

APPENDIX D:

Calculation of Delivered Dose

Example of an alternate delivery system

Recent work[1] has been conducted to evaluate dose delivery from nebulizer systems having higher output than the English Wright. *In vitro* data suggest that tidal breathing from one high efficiency device, driven by a 50 psi dry gas source, would result in pulmonary deposition equivalent to two minutes from the English Wright in approximately 12 seconds. Because of concern that 12 seconds could lead to too much variability in the number of breaths, a comparative *in vivo* study done in children[2] was carried out using a 20 second time period. Data from that study showed that the PC₂₀ was approximately one doubling concentrations less for the high output delivery system compared to two minutes of tidal breathing with the English Wright. A recent study has confirmed these results in adults[3]. However, when the cumulative *dose* of methacholine required to cause a 20% fall in FEV₁, the PD₂₀, was calculated[2], the results using the two devices were virtually identical. In a reanalysis of this data, the PD₂₀ results calculated from the non-cumulative final step doses for the two devices were also virtually identical[4]. The step doses were the expected pulmonary dose delivered, based on the nebulizer performance *in vitro*, a Ti/Ttot ratio of 0.4 and the duration of breathing[1]. This demonstrates a major advantage of using the PD₂₀ as compared to the PC₂₀; that is, if the performance characteristics of the delivery systems are known, there should be little difference in the PD₂₀ calculated from one device or protocol compared to another. This is clearly not the case for the PC₂₀, which may give rise to error and confusion when devices or protocols other than those for which reference data exist are used. An example of calculating the dose steps based on device output is shown below.

For two minutes of tidal breathing from the English Wright:

With a 16 mg/mL solution, a filter at the “mouth” of a breath simulator collected 0.19 mg/min, all of which was carried in droplets < 5 µm so would be expected to deposit in the lungs if inhaled (a Respirable Fraction of 1). Hence, for 2 min breathing, the delivered dose would be:

$$0.19 \text{ mg/mL} \times 1 \times 2 = 0.38 \text{ mg (380 } \mu\text{g)}$$

and for other dilutions:

$$\text{Dose} = [\text{conc}(\text{mg/mL})/16 \text{ mg/mL}] \times 380 \text{ } \mu\text{g}.$$

For 20 seconds of tidal breathing from the high output device:

With a 16 mg/mL solution, the rate of a filter collection at the “mouth” was 2.70 mg/min with 76% in droplets < 5 µm. Hence for 20 seconds breathing 16 mg/mL, the delivered dose would be:

$$2.70 \text{ mg/min} \times 0.76 \times 20/60 \text{ min} = 0.68 \text{ mg (680 } \mu\text{g)}$$

and for other dilutions:

$$\text{Dose} = [\text{conc}(\text{mg/mL})/16 \text{ mg/mL}] \times 680 \text{ } \mu\text{g}.$$

If the only data available is the continuous output of the nebulizer carried in droplets $< 5 \mu\text{m}$, the output should be multiplied by a T_i/T_{tot} ratio of 0.4 to give the expected rate of pulmonary deposition during tidal breathing.

The same principles of dose calculation would apply to a dosimeter driven delivery system. If a dosimeter is used with tidal or submaximal inspirations, then the calculation requires output per actuation, fraction of the aerosol carried in droplets $\leq 5 \mu\text{m}$ and breath number.

[1] Coates AL, Leung K, Dell SD. Developing alternative delivery systems for methacholine challenge tests. *J Aerosol Med Pulmon Drug Deliv* 2014; 27: 66–70.

[2] Dell SD, Bola SS, Foty R, *et al.* Provocative dose of methacholine causing a 20% drop in FEV1 should be used to interpret methacholine challenge tests with modern nebulizers. *Ann Am Thorac Soc* 2015; 12: 357–363.

[3] El-Gammal A, Killian KJ, Scime TX, *et al.* Comparison of the provocative concentration of methacholine causing a 20% fall in FEV1 between the AeroEclipse II breath-actuated nebulizer and the Wright nebulizer in adult subjects with asthma. *Ann Am Thorac Soc* 2015; 12: 1039–1043.

[4] Coates AL, Dell SD, Cockcroft DW, *et al.* The PD20 but not the PC20 in a methacholine challenge test is device independent. *Ann Asthma Allergy Immunol* 2017; 118: 508–509.