# Supplemental Information

A: Lung deposition patterns

Lung deposition patterns were calculated using Mimetikos Preludium inbult deposition functions parameterized as in Table A1. Parameters were selected to represent a healthy subject inhaling at flow and particle size distribution ranges covering a typical product types on market (nebulizers, pressurized metered dose inhalers (pMDI's) and dry powder inhalers (DPI's)).

Table A1: Parametrization of Deposition model

Parameter	Value	Comment/Source
Lung Model	Weibel	[3]
Large conducting airways (BB)	Generation 0-8	[3]
Small conducting airways (bb)	Generation 9-16	[3]
Respiratory region (AI)	Generation 17-23	[3]
Functional Residual Capacity	3300 L	[4]
Deposition model (mouth-throat)	DeHaan	[1]
Deposition model (Lung)	NCRP	[2]
Bolus Volume	450 mL	
Tidal Volume	1500 mL	
Breath Hold	10s	
Inspiratory Flow	15-90 L/min	
Expiratory Flow	= Inspiratory Flow	
Mass Median Aerodynamic Diameter	1-6 µm	
Geometric Standard Deviation	2	
Coarse fraction	0%	

Figure A1 depicts the simulated lung deposition patterns expressed as the ratio of conducting airway dose Bb (BB+bb) over total lung dose (LD) (Figure A1A), and as the ratio of large conducting airway dose (BB) over small conducting airway dose (bb) (Figure 1B).
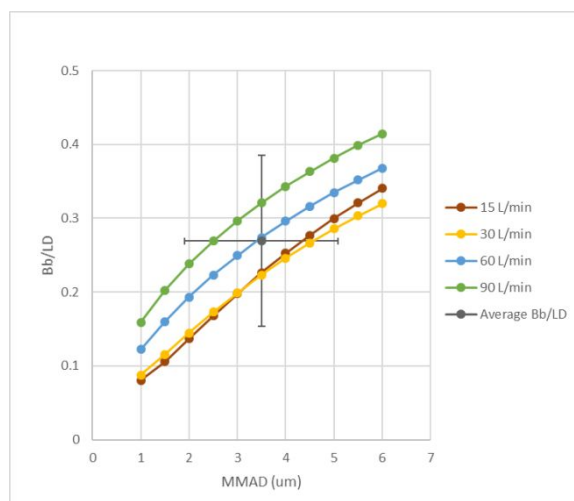
A   B
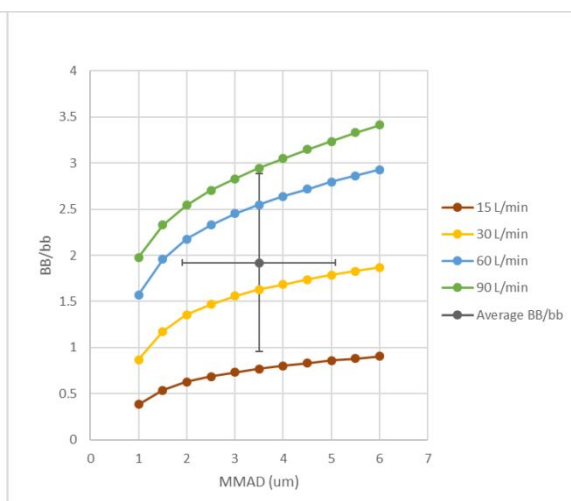
Figure A1: Simulated lung deposition expressed as conducting airway deposition over total lung deposition Bb/LD (**A**), and large conductiong airway deposition over small airway deposition BB/bb (**B**) as a function of the mass median aerodynamic diameter (MMAD) at inhalation flows ranging from 15 L/min to 90 L/min). The black marker represents the global arithmetic mean ± SD.

As expected, there is an increase in both total airway deposition (Figure A1A) and large airway deposition (Figure A1B) fractions as impaction of aersol increases with increased inhalation flow and MMAD. The average airway deposition is about 27% of the total lung deposition (Figure A1A) and it is roughly divided 2:1 between large and small airways (Figure A1B). However, given the attributes of real products on market, all combinations of MMAD and inhalation flow cannot be regarded as likely. For example, large MMAD's around 5-6 µm are normally associated with nebulizer products inhaled at tidal flows < 20 L/min), whereas low resistance dry powder inhalers inhaled at 90 L/min normally have MMAD's around 2-3 µm. For the purpose of understanding the sensitivity of the modelling outcomes to variations M_{Bb}/M_{Al} ratio, model outcomes were generated for all Cs, lung dose and P_{eff} combinations in Table 2 as the average of three different deposition ratios (4:6, 3:7 and 2:8), representing a range of deposition outcomes that includes the majority of the flow and MMAD combinations depicted in Figure A1A.

References

1. DeHaan, W.H.; Finlay. W.H. Predicting extrathoracic deposition from dry powder inhalers, *Aerosol Sci.* **2004**, *35*, 309-331.

2. NCRP Report 125: *Deposition, Retention and Dosimetry of Inhaled Radioactive Substances*, ISBN 0-929600-54-1: **1997**.

3. Weibel, E.R. *Morphometry of the human lung*. Springer, Berlin: **1963**.

4. Yu, C.P., Diu, C.K. A comparative study of aerosol deposition in different lung models. *Am Ind Hyg Assoc J.* **1982**, 43:54.

Supplemental Information

B: Dose, solubility and effective pulmonary permeability for some marketed drug products

Table B1 summarizes data on nominal doses, water solubility and effective permeability (P_{eff}) for some commercial inhaled medicines. The products selected are dry powder inhalers (DPI's), pressurized metered dose inhalers (pMDI's) or soft mist inhalers and as such the actual lung deposited doses are likely to be significantly lower than the nominal doses (<50%). Hence dose numbers for the lung ($Do_{,Lung}$) were calculated based on the assumption that the lung dose would be 50% of the nominal. This is likely to still result in an overestimation of the dose number. Data on aqueous solubility (PBS, pH7.4) and P_{eff} were sourced from literature. Aqueous solubility may be an underestimate of actual ELF solubility (given its high lipid content). Hence, the Do-numbers in table B1 may be overestimated. As can be seen from Table B1, calculated $Do_{,Lung}$ range from 1E-5 to 2.5E2 whereas P_{eff} values range from 0.5E-5 to 2E-8 cm^2/s.

Table B1: Nominal Dose, Solubility, Dose numbers and Permeability for Some Marketed Drug Products

Drug	Product[1]	Nominal Dose[1] (µg)	Aqueous solubility[2] (µg/mL)	Do[3]	P_{eff}[4] (E-6 cm^2/s)
Budesonide	Pulmicort Flexhaler	90	26.3[5]	0.17	5.2[6]
Fluticasone Propionate	Flovent Diskus	250	0.09[5]	139	3.8[6]
Fluticasone Furoate	Arnuity Ellipta	100	0.02[5]	250	3.5[6]
Mometasone Furoate	Asmanex HFA	100	0.26[16]	19.2	3.8[7]
Terbutaline	Bricanyl Turbuhaler	500	666000[8]	0.000038	1.4[6]
Vilanterol Trifenetate	Anoro Ellipta	25	33[9]	0.04	1.1[10]
Salbutamol Sulfate	Albuterol Sulfate HFA	90	17700[13]	0.00025	0.82[6]
Salmeterol Xinafoate	Serevent Diskus	50	107[14]	0.0234	0.86[6]
Tiotropium Bromide	Spiriva Handihaler	18	25000[15]	0.000036	0.55[6]
Ipratropium Bromide	Atrovent HFA	17	90000[12]	0.0000094	0.28[11]

1. Product information obtained from Drugbank https://go.drugbank.com/drugs/;
2. Solubility in phosphate buffered saline, pH 7.4
3. Do calculated as per Equation 4 in (main article) assuming lung lining fluid volume to be 10 mL [8] and lung dose to be 50% of nominal dose
4. Effective permeability across lung epithelium
5. Solubility in PBS pH 7.4 (Figure 2 in [7])
6. Effective permeability across lung epithelium as derived from isolated perfused rat lung [5]
7. Crim et al 2001, [2]
8. Encyclopedia of Toxicology (3rd Ed)[4]
9. Solubility in water as obtained from PubChem https://pubchem.ncbi.nlm.nih.gov/bioassay/483572#sid=103757352&section=Test-Results
10. Calculated from passive in vitro permeability (EMEA Assessment report Trelegy Ellipta), using Eriksson (2017) correlation to P_{eff}
11. Calculated from in vitro permerability [10], using Eriksson [5] correlation to P_{eff}
12. Taylor et al 2006, [11]
13. Marques et al. 1990., [9]
14. Johanna Eriksson , personal communication
15. FDA pharmacology review Spiriva Respimat [6]
16. Solubility in PBS pH 7.4 [8]

References

1. Berg, M.M.; Kim, K-J.; Lubman, R.L.; Crandall, E.D. Hydrophilic solute transport across rat alveolar epithelium. *J Appl Physiol.* **1989**, *66* (5), 2320-2327.

2. Crim, C.; Pierre, L.N.; Daley-Yates, P.T. A review of the pharmacology and pharmacokinetics of inhaled fluticasone propionate and mometasone furoate. *Clin Ther.* **2001** *23*(9), 1339-54.

3. EMEA Assessment report Trelegy Ellipta (2017), p40. https://www.ema.europa.eu/en/documents/assessment-report/trelegy-ellipta-epar-public-assessment-report_en.pdf

4. Encyclopedia of Toxicology, 3rd Edition - March 11, 2014, Editor-in-Chief: Philip Wexler, Academic Press Inc. (2014). ISBN: 9780123864543

5. Eriksson J, Sjögren E, Thörn H, Rubin, K, Bäckman P, Lennernäs H: Pulmonary absorption - estimation of effective pulmonary permeability and tissue retention of ten drugs using an ex-vivo rat model and computational analysis. *Eur J Pharmaceut Biopharmaceut* 2017, doi: https://doi.org/10.1016/j.ejpb.2017.11.013

6. FDA pharmacology review Spiriva Respimat (2015) https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM473565.pdf

7. Forbes, B.; Bäckman, P.; Christopher, D.; Dolovich, M.; Li, B.V.; Morgan, B.; In Vitro Testing for Orally Inhaled Products: Developments in Science-Based Regulatory Approaches. *The AAPS Journal*, **2015**, *17*, (4), () 837-852. https://doi.org/10.1208/s12248-015-9763-3

8. Hastedt, J.E.; Bäckman, P.; Clark, A.R.; Doub, W.; Hickey, A.; Hochhaus, G.; Kuehl, P.J.; Lehr, C.-M.; Mauser, P.; McConville, J. ; Niven, R.; Sakagami, M.; Weers. J.G. Scope and relevance of a pulmonary biopharmaceutical classification system AAPS/FDA/USP Workshop March 16-17th, 2015 in Baltimore, MD, *AAPS Open*, **2016**, 2, (1)

9. Marques, H.M.C.; Hadgraft, J.; Kellaway, I.W. Studies of cyclodextrin inclusion complexes. I. The salbutamol–cyclodextrin complex as studied by phase solubility and DSC. *International Journal of Pharmaceutics*, **1990**, *63*, 259–66,. https://doi.org/10.1016/0378-5173(90)90132-N

10. Panduga, V.; Stocks, M.J.; Bosquillon, C. Ipratropium is 'luminally recycled' by an inter-play between apical uptake and efflux transporters in Calu-3 bronchial epithelial cell layers. *International Journal of Pharmaceutics*, **2017**, *532*, (1), 328-336.http://dx.doi.org/10.1016/j.ijpharm.2017.08.112

11. Taylor, M.K.; Hickey, A.J.; VanOort, M. Manufacture, Characterization, and Pharmacodynamic Evaluation of Engineered Ipratropium Bromide Particles *Pharmaceutical Development and Technology.* **2006** 11, 321–36, http://doi.org/10.1080/10837450600769637