dipropionate							
Beclomethasone dipropionate pMDI	1.4 (0.07)	2.3 (0.12)	282.06 (20.05)	218.12 (16.3)	77.3 (2.4)	58.76%	45.44%
Space Chamber Plus	1.3 (0.02)	2.0 (0.01)	396.83 (13.00)	328.05 (9.9)	82.7 (0.8)	82.67%	68.34%
Compact Space Chamber Plus	1.3 (NA^)	2.0 (0.03)	368.48 (14.05)	308.29 (12.7)	83.7 (1.0)	76.77%	64.23%
Aerochamber Plus Flow Vu Anti-static	1.3 (0.03)	2.0 (0.04)	376.99 (19.62)	316.25 (17.6)	83.9 (1.1)	78.54%	65.89%

Summary

We report a experimental design template and results of *in vitro* bioequivalence evaluation of 3 pMDI spacer devices tested with 3 pMDI drugs. Devices tested include MDI Space Chamber and Space Chamber Plus non-antistatic devices, and AeroChamber Plus Flow-Vu Anti-static device. We tested n=6 samples of each device in triplicate to obtain suitably robust statistical measures. Further, we tested 2 flow rates for NGI cascade impaction at 15 L/min and 30 L/min to approximate both child and adult inhalation rates. Normative and Cumulative aerosol size distributions were processed using validated SolAero Ltd software. From the cumulative size distributions, estimates of MMAD and GSD were calculated along with Respirable Fraction defined as aerosol within 0.5 to 4.7 µm size range. Results of aerosol size metrics were highly repeatable with low inter- and intra- variation. We conclude:

1. Experienced and skilled aerosol science technical support is important in order to obtain highly repeatable and accurate results.
2. *In vitro* bioanalytical data demonstrate the devices tested give comparable performance and are therefore interchangeable without the risk of delivering significantly different doses to the same patient were they to change device for another for ease of use due to patient choice reasons.