Clinically Relevant In Vitro Testing of Oral Inhalation Products Using Realistic Mouth-Throat Models

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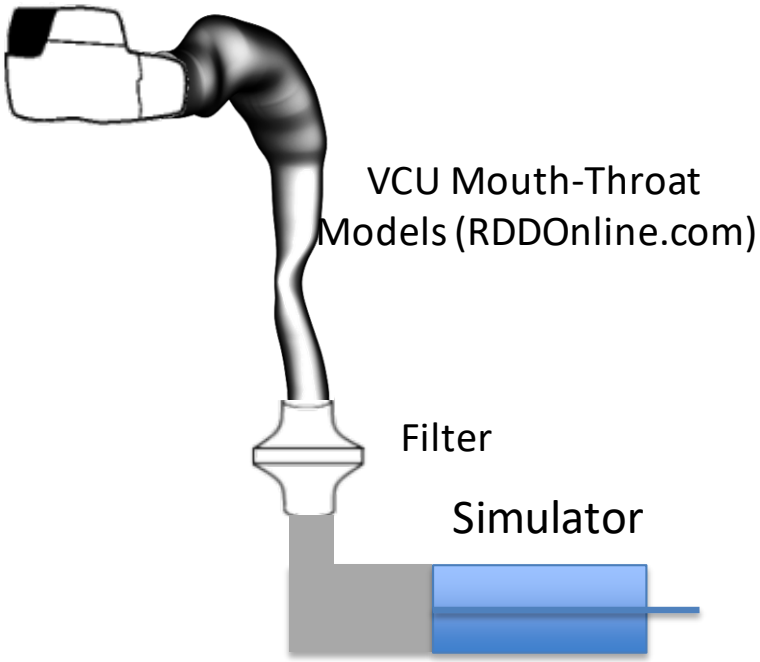
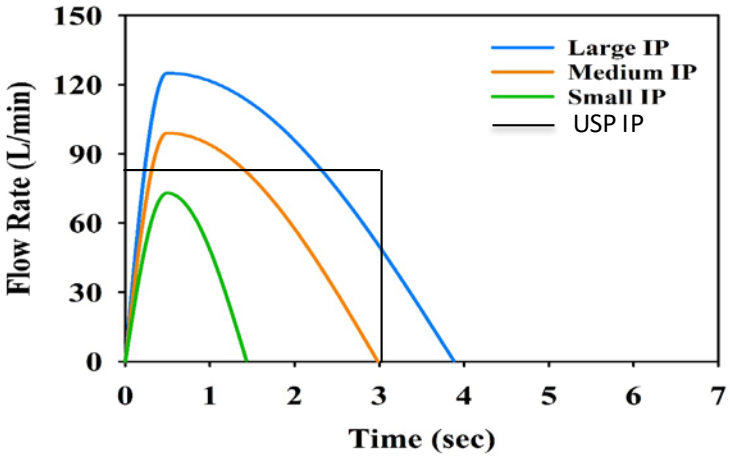
Clinically Relevant (Realistic) Testing

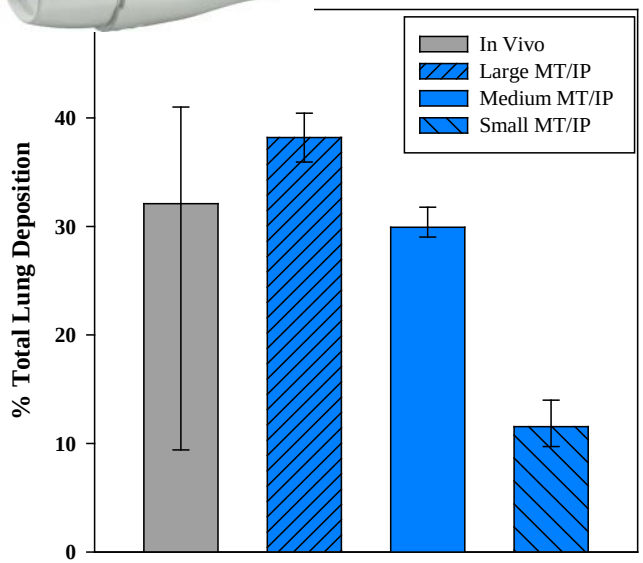


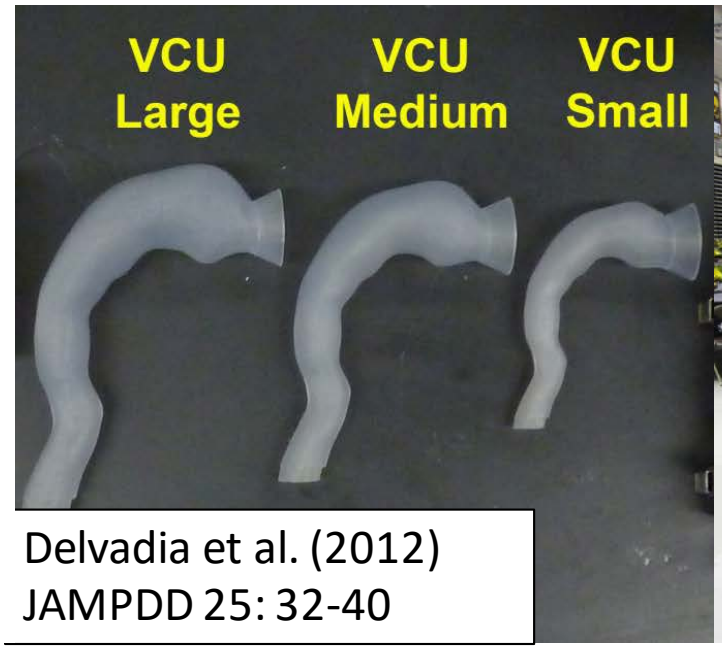


Andersen Cascade Impactor in QC Testing

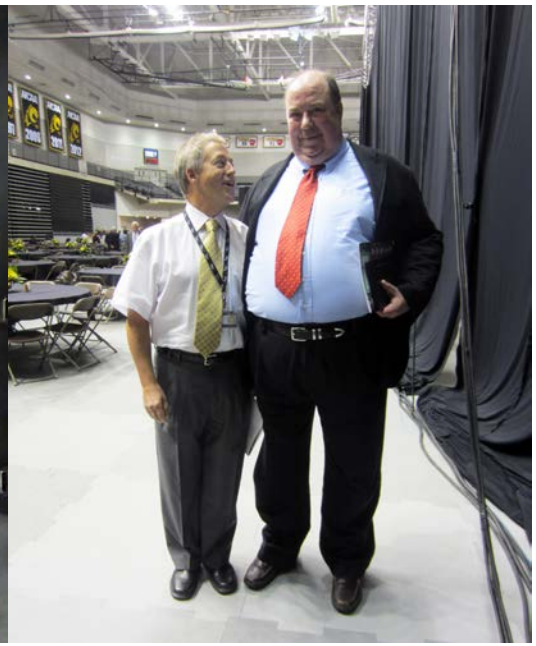
- Traditional inhaler QC testing tells little about clinical performance or the variability of lung delivery
- *Clinically-relevant in vitro test methods partner realistically-designed upper airway models with representative inhalation profiles (IPs;* Delvadia et al. JAMPDD (2016) 29, 196-206*) to characterize aerosol drug input conditions <u>at the trachea</u> by measuring* $\mathbf{TLD_{in\ vitro}}$ *and* $\mathbf{APSD_{TLDin\ vitro}}$

Budelin Novolizer: $TLD_{In\ Vivo}$ vs $TLD_{In\ Vitro}$



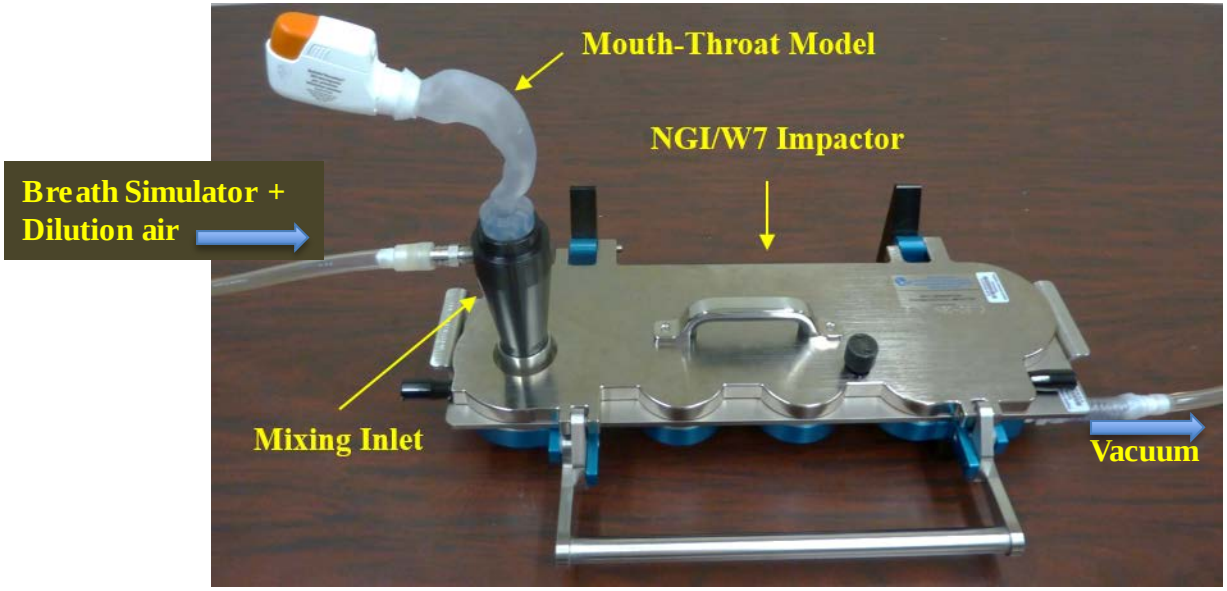


Delvadia et al. (2012) JAMPDD 25: 32-40



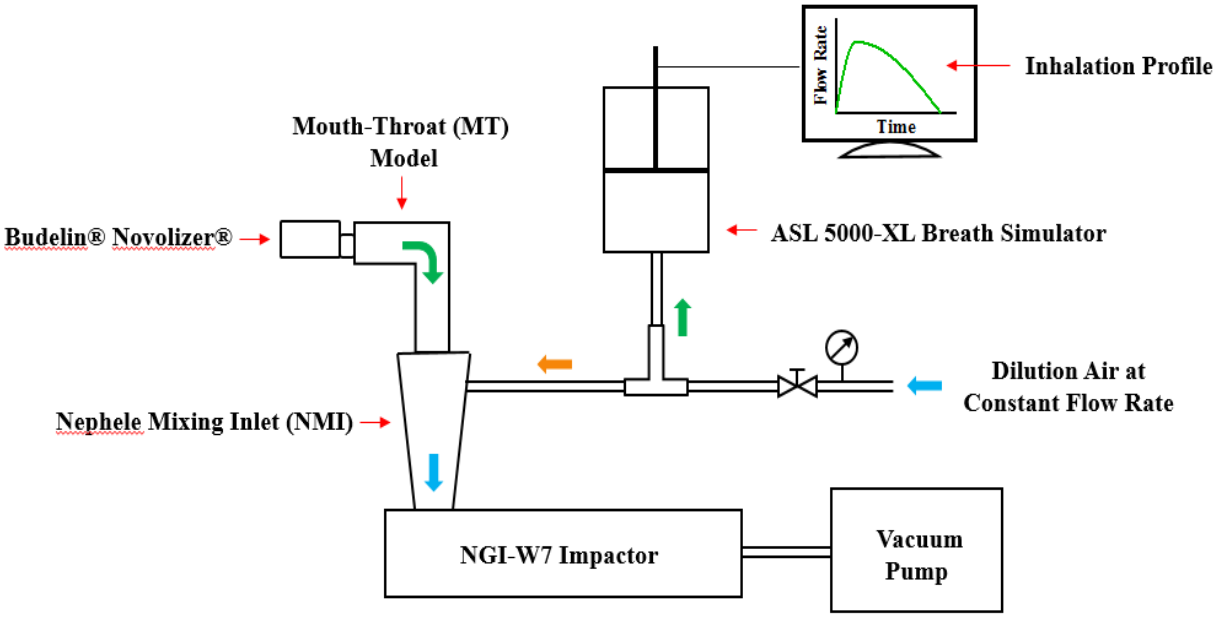
- In Vivo results [Scintigraphy, median & range; Newman, Eur. Resp. J. 2000,16: 178]
- VCU Large model paired with a simulated Newman "large profile"
- VCU Medium model paired with a simulated Newman "medium profile"
- VCU Small model paired with a simulated Newman "small profile"
  - In vitro methods utilize internally coated MT models; dimensions mimic variations in MT geometry & inhalation profiles in trained normals
  - How can we best estimate $APSD_{TLD\ in\ vitro}$ and its range in humans?

$APSD_{TLD\ in\ vitro}$ - NGI (constant flow) & DPI (variable flow) interfaced via the Nephele Mixing Inlet



- Cascade impactor (NGI) - constant flow controlled by vacuum
- Dilution air supplied to counterbalance vacuum flow
- Breath Simulator enables aerosol cloud to be withdrawn and sized using a realistic inhalation profile (IP)

NGI & NMI give TLD & APSD$_{TLD\ in\ vitro}$ for DPIs

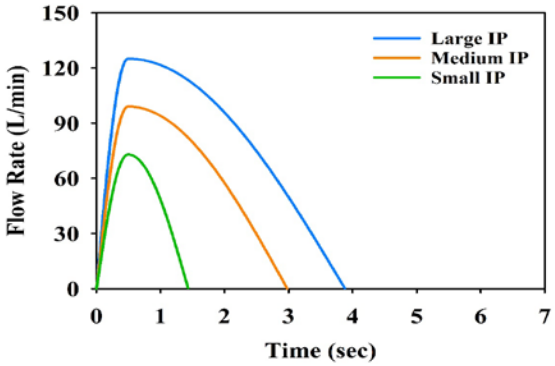


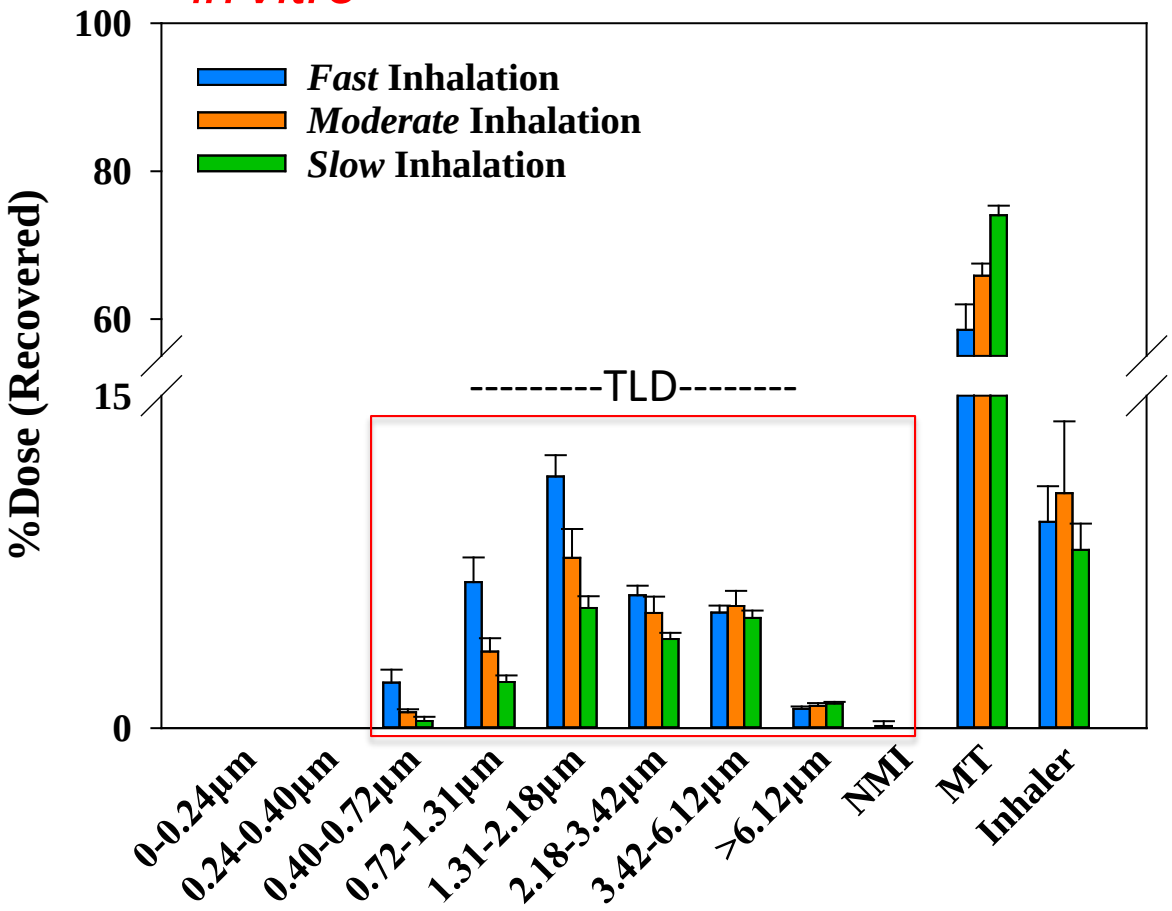
- ❑ Complete delivered dose capture at realistic IP while maintaining constant flow through cascade impactor
  - ❑Constant Dilution Airflow balances Vacuum Flow (flow at MT = 0±2 L/min)
  - ❑Simulated Breath (IP) duplicated at MT entry [Byron et al, RDD 2014, v1, 295].
- ❑ NMI captures <2% of ***TLD$_{in\ vitro}$*** [Byron et al, RDD 2014, v2, 533]
- ❑ NGI recalibration enabled realistic tests at high flow rates

Wei X, et al (2017). JAMPDD 30: 339 - 348

The range of $APSD_{TLD in\ vitro}$ from Novolizer DPI

- Budesonide (Mean ±SD); using Medium VCU MT
  - In vitro TLD & APSD affected by IP
  - More to lung in smaller aerosol with "*Fast* inhalation (large IP)"

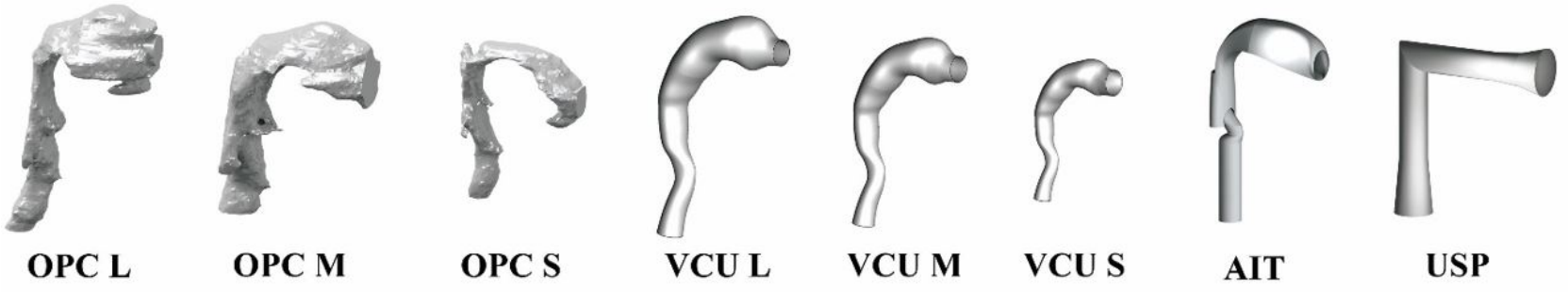




- Inhalers may be also be tested across MT models (different mouth-throat geometries)

FDA asked: Which MT Models are best?

Internal Volume							
84.4 cm^3	91.7 cm^3	27.6 cm^3	96.1 cm^3	61.6 cm^3	26.6 cm^3	75.4 cm^3	67.3 cm^3



Oropharyngeal Consortium **VCU Models** **Alberta Idealized Throat** **USP**

- and …do methods also work with MDIs and SMIs?

Methods

- January 2015: Search (PubMed and Web of Science) and select clinical scintigraphy literature for good quality publications on drug deposition from inhalers that
  - could be obtained for testing
  - described *the reported range of trained inhalation maneuvers*
  - used volunteers of both genders
  - validated radiolabeling (compared CI profiles for drug and radiolabel)
  - covered existing inhalers (DPI, MDI and SMI)
- Purchase inhalers, design and perform realistic tests to compare in vitro deposition to that described in the clinical literature.

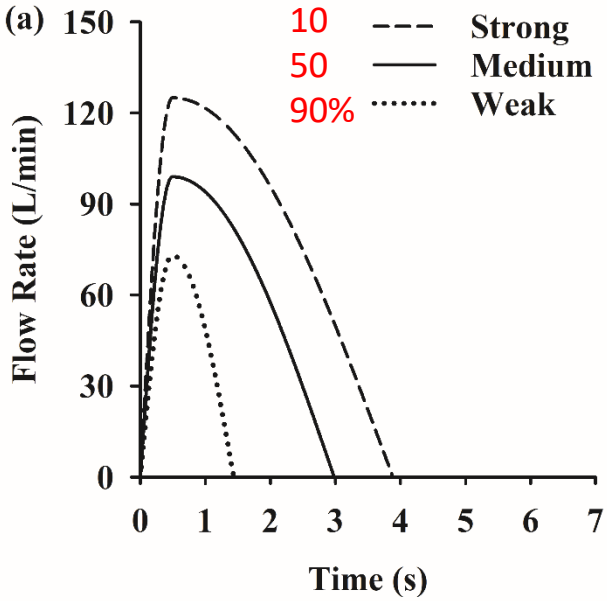
0.84%w/v fenoterol HBr
0.037%w/v EDTA disodium
0.0073%w/v BAC

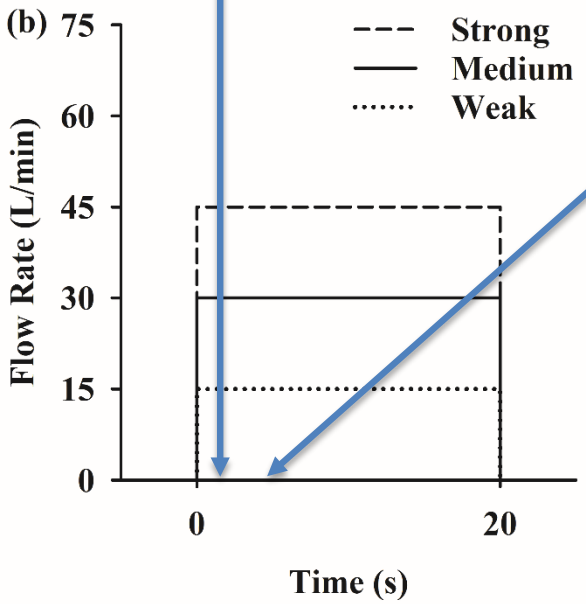
Newman SP et al. *Eur Respir J*. 2000;16:178-183.
Hirst PH et al. *Pharm Res*. 2002;19:258-264.
Newman SP et al. *Chest*. 1998;113:957-963.
Brand P et al. *Int J Chron Obstruct Pulmon Dis*. 2008;3:763-770 (Respimat deposition in COPD)

“Modes of Inhalation” used for testing

Spray duration = 1.5 sec

Spray duration = 0.15 sec





Trained Inhalation	Respimat	pMDI
Duration (sec) (SD)	4.04 (1.17)	4.34 (0.92)
Firing lag time (sec)	0.00 (0.23)	0.12 (0.27)
Volume inhaled (L)	2.32 (0.90)	2.24 (0.53)
Mean Inspiratory flow L/min	35.2 (10.6)	33.2 (10.0)

Mean (SD) from Brand et al. 2008

Mean in vitro drug deposition (% delivered dose; dd) in 8 mouth-throat models for DPI, MDI and SMI at weak, medium and strong flow conditions (72 experiments; n=5).

MT Model	-------DPI-------			-------MDI-------			-------SMI-------			Mean
	Weak	Medium	Strong	Weak	Medium	Strong	Weak	Medium	Strong	
VCU_S	73	70	66	90	85	81	14	17	22	57.7
VCU_M	73	65	62	86	76	70	11	14	21	53.1
VCU_L	68	65	60	84	74	72	7	11	14	50.5
OPC_S	75	75	71	**93**	92	91	30	32	42	66.7
OPC_M	68	67	63	88	79	79	19	15	15	54.7
OPC_L	62	55	49	68	62	50	10	10	13	42.2
AIT	66	64	55	58	62	55	11	17	24	45.8
USP	67	64	59	68	45	44	**7**	8	12	41.7
Mean	68	65	61	85	75	71	11	14	18	52.0

MT deposition (% dd) decreased as models became larger; impaction decreased as flow restrictions and turbulence decreased

MT Model				-------MDI-------			-------SMI-------			Mean
	Weak	Medium	Strong	Weak	Medium	Strong	Weak	Medium	Strong	
VCU_S	73	70	**66**	90	85	81	14	17	**22**	57.7
VCU_M	73	65	**62**	86	76	70	11	14	**21**	53.1
VCU_L	68	65	**60**	84	74	72	7	11	**14**	50.5
OPC_S	75	75	71	93	**92**	91	30	32	42	66.7
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- MT deposition (%dd) by inhaler can decrease or increase with inspiratory flow (not intuitive).
- Variation in MT deposition increases when tests include small and large models.

MT Model	-------DPI------			-------MDI-------			-------SMI------			Mean
	Weak	Medium	Strong	Weak	Medium	Strong	Weak	Medium	Strong	
VCU_S	73	70	66	90	85	81	14	17	22	57.7
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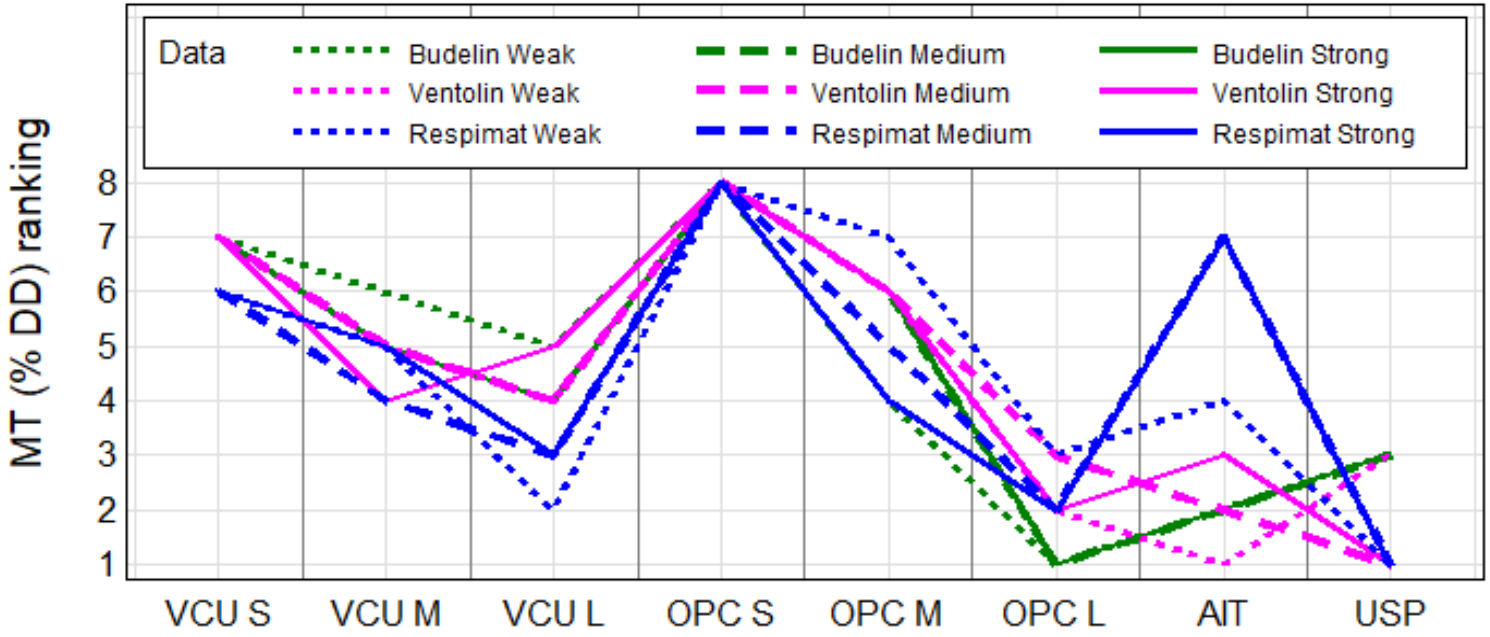
MT Deposition Ranking in Coated Models

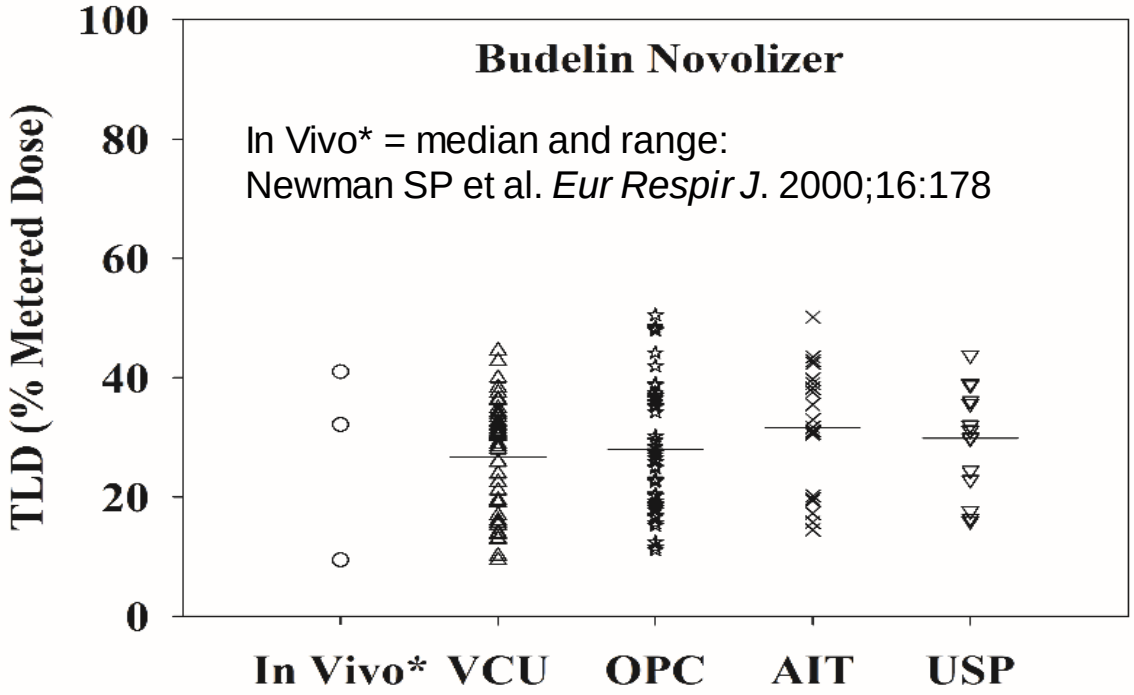


- On average, the rank order of the coated MT models as fractional collectors of delivered dose was statistically independent of both inhaler and flow (ANOVA)

$$\mathbf{USP < OPC_L < AIT < VCU_L < VCU_M < OPC_M < VCU_S < OPC_S}$$

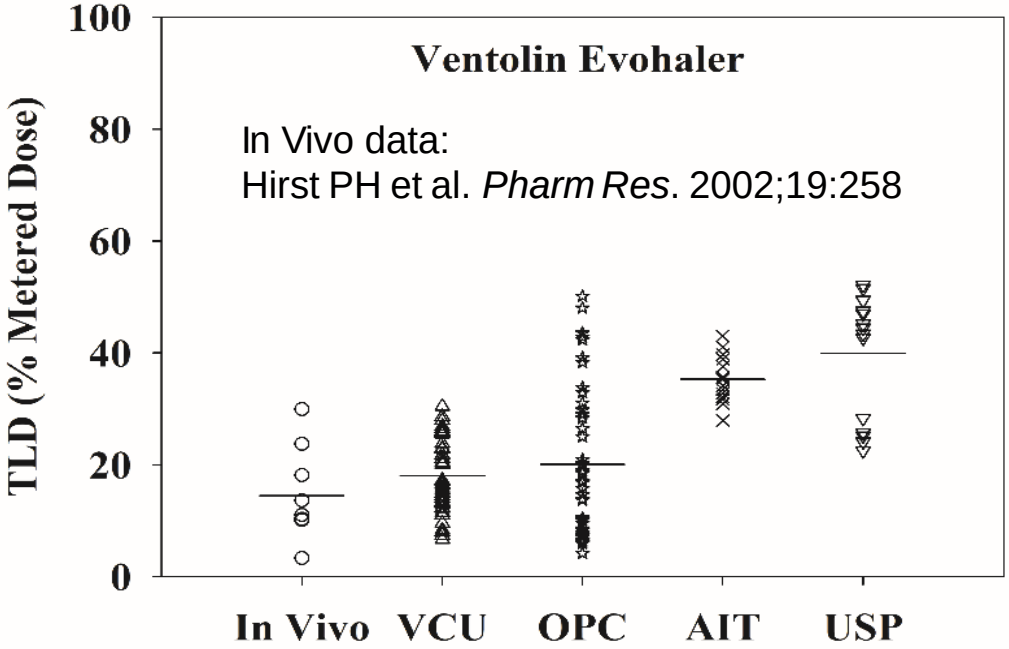
- MT_{max} was Ventolin (93% in OPC_S); MT_{min} was Respimat (7% in USP)
  - Selecting MT model and flow condition is important
  - Flow trends not obvious - need to test.

IVIVCs: Post Hoc Comparisons of TLD - (% metered dose that escapes MT)



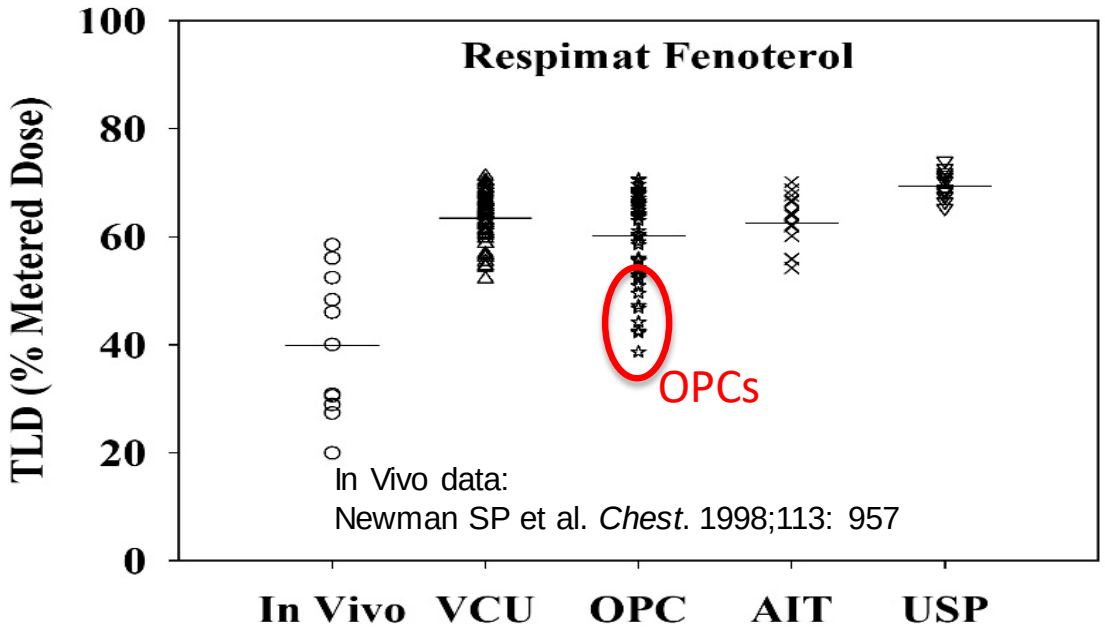
- **Novolizer DPI (200μg budesonide); weak – strong realistic IPs**
  - Metered Dose effectively constant; DD strongly flow-dependent
  - Variance of $TLD_{in\ vitro}$ mostly due to flow; MT selection less important
  - IVIVCs best with VCU and OPC

IVIVCs: Post Hoc Comparisons of TLD - (% metered dose that escapes MT)



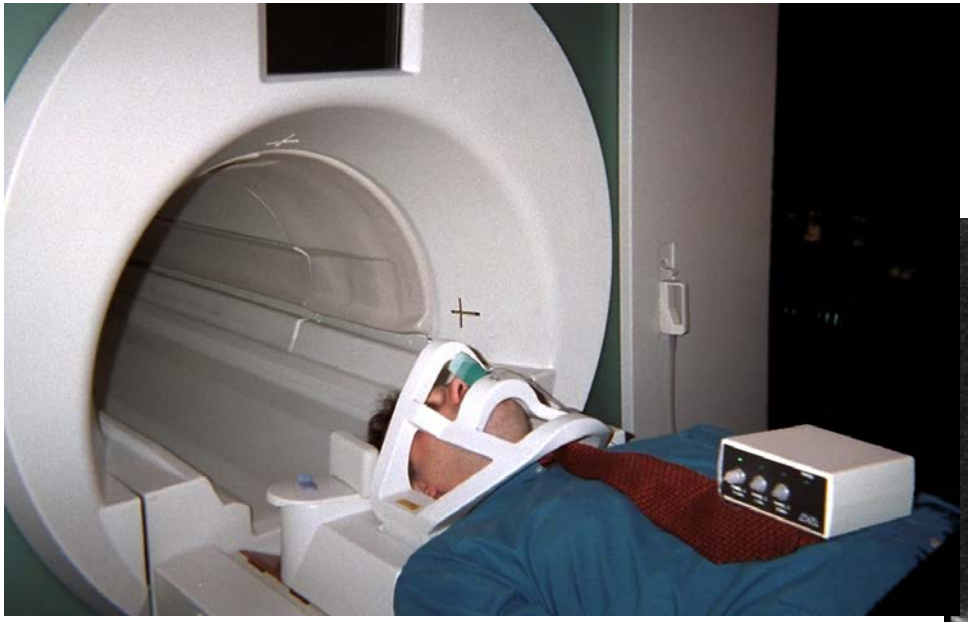
- **Ventolin Evohaler pMDI (100μg albuterol as sulfate); 15 – 45 L/min**
  - Metered Dose and Delivered Dose effectively constant
  - Variance of $TLD_{in\ vitro}$ mostly due to MT geometry
    - MT selection essential (+ tests across S & L models)
  - IVIVCs (normal volunteers) appeared best with VCU models

IVIVCs: Post Hoc Comparisons of TLD

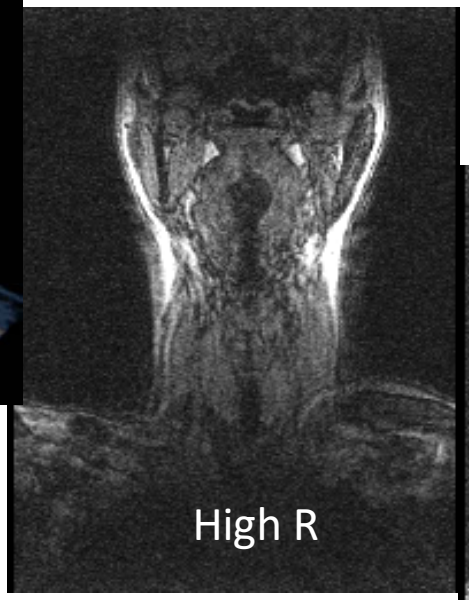


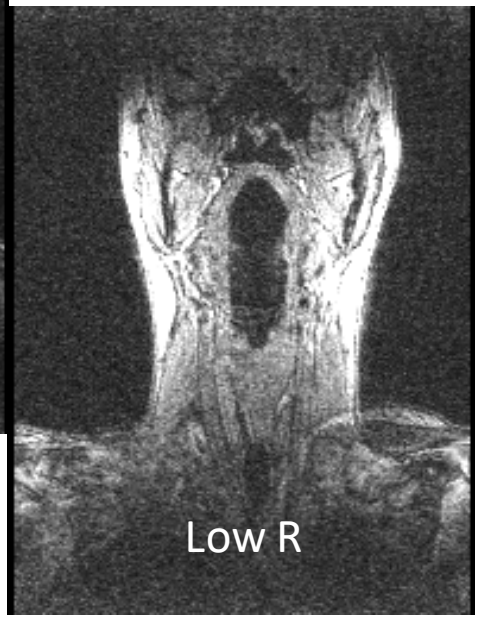
- **Respimat SMI (100μg fenoterol as HBr); 15 – 45 L/min**
  - Variance of $TLD_{in\ vitro}$ due to MT geometry and flow
  - In vivo results consistent with other Respimat literature (trained users)
  - Low flow tests produce TLD overestimates (at 25/50 & 25°/100%RH)
  - Realistic testing at high flow rates produced good IVIVCs (all models except USP) in accord with Brand et al. (*Int J Chron Obstruct Pulmon Dis*. 2008;3:763)

MT Models have limitations!



McRobbie & Pritchard (2005). *J Aerosol Medicine* 18:325

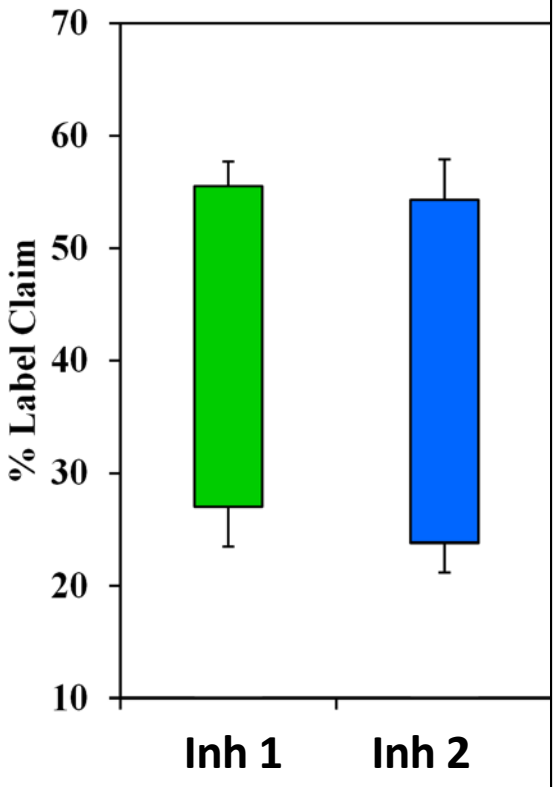




Models neglect effects of:

- ❑ posture, mouthpiece design, teeth….
- ❑ laryngeal hyper-variability
  - ❑ Breathing dynamics
  - ❑ Inhalation against a resistance.

Conclusions



Realistic testing can bridge the disconnect between the QC lab (batch release tests with tight specs that purport to define "delivered dose" and APSD) and the clinic (expensive studies that reflect the high variability of dose deposition in patients). We recommend:

- ❑ OPC or VCU MT models and a realistic range of inhalation profiles to compare the likely aerosol performance properties of each product in the clinic
- ❑ Use of realistic in vitro tests that take account of patient-derived variables inexpensively
- ❑ Realistic in vitro tests are:
  - ❑ More likely to predict batch-to-batch variations
  - ❑ More useful than compendial methods to compare likely clinical performance of innovator products and generics
    - ❑ $TLD_{in\ vitro}$ (mean and span?)
    - ❑ $APSD_{TLDin\ vitro}$ (most useful for DPIs)