Bioequivalence Assessment for Inhalation Products

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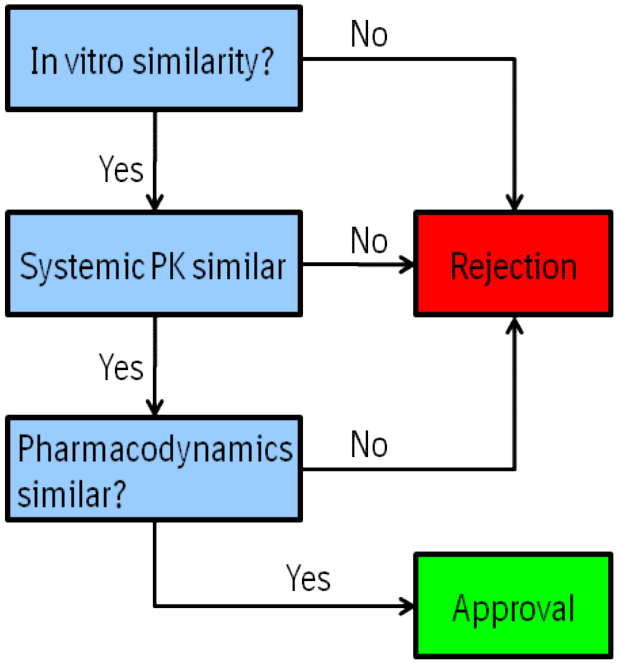
Judging Inhaler Bioequivalence is Complex

- Topic debated in inhalation conferences for >25 years
  - *In vitro* and *In vivo* test requirements have yet to be finalized
- All drug inhalers are considered to be “combination products”
- Many contain multiple actives for topical effects
- Delivered as aerosols to ~ 70m^2 of “variable” epithelia
  - Epithelial characteristics can complicate pharmacologic effect vs time profile(s)
- New drugs trending toward increasing hydrophobicity
  - e.g. ICS/LABA combinations that may exhibit rate-limited dissolution & absorption

Even so, it is logical to believe that the “same aerosol”, produced at the same rate, at the mouth of the same patient from two devices should produce the same effects, [provided the patient inhales in the same way & human factor studies indicate equivalence]

Topical Inhaler BE: FDA vs EMA

FDA



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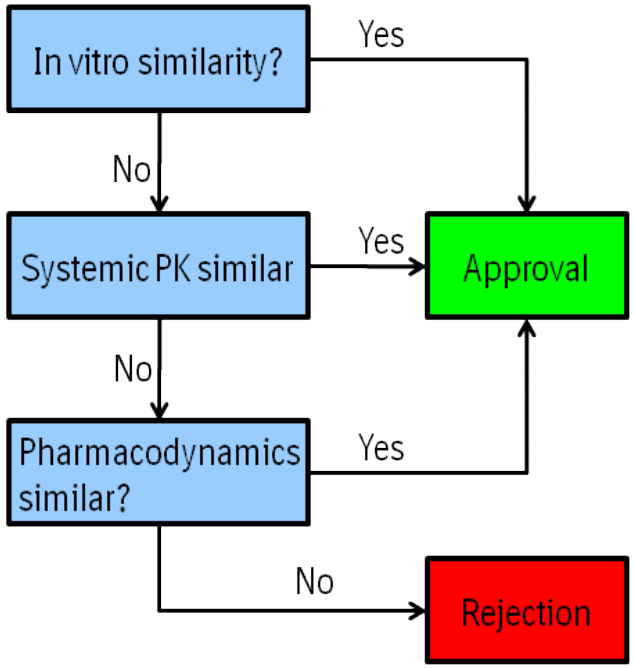
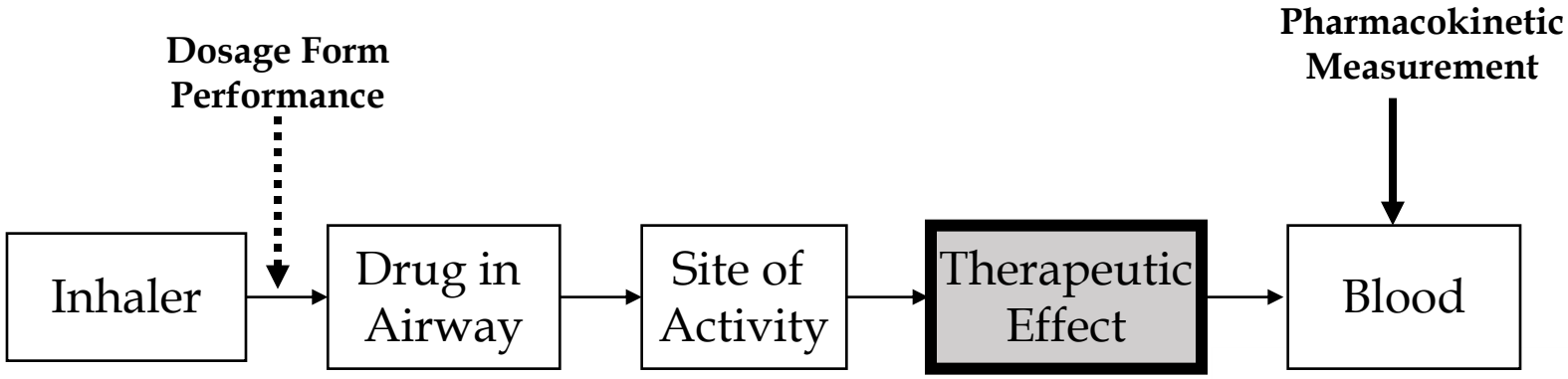


In the USA, in large part because of the way the US statute defines generics & permits pharmacy substitution, all three aspects must be tested & proven (a weight of evidence approach). In the EU, even if inhalers are dissimilar (e.g. not a "generic" in the USA), approval possible based on PK or PD.

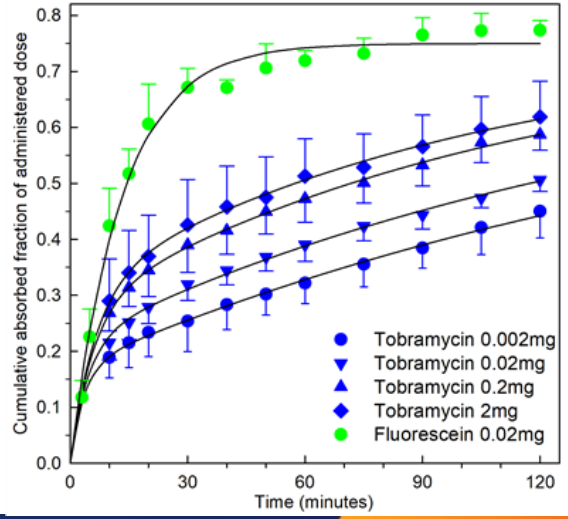
Figure courtesy of Steve Horhota, RDD 2012, p.283

Bioequivalence (BE) – topical conundrum

Therapeutic effects occur topically, in "first-pass tissue", before blood is reached. Several inhaled drugs either show no relationship between plasma levels and effect or show effects that relate to lung levels.



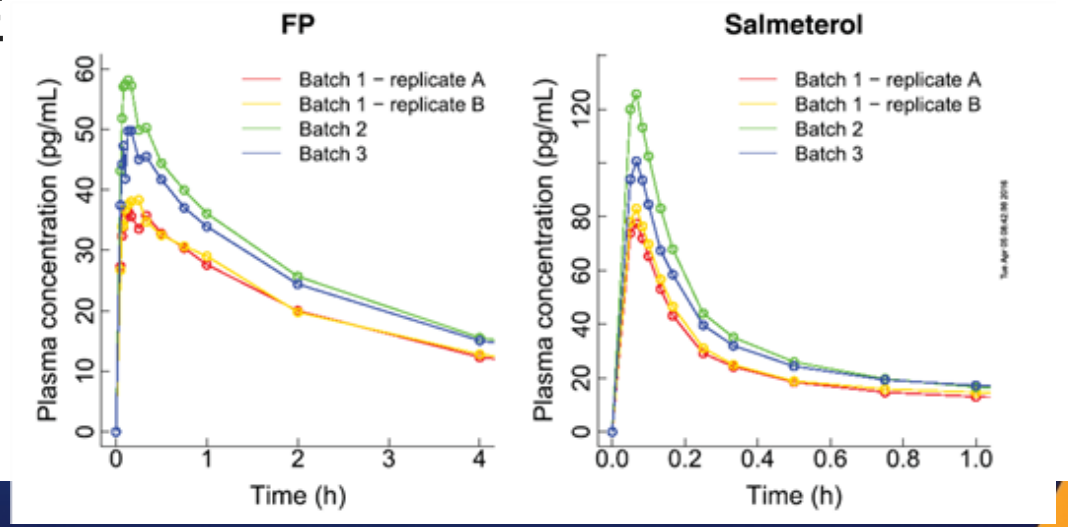
- Tobramycin lung tissue duration dose-dependent due to cell binding. Li M, Byron P: JPET 347(2):318 (2013)
- Fluticasone propionate mean lung absorption time (reflects duration) = 4-6h. Krishnaswami, Int J Clin Pharm.Ther (2005)
- Budesonide intracellular esterification defines duration. Maassen van den Brink et al. Br J Clin Pharmacol. 66, 27 (2008)
- Human lung tissue inaccessible for assay in BE trials



The challenge is to prove "sameness" in ANDAs that comport with 21 CFR 320.1 [BE means the absence of a significant difference in the rate and extent to which the active becomes available at the site of drug action; e.g. lung tissues]

1. Total lung doses from inhalers are usually highly variable in clinical trials
   - CV values >40% quite normal even in CTs Borgstrom et al, J. Aer. Med 19, 473, 2006
2. Comparative PD testing is reasonable in theory but not in practice
   - Poor discrimination between T and R at clinical doses (bronchodilators)
   - No discriminatory efficacy tests for ICS & drugs in combination
3. RLD batch variability can make selection a problem for generic developers
   - Advair batches fail PK BE

Burmeister Getz et al (2016).
Clin. Pharmacol. Therap. 100: 223-231



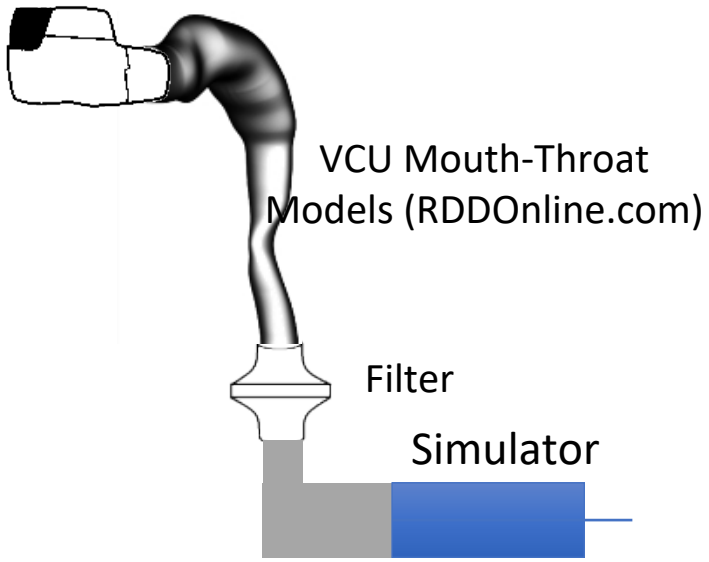
Given the difficulties with clinical testing, we sought improved *In vitro* & *In silico* tests that could be used to assure "sameness"

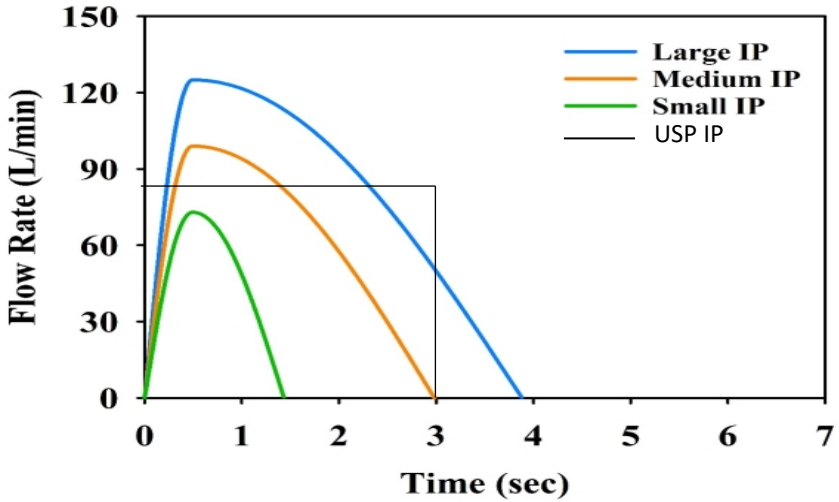
We know that well-planned in vitro experiments (such as "realistic testing" that includes relevant APSD comparisons at the trachea) are able to generate equivalence metrics for comparison between products that are superior (in discriminatory power) to both PK and PD trials.

We know that well designed CFD modeling can be used to predict and compare aerosol deposition patterns in the airways.

We are beginning to see evidence of different dissolution behavior from powder aerosols of poorly soluble drugs depending on the Q3 characteristics of microfine drug-lactose agglomerates in deposited blends. Price R et al. RDD 2018, 265 – 276

Clinically Relevant (Realistic) Testing

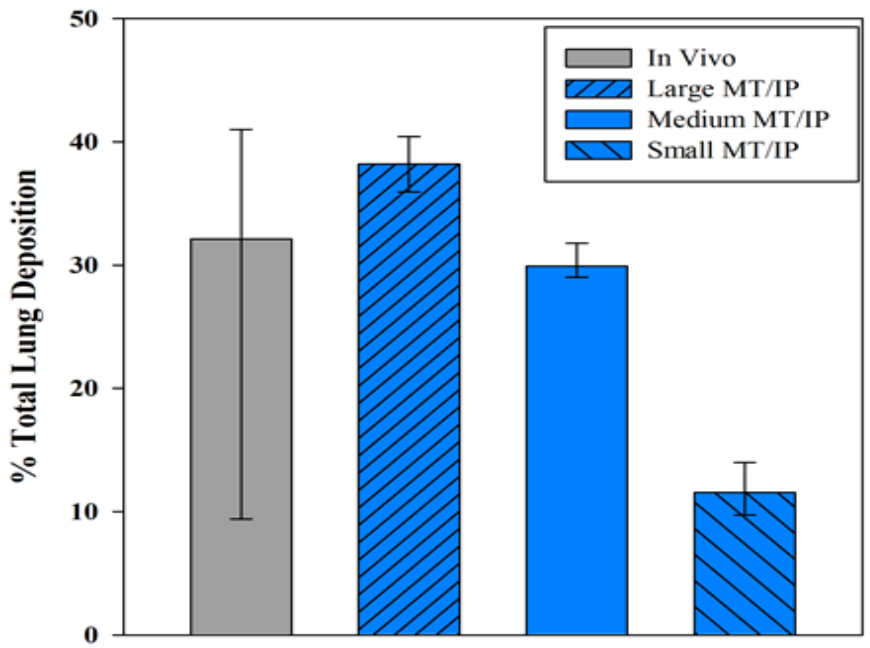


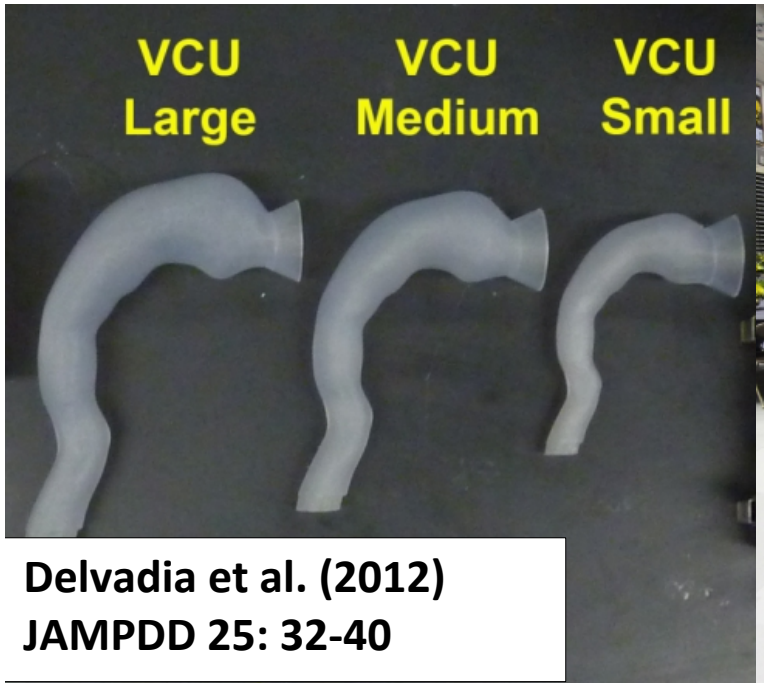


Andersen Cascade Impactor in QC Testing

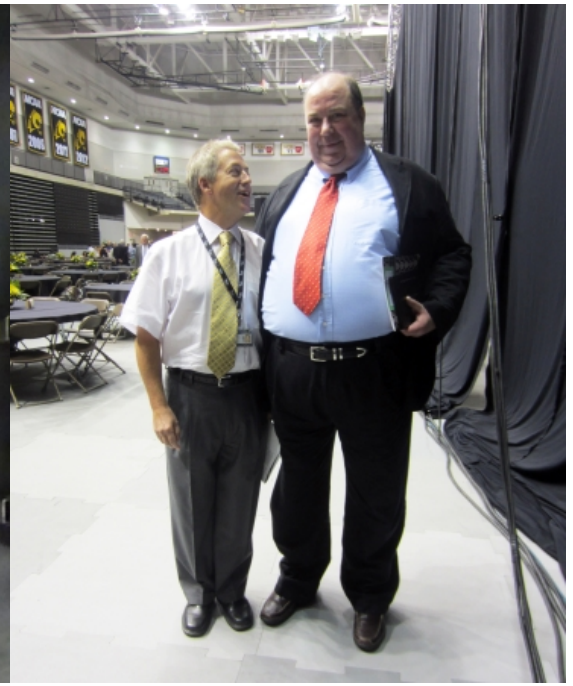
- Traditional inhaler QC (Dose and APSD following square wave testing] tells little about clinical performance or the variability of lung delivery
- Clinically-relevant in vitro test methods partner realistically-designed upper airway models with representative inhalation profiles *(IPs)* to characterize aerosol drug input at the trachea
- Validated & realistic MT geometries are used with internal coatings to retain deposited drugs
- Realistic airflow profiles are simulated to cover 95% of the range seen in the clinic
- Total Lung Dose in vitro **= $TLD_{in\ vitro}$** = Drug mass escaping MT; Size distribution **= $APSD_{TLDin\ vitro}$**

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



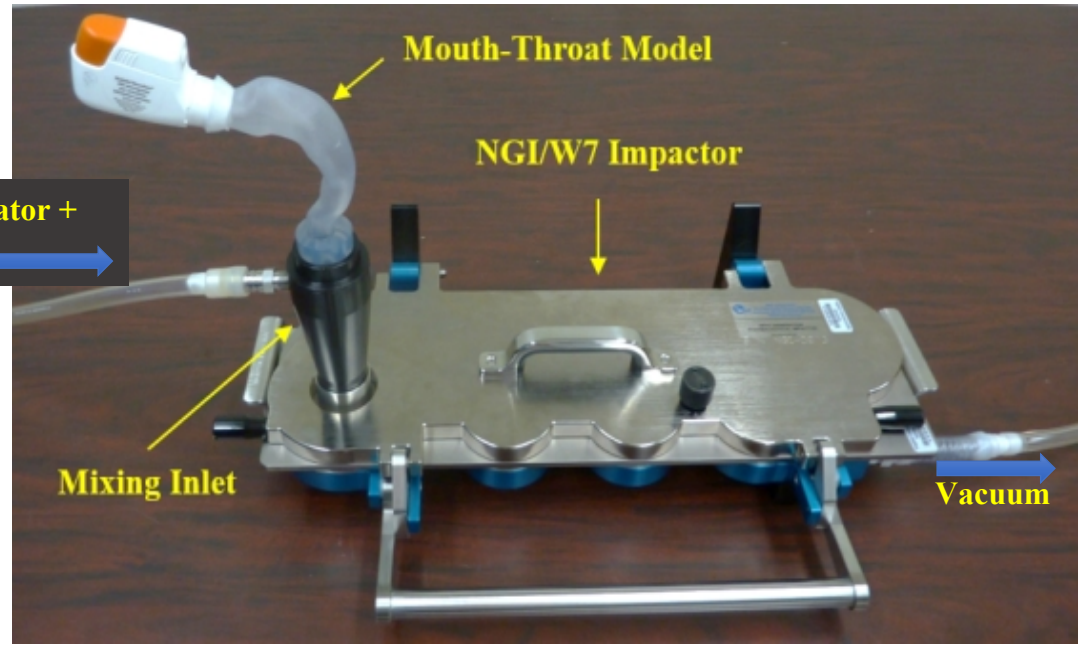


Delvadia et al. (2012)
JAMPDD 25: 32-40

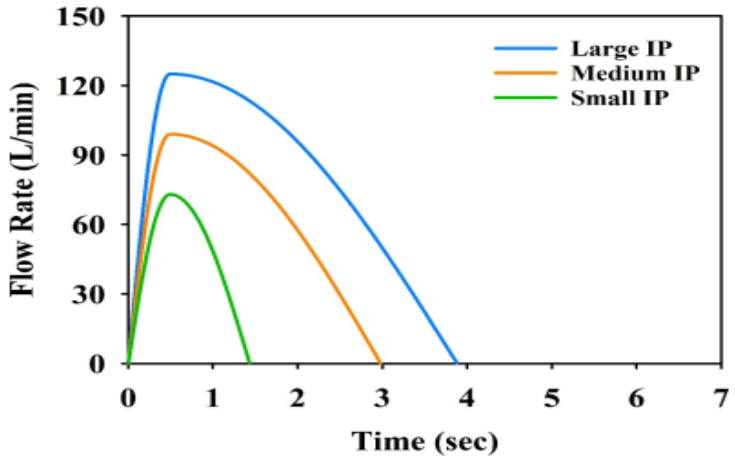


- MT model volumes [large to small] span 95% of the anatomic range for human adults
- In vivo results [Scintigraphy; Newman, Eur. Resp. J. 2000,16: 178]
- Error bars show complete range of data
- Flow profiles were simulated to match Newman's training (healthy adults, M&F)
- VCU MT models paired with simulated Newman "profiles" Large/Large; Medium/Medium; Small/Small.

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



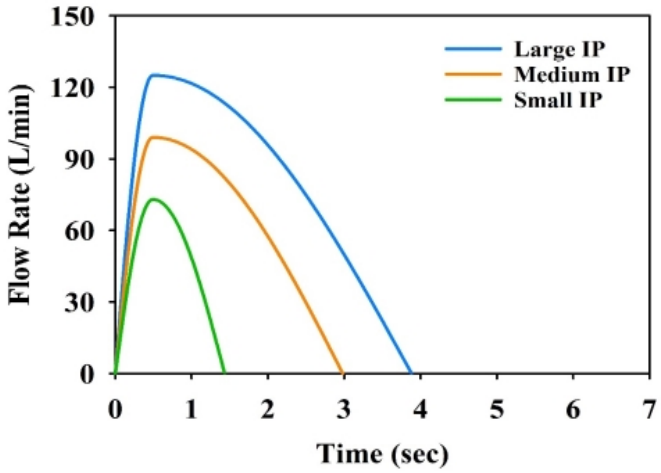
- Cascade impactor (NGI) - constant flow controlled by vacuum
- Dilution air supplied via Nephele Mixing Inlet to counterbalance vacuum flow
- Breath Simulator enables aerosol cloud to be withdrawn through coated MT model using realistic, inhaler - specific, inhalation profiles

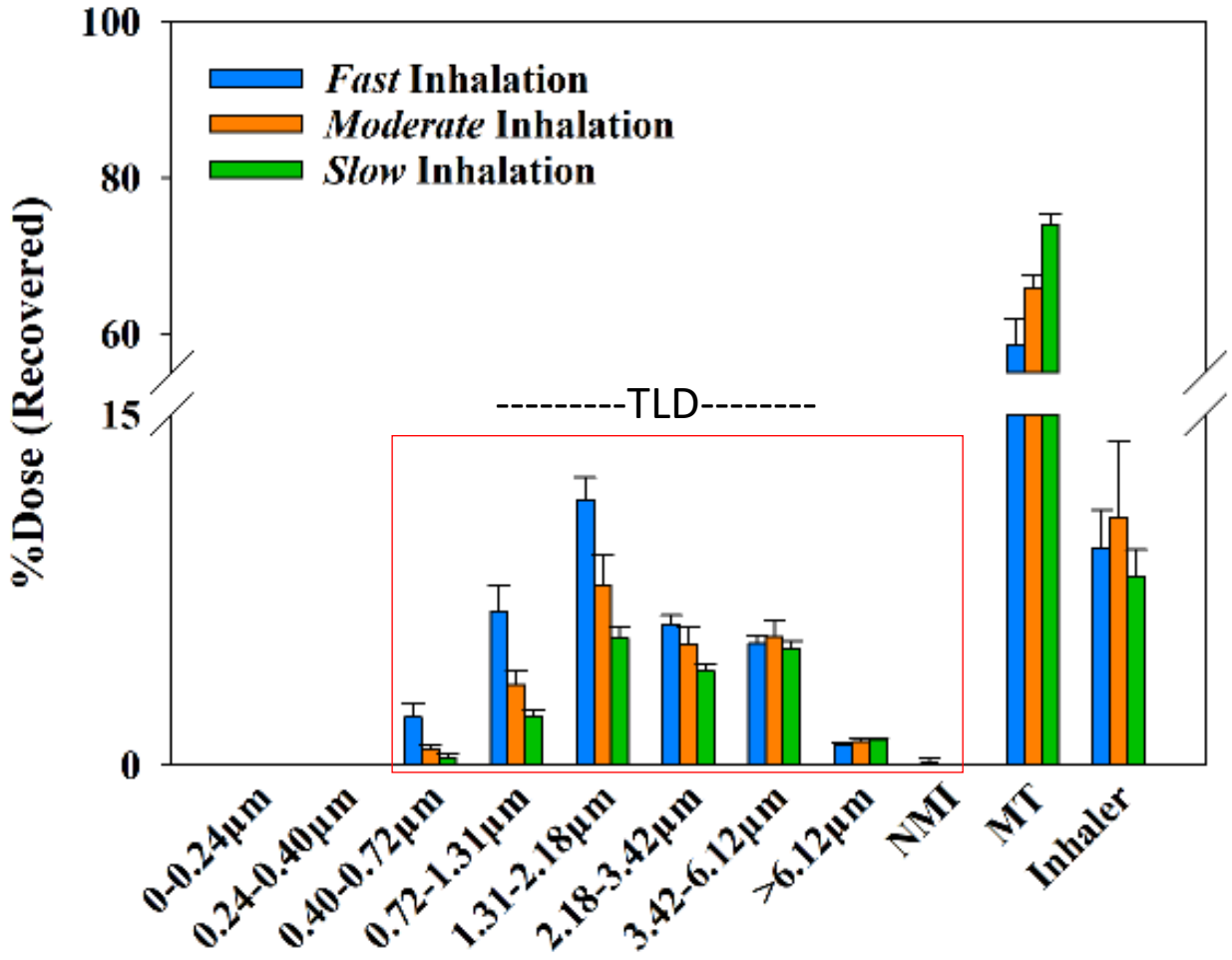


- $TLD_{in\ vitro}$ sized in NGI to give $APSD_{TLD\ in\ vitro}$
- Method: Wei et al (2017). JAMPDD 30: 339 - 348
- Profile Selection: Delvadia et al (2016). JAMPDD 29:196-206

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)"

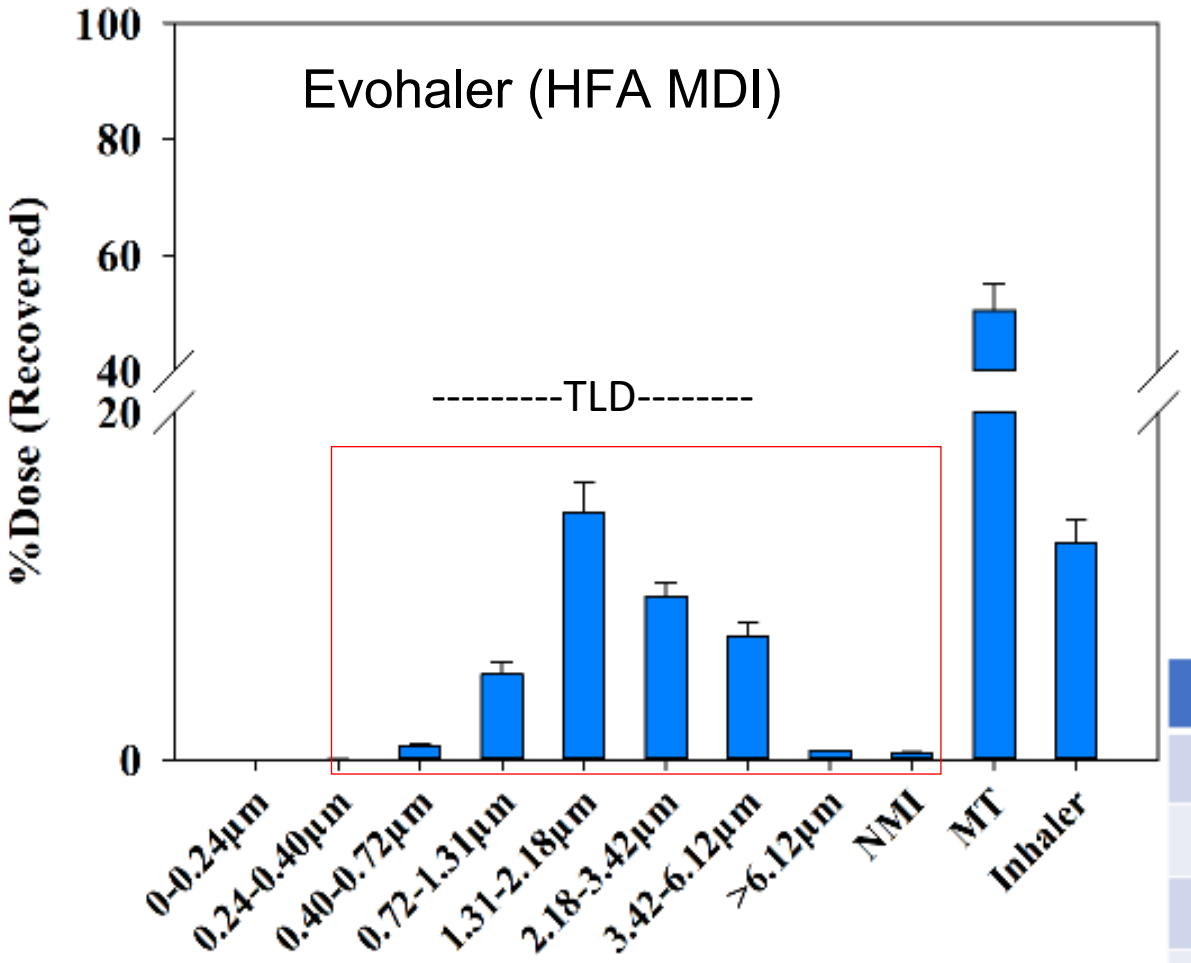




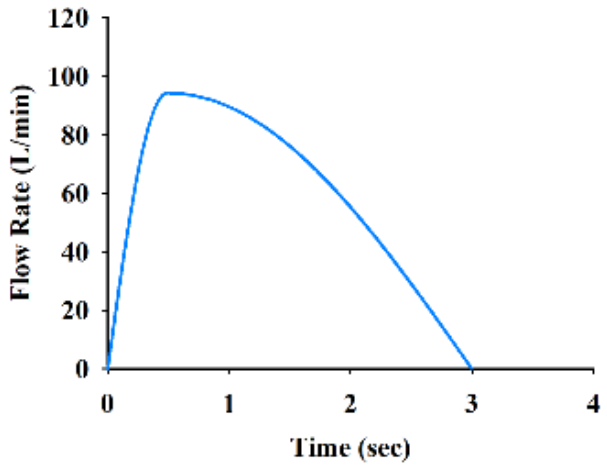
- Inhalers tested across MT models

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

Albuterol Exiting VCU Medium MT – Flow Effects



3L $Q_{average}$ = 60 L/min



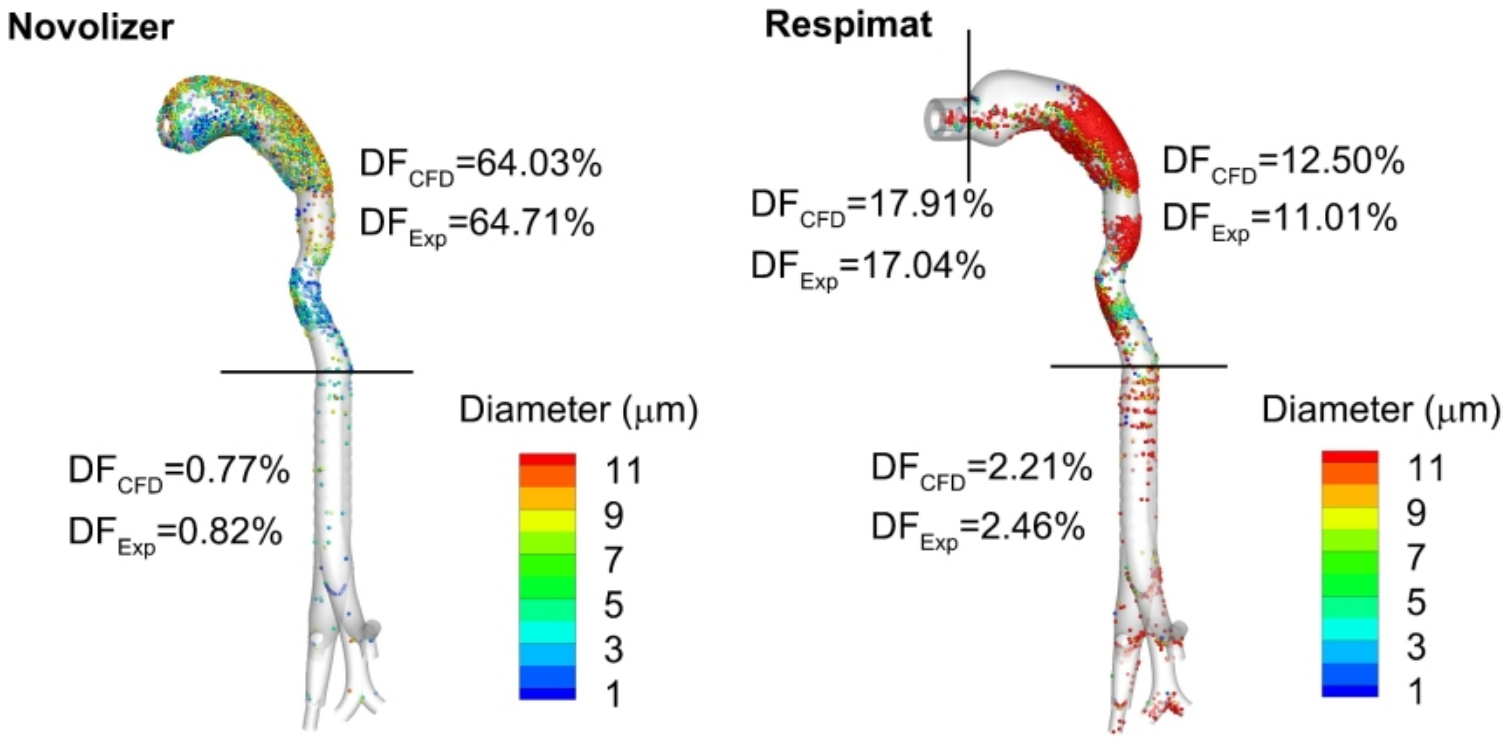
Average Flow Rate (L/min)	TLD (%Dose)	MMAD (µm)
15	12.3±1.2	2.3±0.0
30	21.8±2.7	2.3±0.1
45	26.8±2.6	2.2±0.1
60	37.1±3.8	2.1±0.0

Experimental Summary

- Inhaler testing with anatomically validated MT models and appropriate inhalation profiles produce results where
  - Values for median & range of $TLD_{in\ vivo}$ correlates with $TLD_{in\ vitro}$
  - Multiple inhalers
    - Novolizer, Handihaler, Aerolizer, Easyhaler, Turbohaler, Evohaler
- Effects of inhaler design, flow, formulation, inhaler orientation etc. can be studied inexpensively
- $APSD_{TLDin\ vitro}$ data can be collected simultaneously *either*
  - to compare profiles likely to enter trachea *or*
  - to use as initial conditions for CFD and regional deposition modeling

Computational Fluid Dynamic Models – Upper Airway Validation

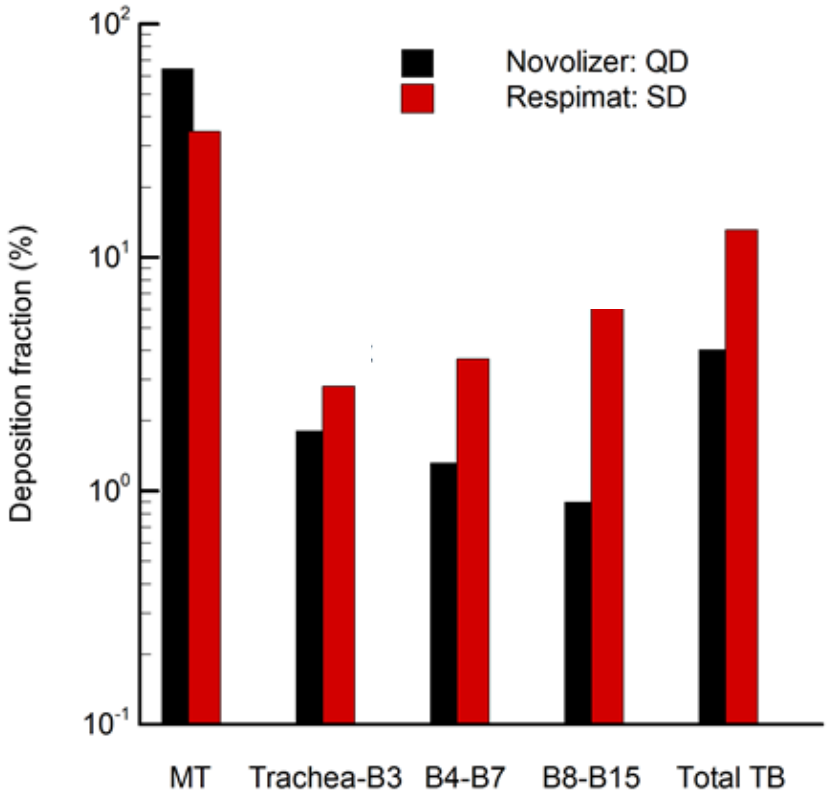
- Coupling careful modeling with *in vitro* testing enables CFD model validation.
  e.g. Novolizer (75 LPM for 4 s); Respimat at 37 LPM (Medium MT + TB model)
- Tian et al. (2012) *Aerosol Sci. Technology* 46, 1271-1285

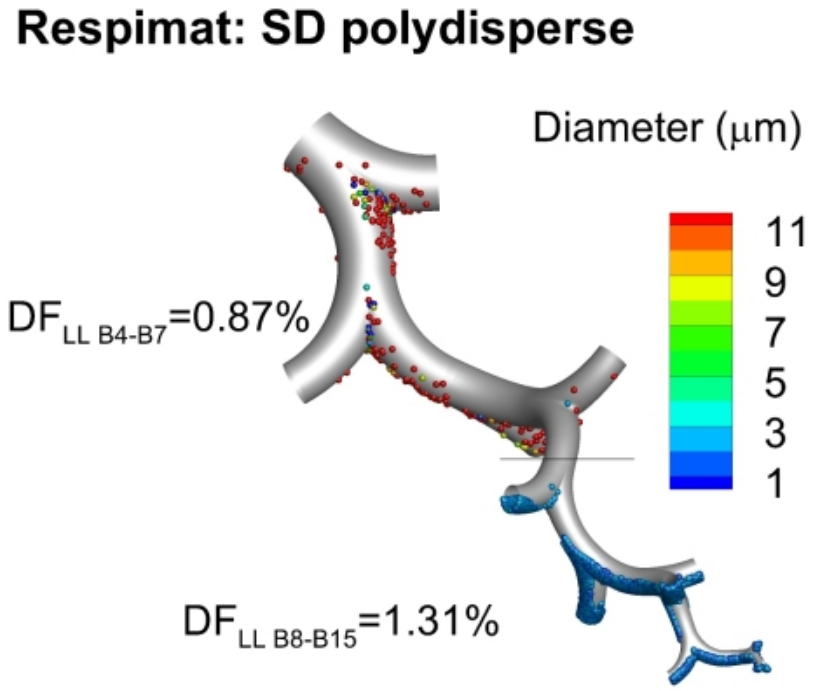


- Turbulence fades rapidly past airway generations 3 and 4

CFD Models for Regional Distribution

- Based on size distribution of $TLD_{in\ vitro}$ (drug aerosol entering lung) and validated CFD model …. predict regional distribution in lung.
- Tian et al. (2012) *Aerosol Sci. Technology* 46, 1271-1285

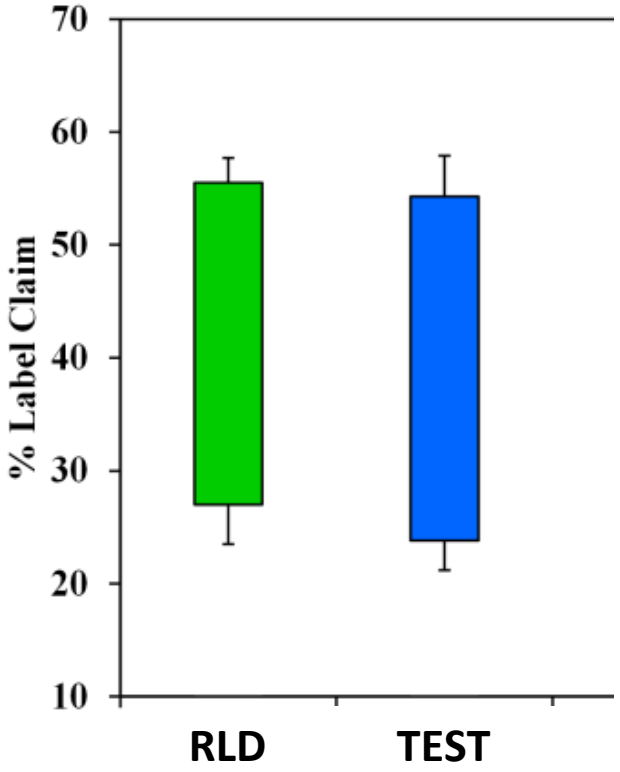




Stochastic Individual Pathway model

- If exhalation is ignored (breath-holding assumed) mass balance gives Gen 16 – 23.

The way forward… ?



- ❑ Compare values for $TLD_{In\ Vitro}$ using a range of inhaler - representative breath profiles in S, M and L models.
- ❑ Debate the rules for BE with the biostatisticians
  - ❑T/R = 0.8 ~ 1.2 for mean and span?
- ❑ If BE in vitro… compare regional deposition using CFD at an appropriate inhalation flow rate using $APSD_{TLDin\ vitro}$ profile as determined experimentally at tracheal entry.
- ❑ Assure PK similarity.
- ❑ Follow EU lead; drop PD similarity requirements.

Acknowledgments

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Questions

In Vitro Tests for Aerosol Deposition I – VI.
Journal of Aerosol Medicine and Pulmonary Drug Delivery
Delvadia RR et al, (2012) 25:32-40; (2013) 26: 138–144; (2013 145-156, (2016) 29:196-206
Wei X et al, (2017) 30: 339-348; (2018) 31: (2018) Jun 7. doi: 10.1089/jamp.2018.1454
Wei X, Ph.D Thesis 2015, Virginia Commonwealth University.

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