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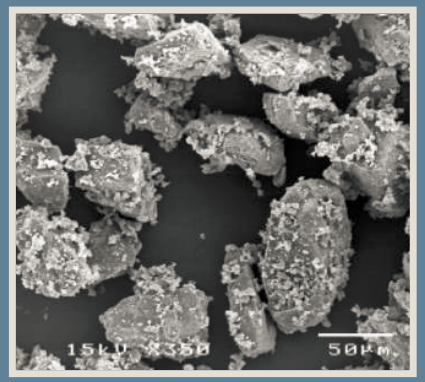
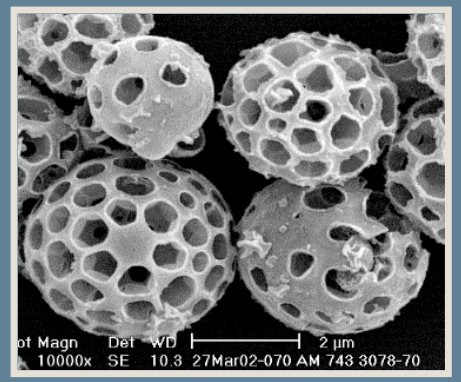
Inspired Inhalation Innovation™

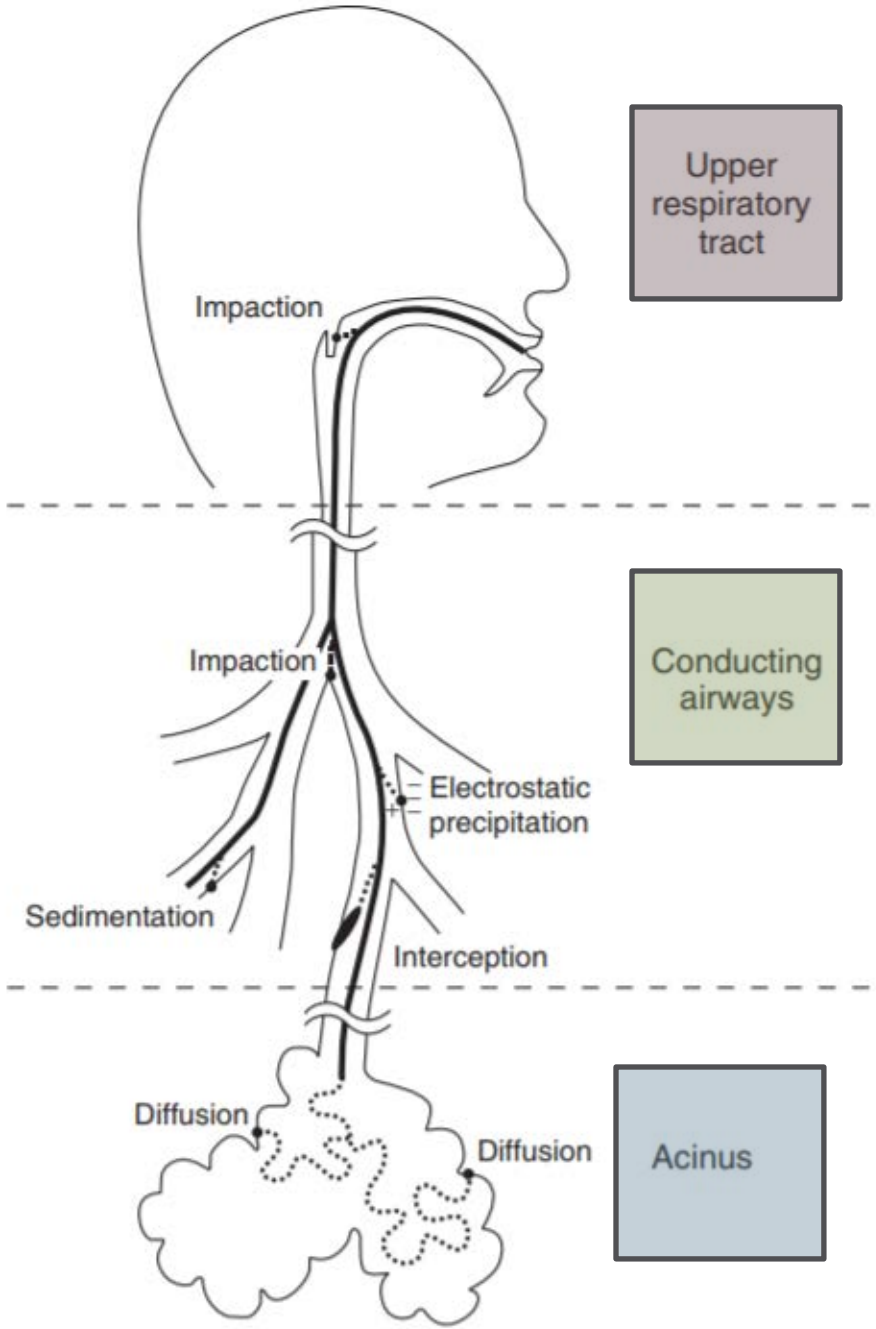
Is Aerodynamic Diameter a Good Metric for Understanding Regional Deposition?



Jeffry Weers, Nani Kadrichu, and Nagaraja Rao

Respiratory Drug Delivery Europe 2019 ; Lisbon, Portugal, May 9, 2019



The TLD is the fraction of particles that bypass deposition in the URT and are not exhaled

"Deposition in the airways is controlled by three factors: airway geometry, aerodynamic particle size, and inhaled flow rate"

Lippman, 1977

$$Stk = \frac{\rho_p d_p^2 u C_c}{18\mu D} \sim \frac{d_a^2 Q C_c}{18\mu D} \quad (Stokes' Equation)$$

d_a^2Q = impaction parameter

$$v = \frac{\rho_p d_p^2}{18\mu} g \sim \frac{d_a^2}{18\mu} g \quad (Terminal\ Settling\ Velocity)$$

Source: Dolovich MB, Mitchell JP, Roberts DL: J Aerosol Med Pulm Drug Deliv. 2018, doi.org/10.1089/jamp.2018.1479.

Source: Darquenne C: Particle deposition in the lung, 2006

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Is there a link between aerodynamic size and regional lung deposition?

JOURNAL OF AEROSOL MEDICINE AND PULMONARY DRUG DELIVERY
Volume 31, Number 0, 2018

Pp. 1–3
DOI: 10.1089/jamp.2017.1396

Letter to the Editor

Harmonizing the Nomenclature for Therapeutic Aerosol Particle Size: A Proposal

Elizabeth V. Hillyer, DVM, ELS, MWC,[1] David B. Price, FRCGP,[1,2] Henry Chrystyn, PhD, FRPharmS,[1,3] Richard J. Martin, MD,[4] Elliot Israel, MD,[5] Willem M.C. van Aalderen, MD, PhD,[6] Alberto Papi, MD,[7] Omar S. Usmani, MBBS, PhD, FHEA, FRCP,[8] Nicolas Roche, MD, PhD[9]; on behalf of the Respiratory Effectiveness Group, Small Airways Study Group

- "We propose the terms 'coarse', 'fine', 'extrafine' to differentiate orally inhaled medical aerosols with particle MMADs of >5 μm, 2.1-5 μm, and <2.1 μm, respectively".
- "Regional lung deposition varies according to aerosol particle MMAD as well as GSD. In general, particles > 6 μm deposit preferentially in the oropharynx, those 2-6 μm in the central airways, and those < 2 μm in the peripheral airways and alveoli".

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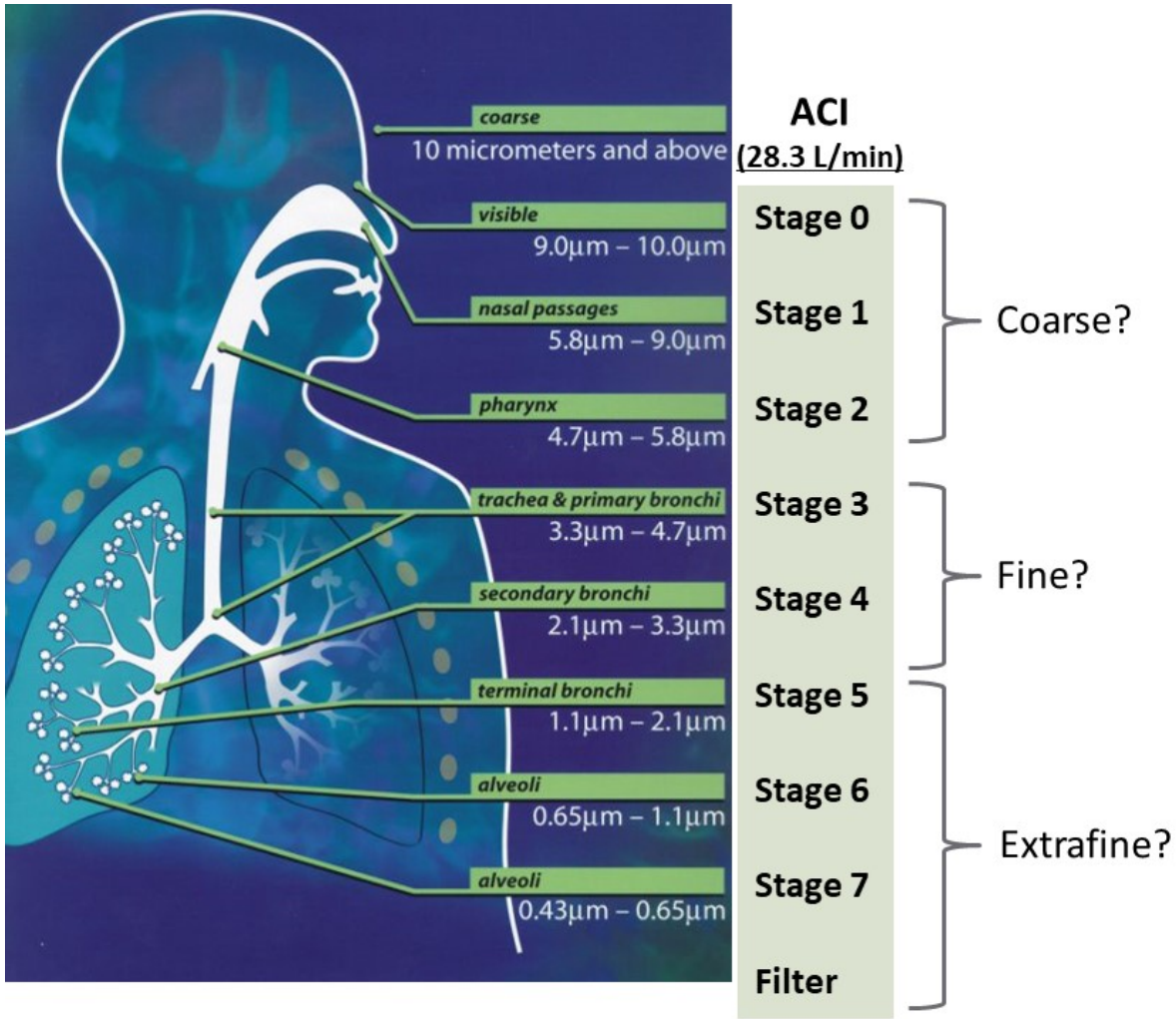
Cascade impactors are not lung simulators



"Cascade impactors are not lung simulators, despite marketing drawings to that effect created historically by some manufacturers of the Andersen cascade impactor". **-Dolovich et al, 2018**

Q = 28.3 L/min

Are cascade impactors just a QC tool?

Source: Hillyer EV et al: Harmonizing the nomenclature for therapeutic aerosol particle size: a proposal. J Aerosol Med Pulm Drug Deliv. 2018, 31:111-113.
Source: Dolovich MB, Mitchell JP, Roberts DL: J Aerosol Med Pulm Drug Deliv. 2018, doi.org/10.1089/jamp.2018.1479.

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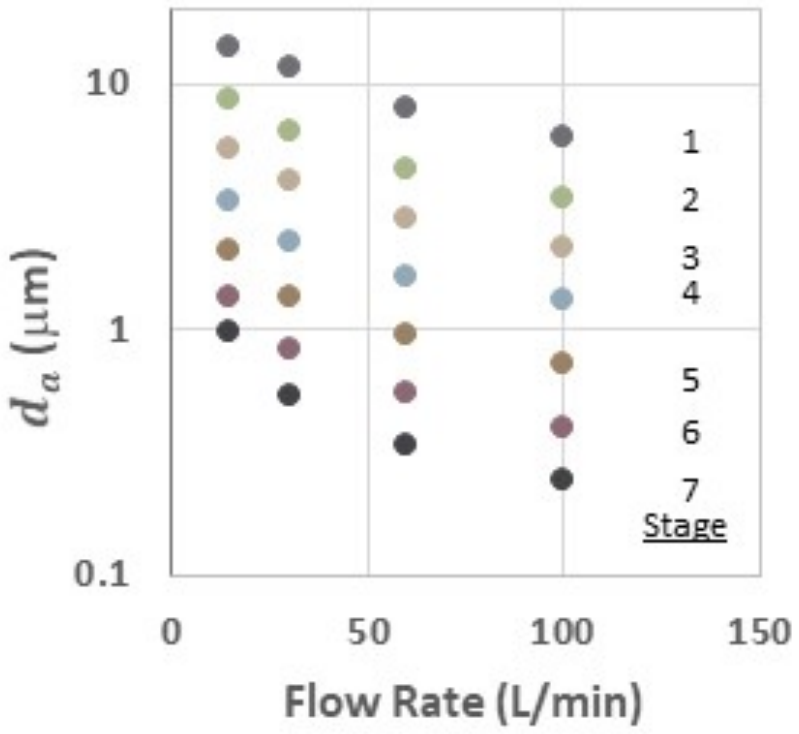
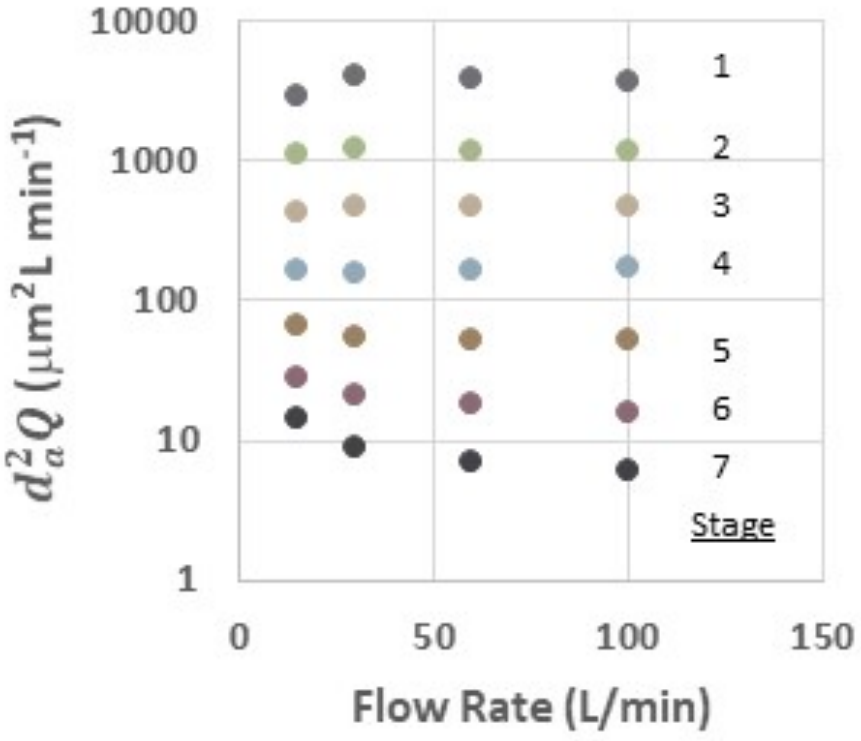
While stage cutoff diameters vary with flow rate, the impaction parameter cutoffs do not

Cutoff Diameters For NGI Stages



Impaction Parameter Cutoffs for NGI Stages



Next Generation Impactor

Source: Marple VA, Olson BA, Santhanakrishnan K, Roberts DL, Mitchell JP, Hudson-Curtis BL. Next generation pharmaceutical impactor. A new impactor for pharmaceutical inhaler testing. Part III. Extension of archival calibration to 15 L/min. J Aerosol Med. 2004;17:335–43.

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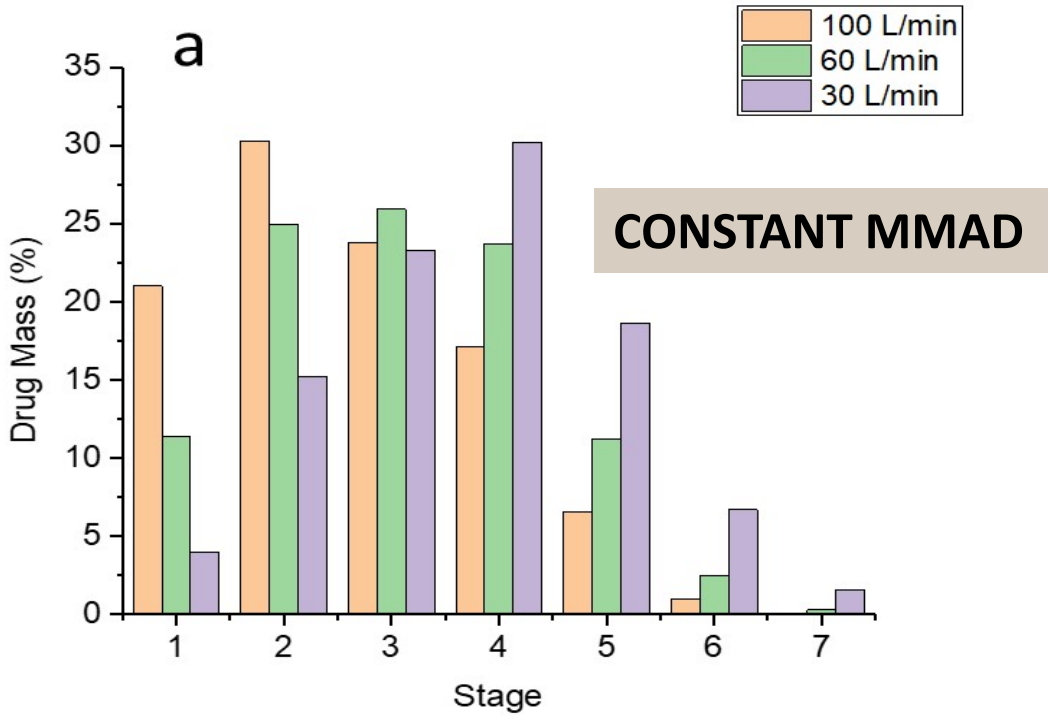
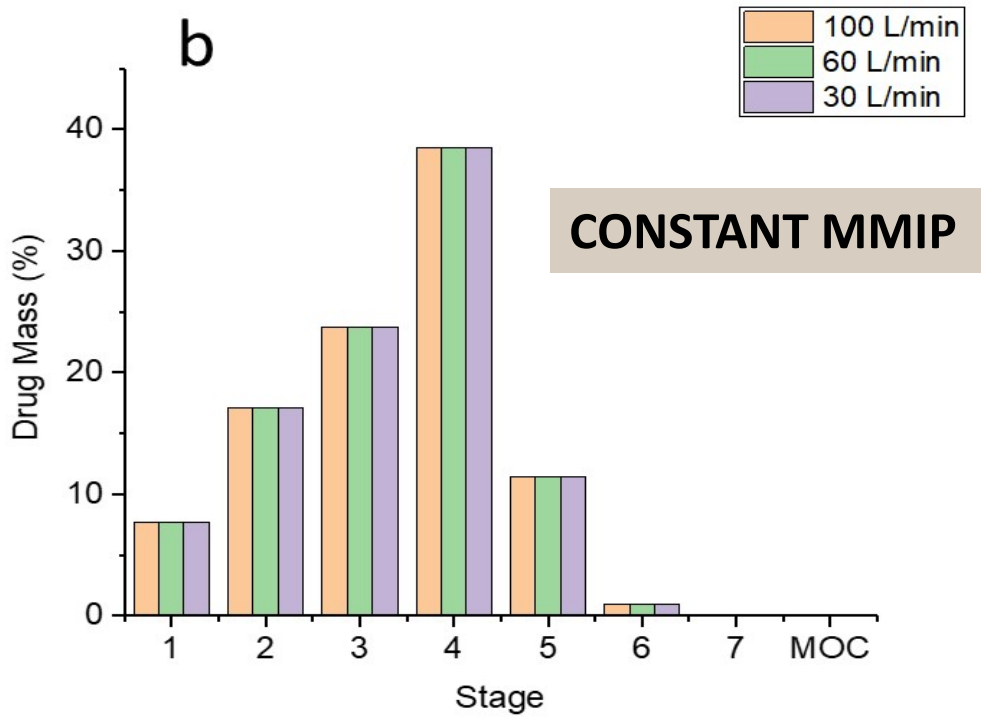
Which *in vitro* measure of flow rate dependence is consistent with *in vivo* delivery?





Q (L/min)	MMAD (μm)	$FPD_{<3.3\mu m}$ (μg)	MMIP (μm^2 L/min)	$FPD_{S4\text{-}F}$ (μg)
30	3.5	45	398	58
60	3.5	45	816	38
100	3.5	46	1282	25

Q (L/min)	MMAD (μm)	$FPD_{<3.3\mu m}$ (μg)	MMIP (μm^2 L/min)	$FPD_{S4\text{-}F}$ (μg)
30	3.9	38	466	43
60	2.8	49	466	43
100	2.2	61	466	43

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Q index:
A quantitative metric for assessing flow rate dependence

$$Qindex = \frac{(TLD_{6kPa} - TLD_{1kPa})}{TLD_{\max}} x100$$

N = 27 Data Sets

Sign: + sign indicates that TLD is increasing with increasing ΔP
- sign indicates that TLD is decreasing with increasing ΔP

Magnitude of *Q index*: ≤ 15% = **low**; 15-40% = **medium**; >40% = **high**

If an <u>impactor</u> is used, *Q index* <u>must</u> be calculated from stage groupings (d_a^2Q cutoffs as opposed to size cutoffs)

Source: Weers J, Clark A: The impact of inspiratory flow rate on drug delivery to the lungs with dry powder inhalers. Pharm Res, 2017, 34: 507-528.

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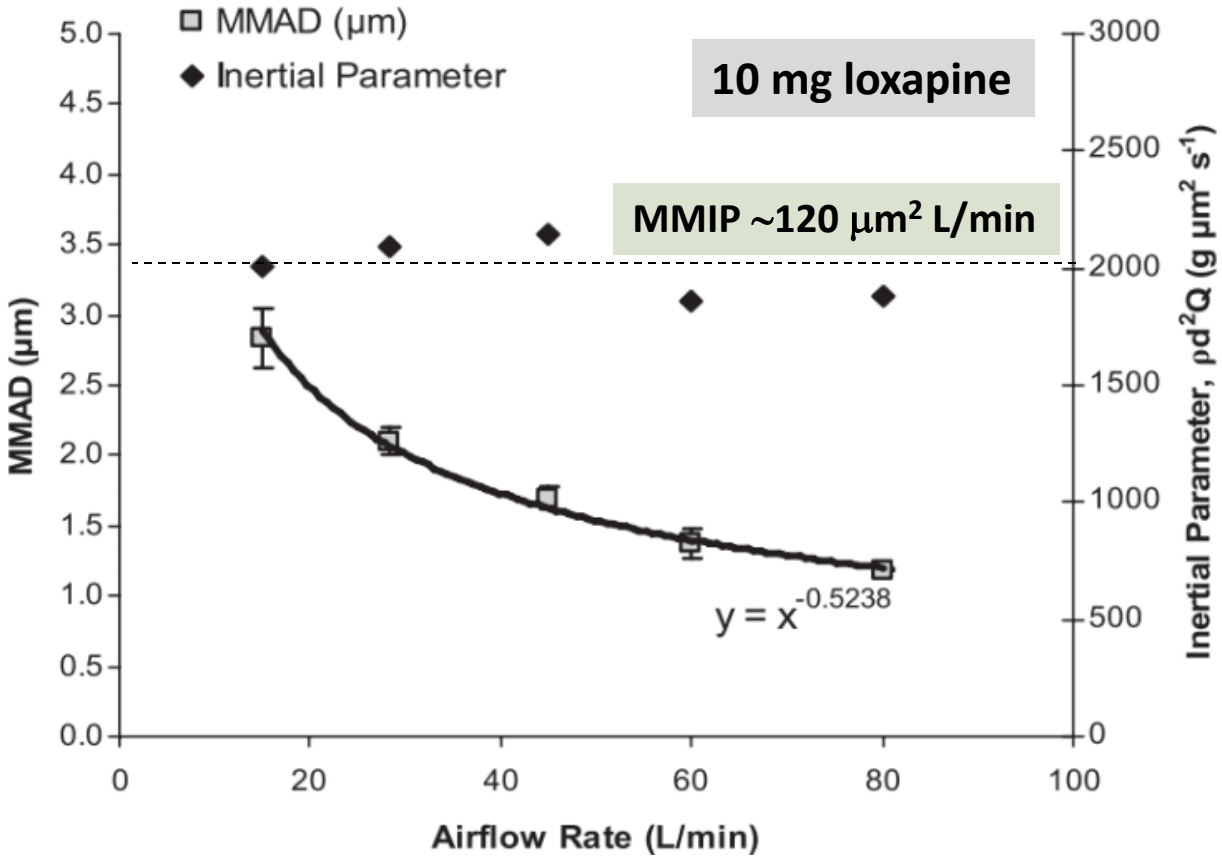
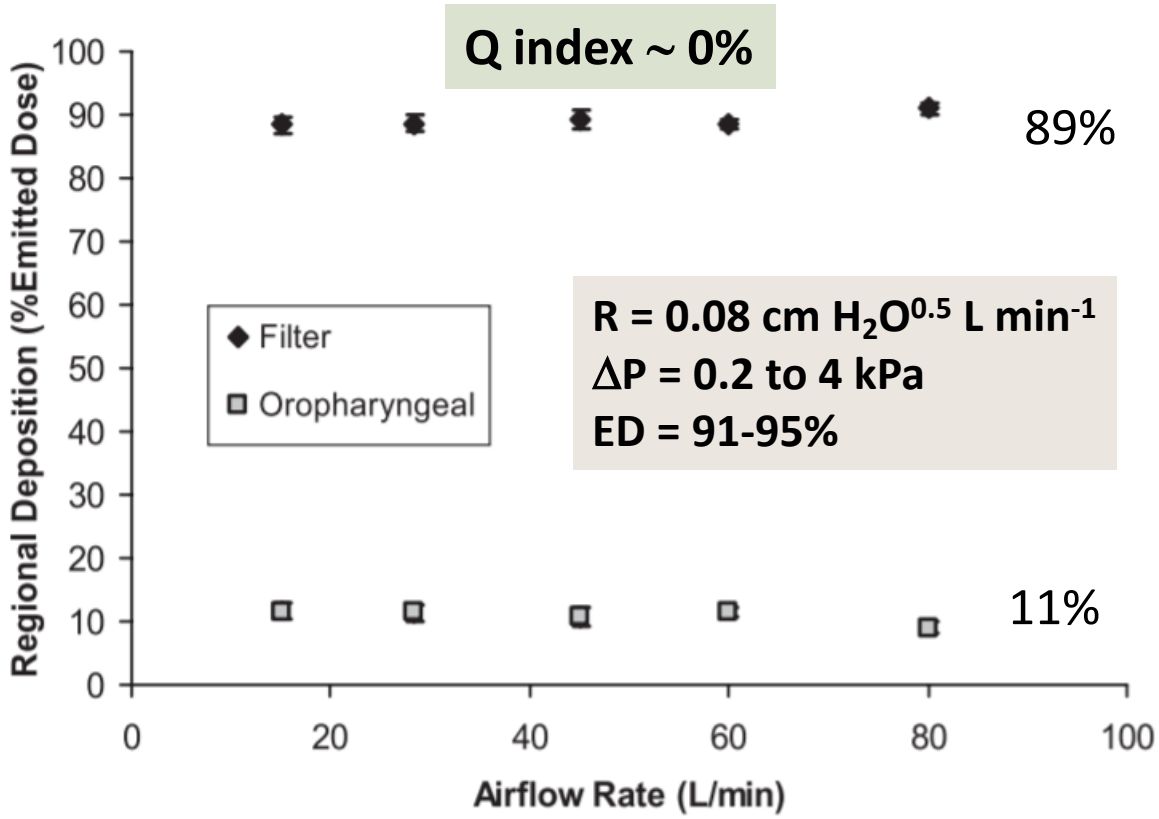
Constant MMIP as a function of Q leads to constant deposition in the URT and LRT (condensation aerosol)





Source: Dinh et al: In vitro aerosol deposition in the oropharyngeal region for Staccato® loxapine. J Aerosol Med Pulm Drug Deliv. 2010;23:253-260.

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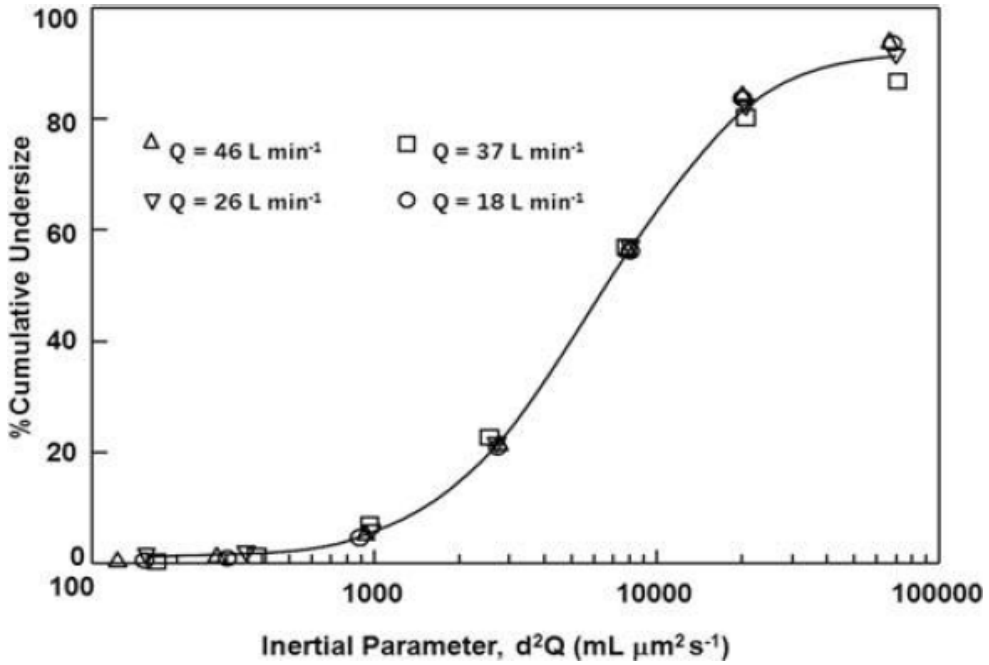
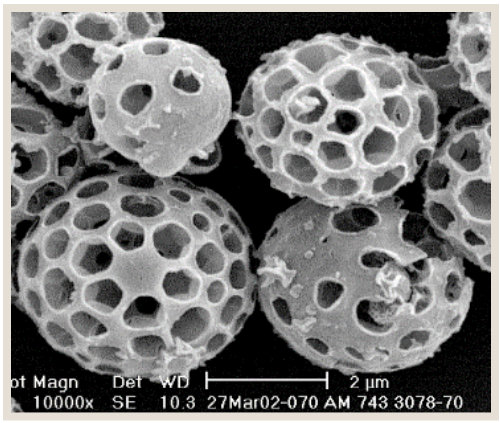
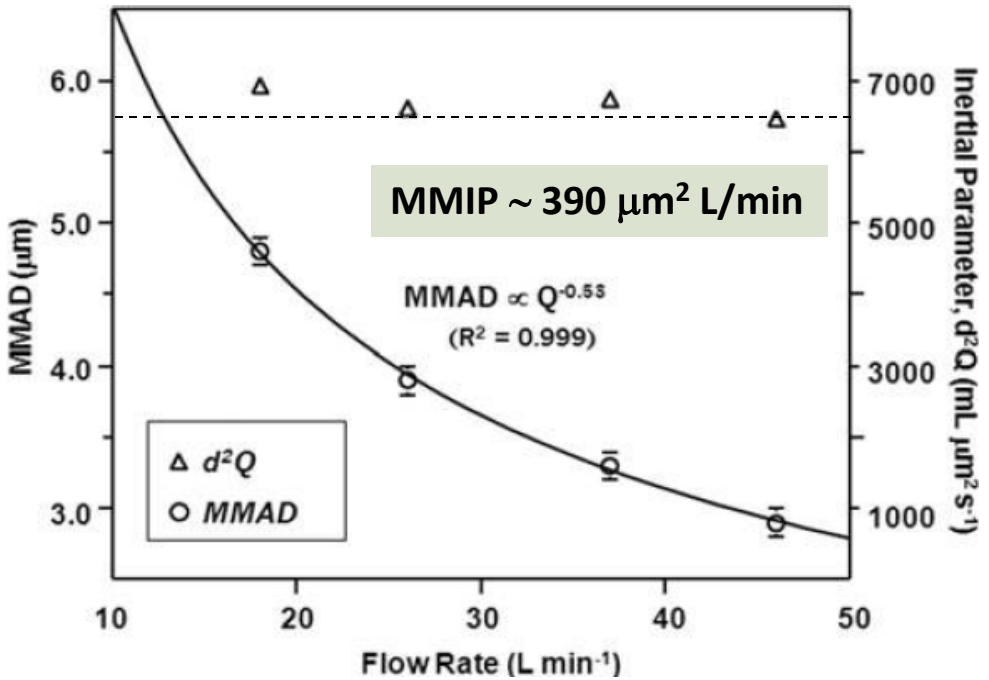
Constant MMIP as a function of Q leads to constant deposition in the URT and LRT (dry powder aerosol)







***Q index* = +2.7%**

ΔP (kPa)	Q (L min^{-1})	DD (%ND)	URT (%DD)	TLD (%DD)
1.0	16	85	17.6	82.4
2.0	22	88	14.8	85.2
4.0	32	90	16.7	83.3
6.0	40	92	14.1	85.9

Source: Weers et al: Dose emission characteristics of placebo PulmoSphere™ particles are unaffected by a subject's inhalation maneuver.
J Aerosol Med Pulm Drug Deliv. 2013;26:56-68.

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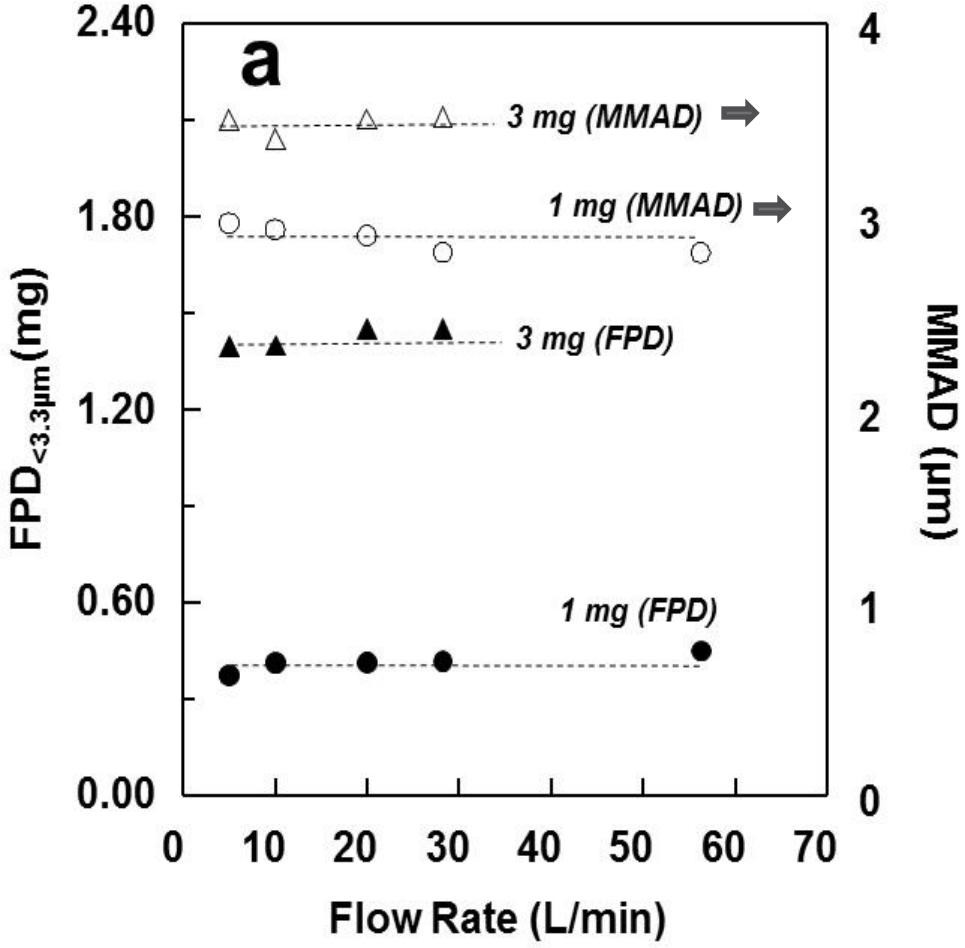
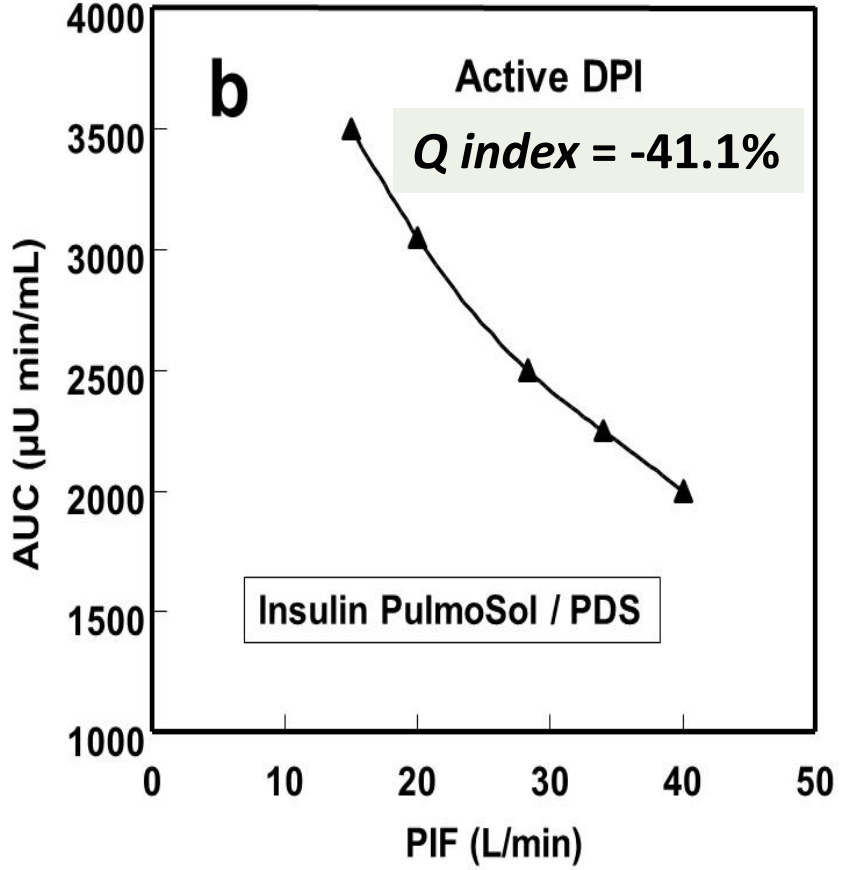
Delivery of insulin inhalation powder (Exubera®) with an 'active' dry powder inhaler





Source: Weers J, Clark A: The impact of inspiratory flow rate on drug delivery to the lungs with dry powder inhalers. Pharm Res, 2017, 34: 507-528.

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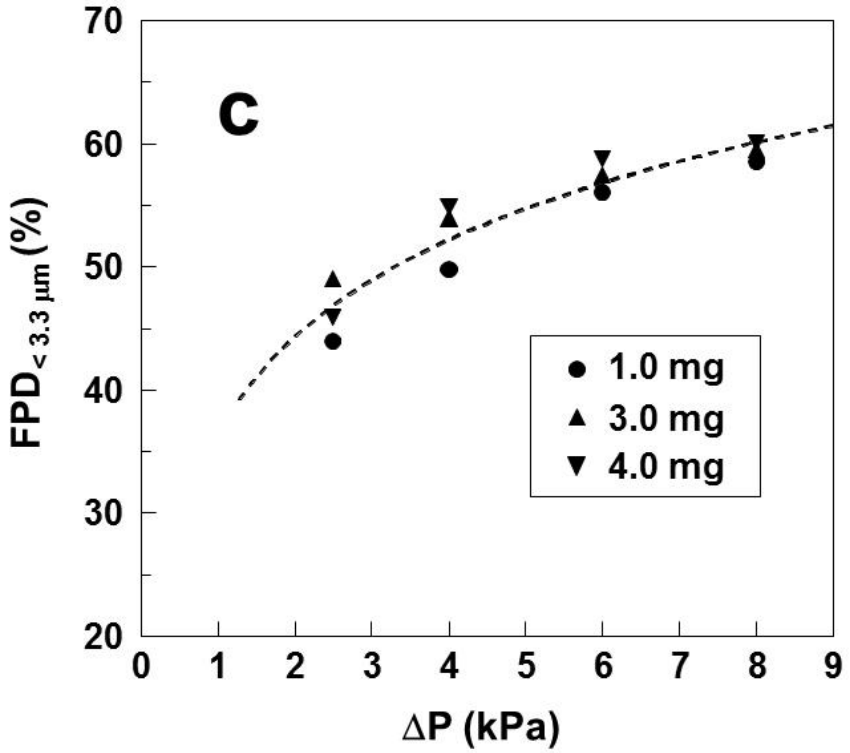
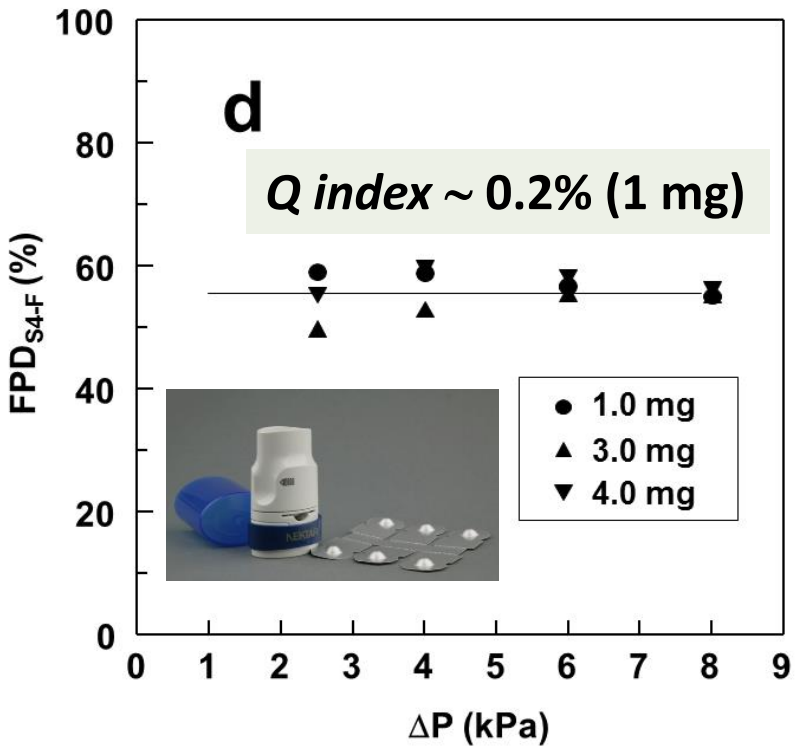
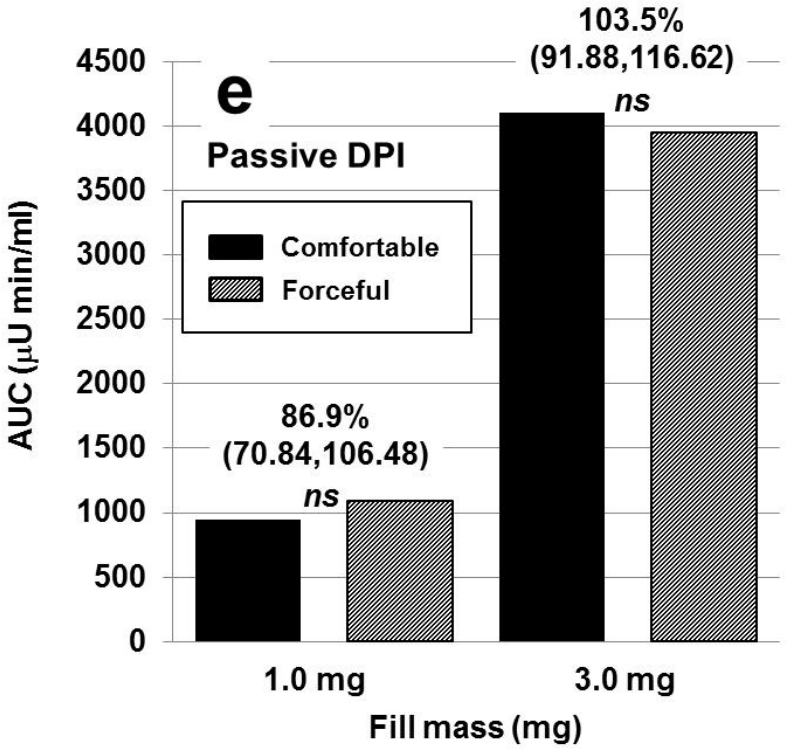
Delivery of insulin inhalation powder with a 'passive' dry powder inhaler







Source: Weers J, Clark A: The impact of inspiratory flow rate on drug delivery to the lungs with dry powder inhalers. Pharm Res, 2017, 34: 507-528.

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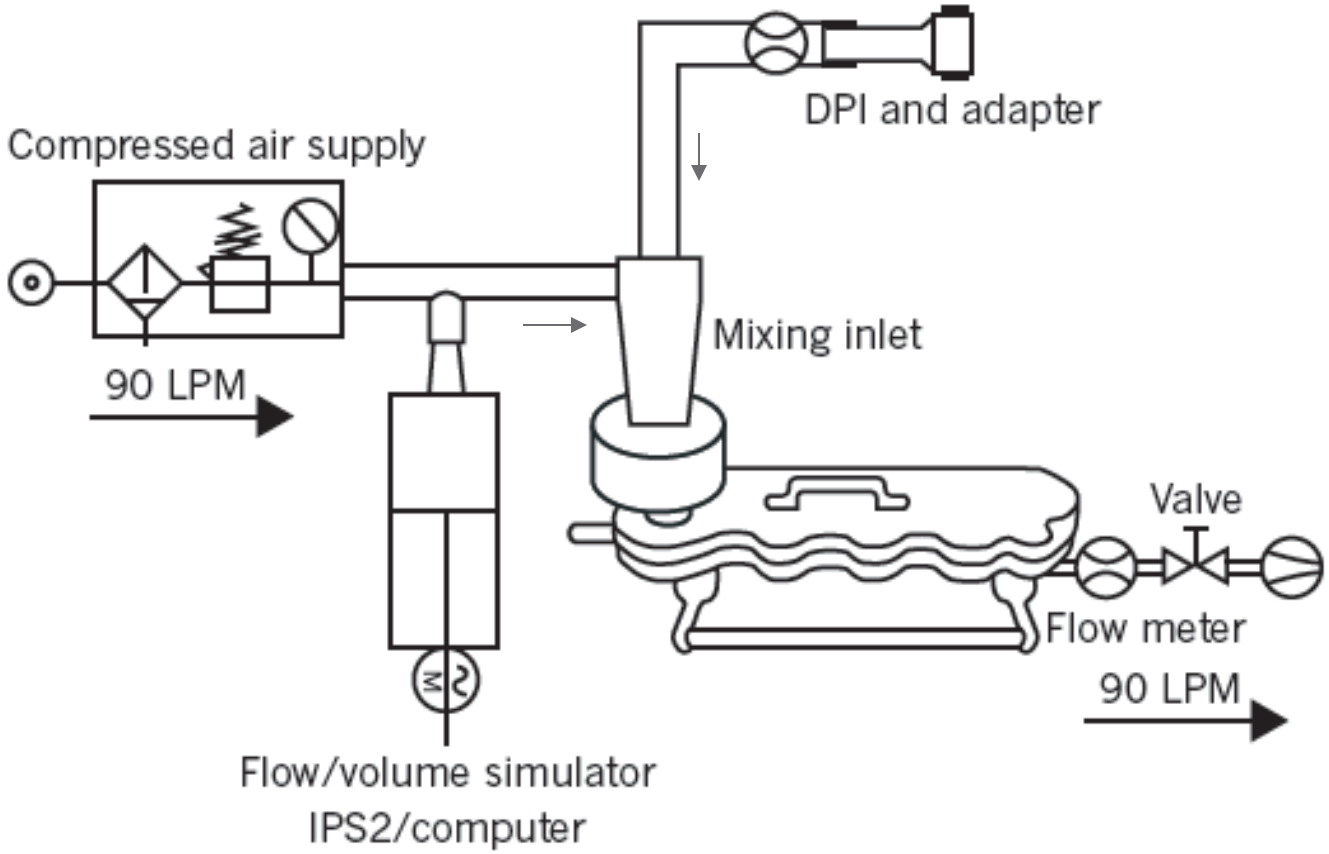
A flow/volume simulator and mixing inlet enables assessment of realistic breathing profiles with an NGI



DPI = dry powder inhaler; LPM = liters per minute.

- **Bypass flow is added to achieve a constant air flow in the impactor**
  - This enables calculation of an aerodynamic size
- **Unfortunately, this method shifts the distribution of particles on the impactor stages, thereby destroying the IVIVC with respect to particle deposition in the respiratory tract**
- **Better off using realistic breathing profiles with no mixing inlet, assessing MMIP and stage groupings!**

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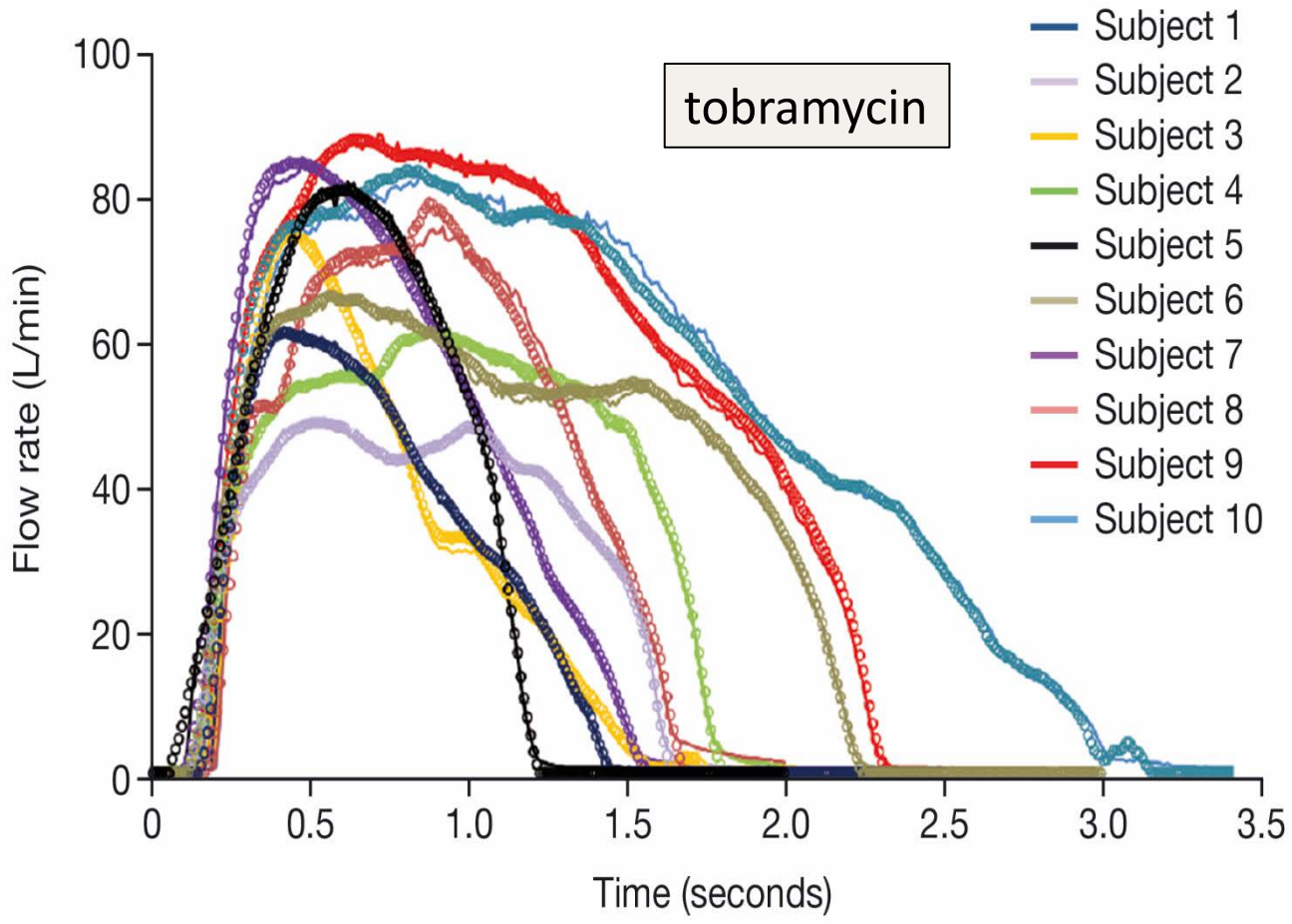
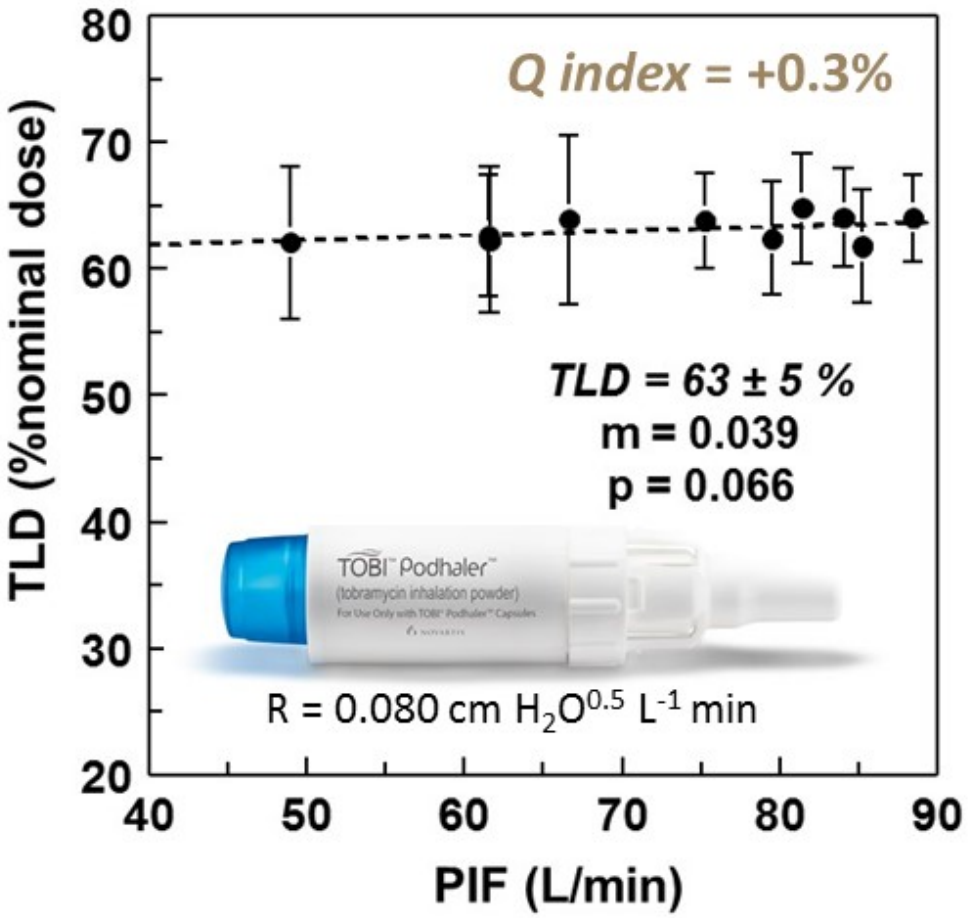
Flow rate independence in TOBI® Podhaler™

Patients need not inhale forcefully – Reduced Q lowers cough response





Source: Haynes et al: Inhalation of tobramycin using simulated cystic fibrosis patient profiles. *Pediatr Pulmonol*. 2016, 51: 1159-1167.

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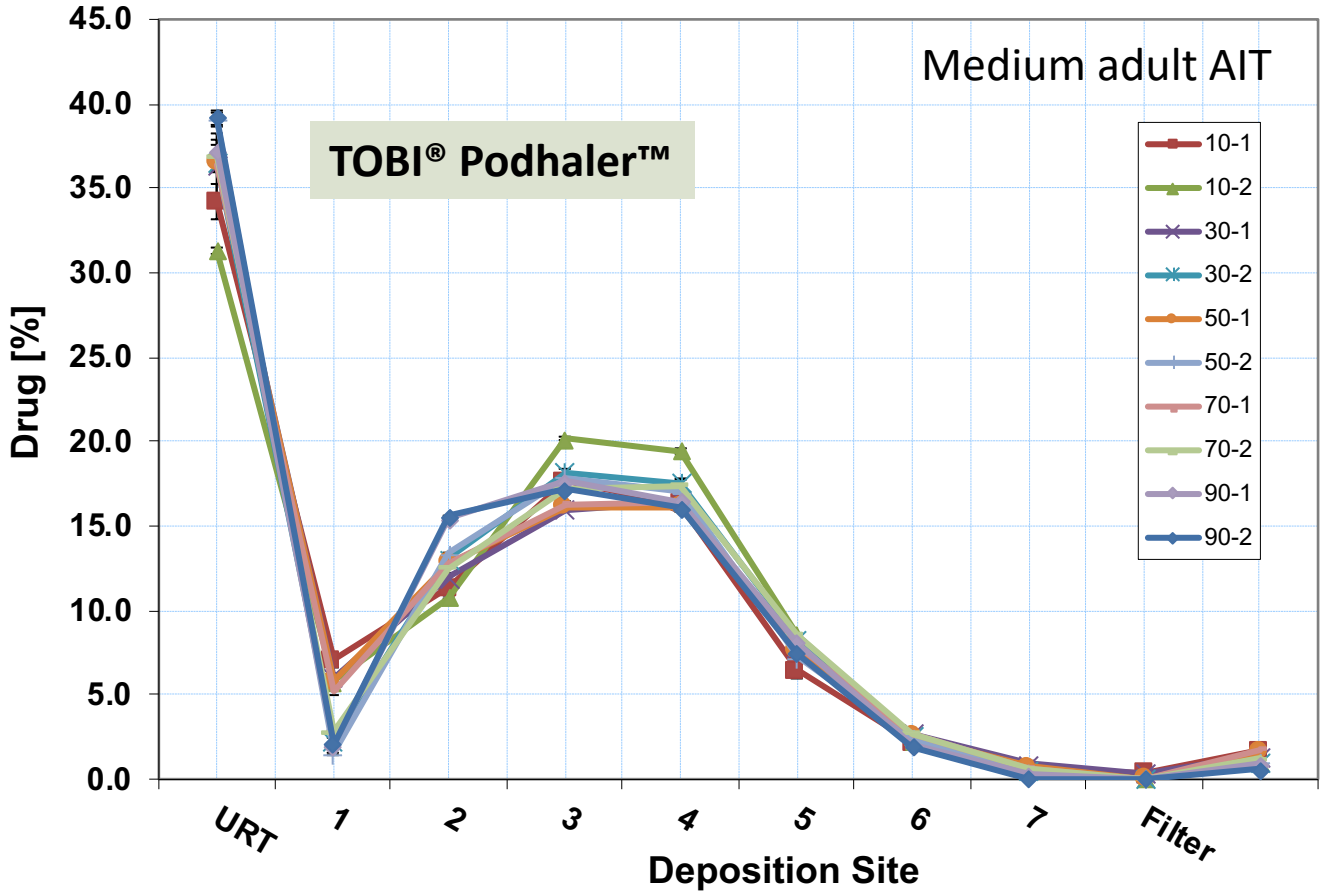
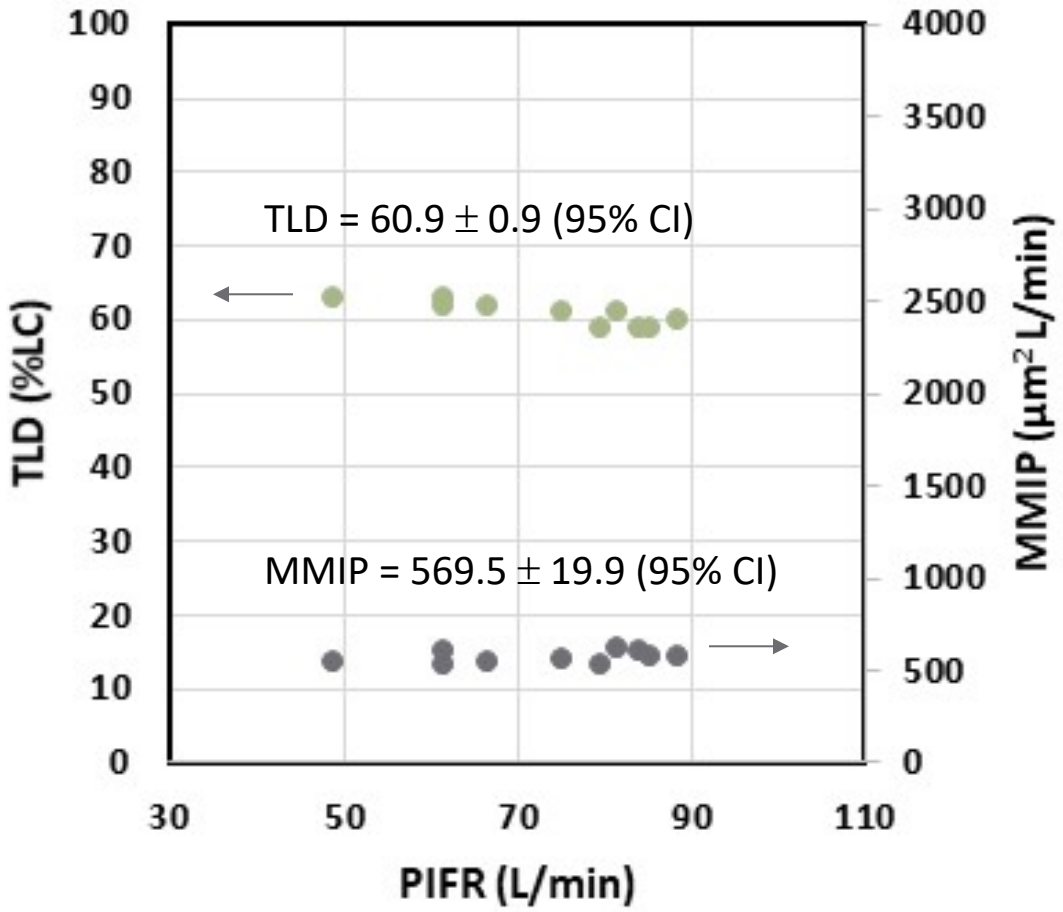
Stage deposition post-AIT is largely independent of PIFR for TOBI® Podhaler™ (constant TLD and MMIP)

Realistic Breathing Profiles / Alberta Idealized Throat / Next Generation Impactor





Source: A. Haynes et al: Pediatr. Pulmonol., 48 (Suppl 36) (2013) 352.

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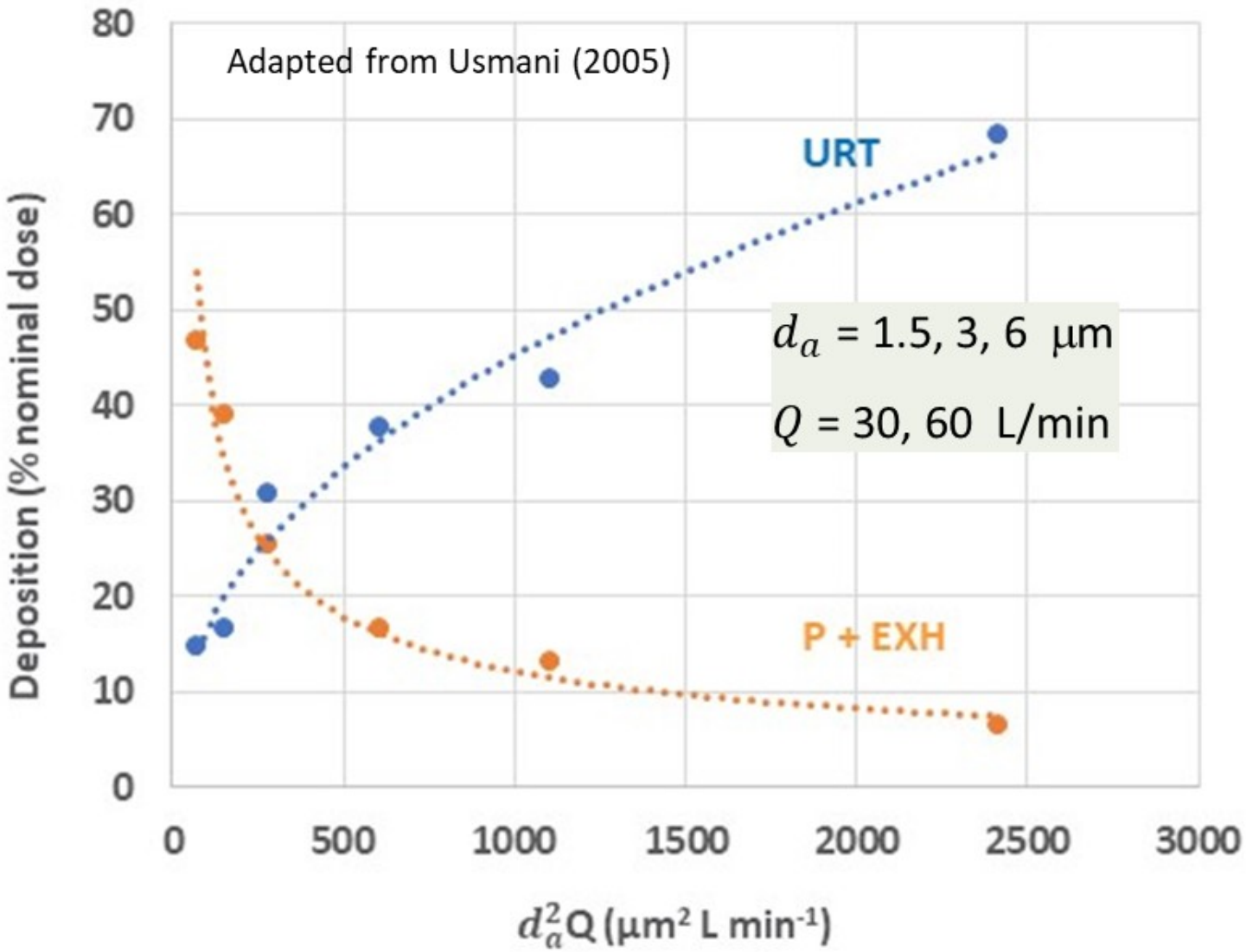
Inertial impaction controls regional deposition of monodisperse albuterol droplets in adult asthmatics



Source: Usmani et al: Regional lung deposition and bronchodilator response as a function of beta2-agonist particle size. Am J Respir Crit Care Med. 2005; 172:1497-1504.

Can we develop drug/device combinations that more effectively shift drug deposition from the URT to the small airways?

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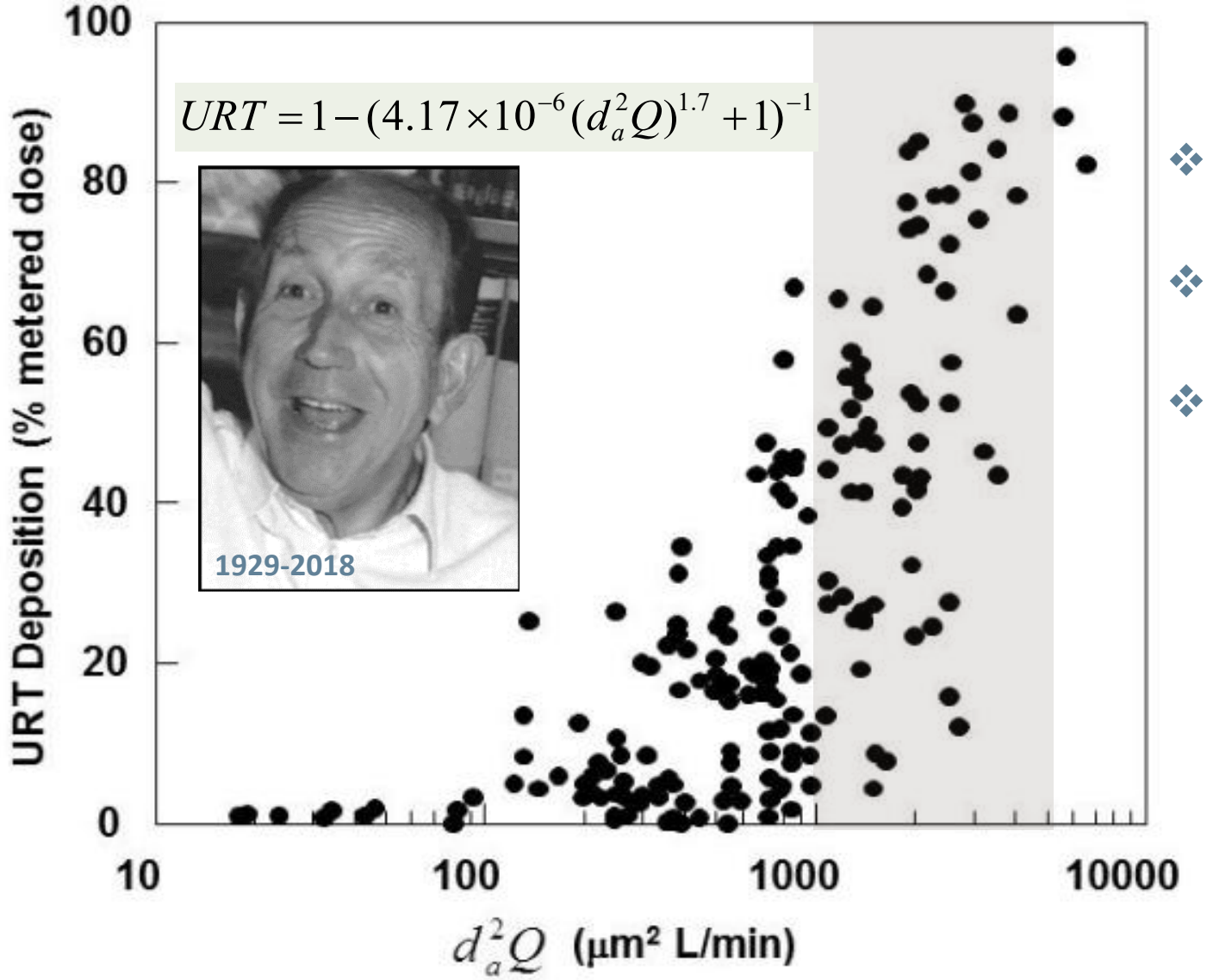
Current marketed formulations are right in the sweet spot to achieve high interpatient variability in lung delivery



- Deposition in the URT is due to **inertial impaction**
- Current marketed inhalers have mean $d_a^2 Q$ values between ~1,000 and 5,000 µm² L/min
- Large variability in URT deposition is the result of anatomical differences in soft tissue in mouth and throat

Source: Stahlhofen W, Rudolf G, James AC: Intercomparison of regional deposition data. J Aerosol Med. 1989, 2:285-308.

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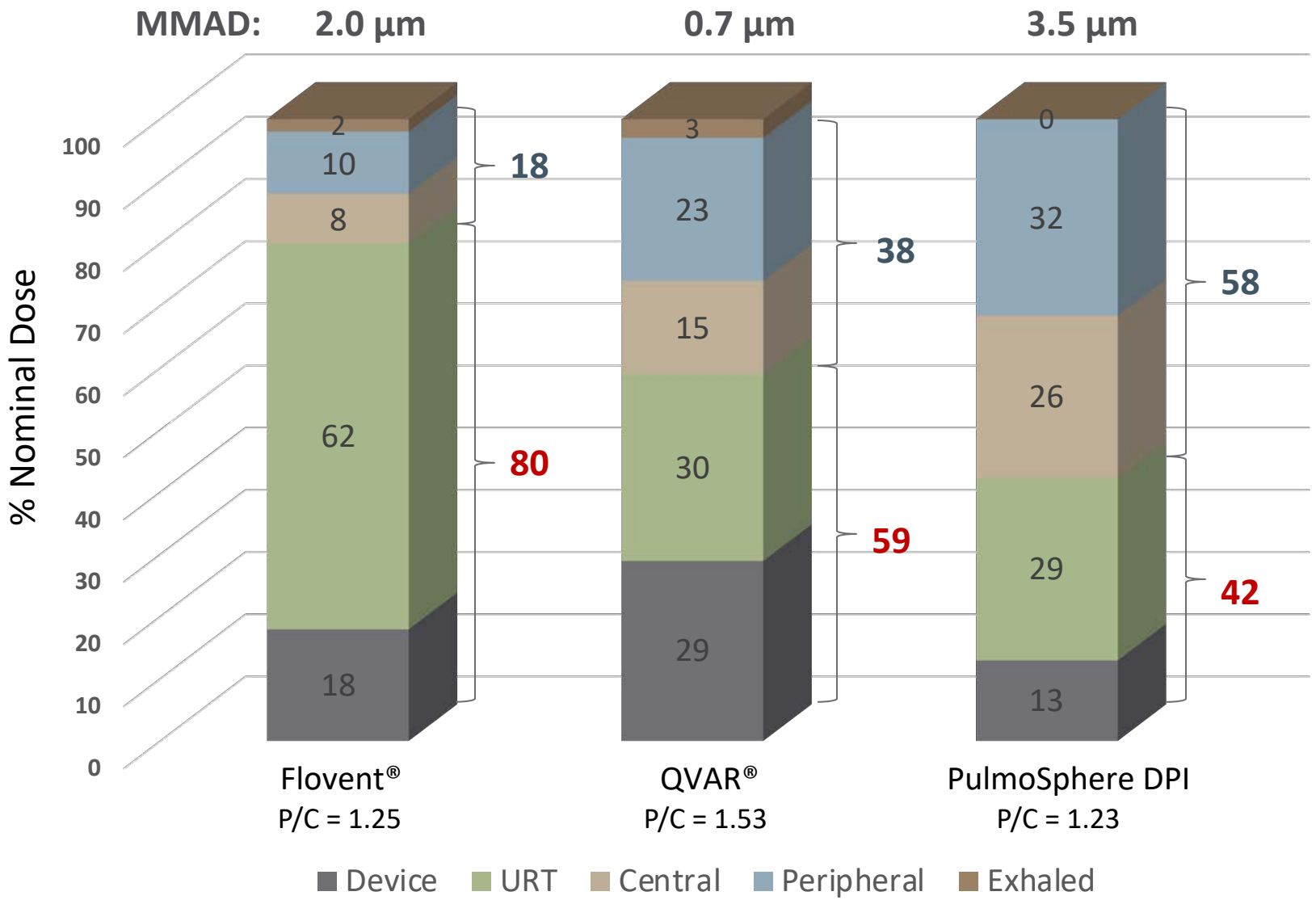
Targeting of Inhaled Corticosteroids in the Lungs

Formulation of 'extrafine' particles is not a prerequisite for delivery to the lung periphery



Source: Leach CL, Kuehl PJ, Chand R, McDonald JD: Respiratory tract deposition of HFA-Beclomethasone and HFA-Fluticasone in asthmatic patients. J Aerosol Med Pulm Drug Deliv. 2016, 29:127-133.

Source: Duddu SP et al: Improved lung delivery from a passive dry powder inhaler using an engineered PulmoSphere powder. Pharm Res. 2002, 19:689-695.

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6.5 µm particles can provide significant deposition in the lung periphery if inhaled slowly

- **Test Substance:** ^{99m}Tc Sulphur colloid in water/propylene glycol (90/10 v/v)
- **Delivery System:** Small-volume nebulizer equipped with a 100-mL aerosol holding chamber, a two-way control valve with integrated mouthpiece
- **Characterization:** Droplet size was determined via laser diffraction (VMD ~ MMAD = 6.5 ± 0.2, GSD ~ 2)
- **Imaging:** Gamma scintigraphy with 24-h clearance measurements to assess peripheral deposition

d_a (µm)	Q (L min^{-1})	$d_a^2 Q$ (µm^2 L min^{-1})	Respiratory Tract Deposition Mean (SD), %ND		
			URT	TLD	P
6.5	30	1267.5	51.9 (14.2)	47.8 (14.1)	27.1 (5.9)
6.5	8	338	28.5 (15.8)	71.3 (15.6)	47.0 (5.5)

Source: Clark AR et al: The effect of biphasic inhalation profiles on the deposition and clearance of coarse (6.5 µm) bolus aerosols. J Aerosol Med. 2007; 20:75-82.

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Control of the inspiratory flow rate and volume of nebulized drug improves delivery of ICS to the small airways

United States Patent
Muellinger et al.

(10) **Patent No.: US 8,834,848 B2**
(45) **Date of Patent: Sep. 16, 2014**

FLOW AND VOLUME REGULATED INHALATION FOR TREATMENT OF SEVERE ORAL CORTICOSTEROID-DEPENDENT ASTHMA

Inventors: **Bernard Muellinger**, Munich (DE); **Gerhard Scheuch**, Wohrathal (DE); **Thomas Hofmann**, Doylestown, PA (US); **Philipp Kroneberg**, Olching (DE)

Assignee: **Activaero GmbH Research & Development**, Gauting (DE)

Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(58) **Field of Classification Search**
USPC 424/43, 45, 400, 489; 128/200.16, 128/200.2, 203.13, 203.15; 514/127, 169, 514/170, 862, 958; 600/538
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,187,765	B1	2/2001	Harris et al.
6,401,710	B1	6/2002	Scheuch et al.

(Continued)

FOREIGN PATENT DOCUMENTS

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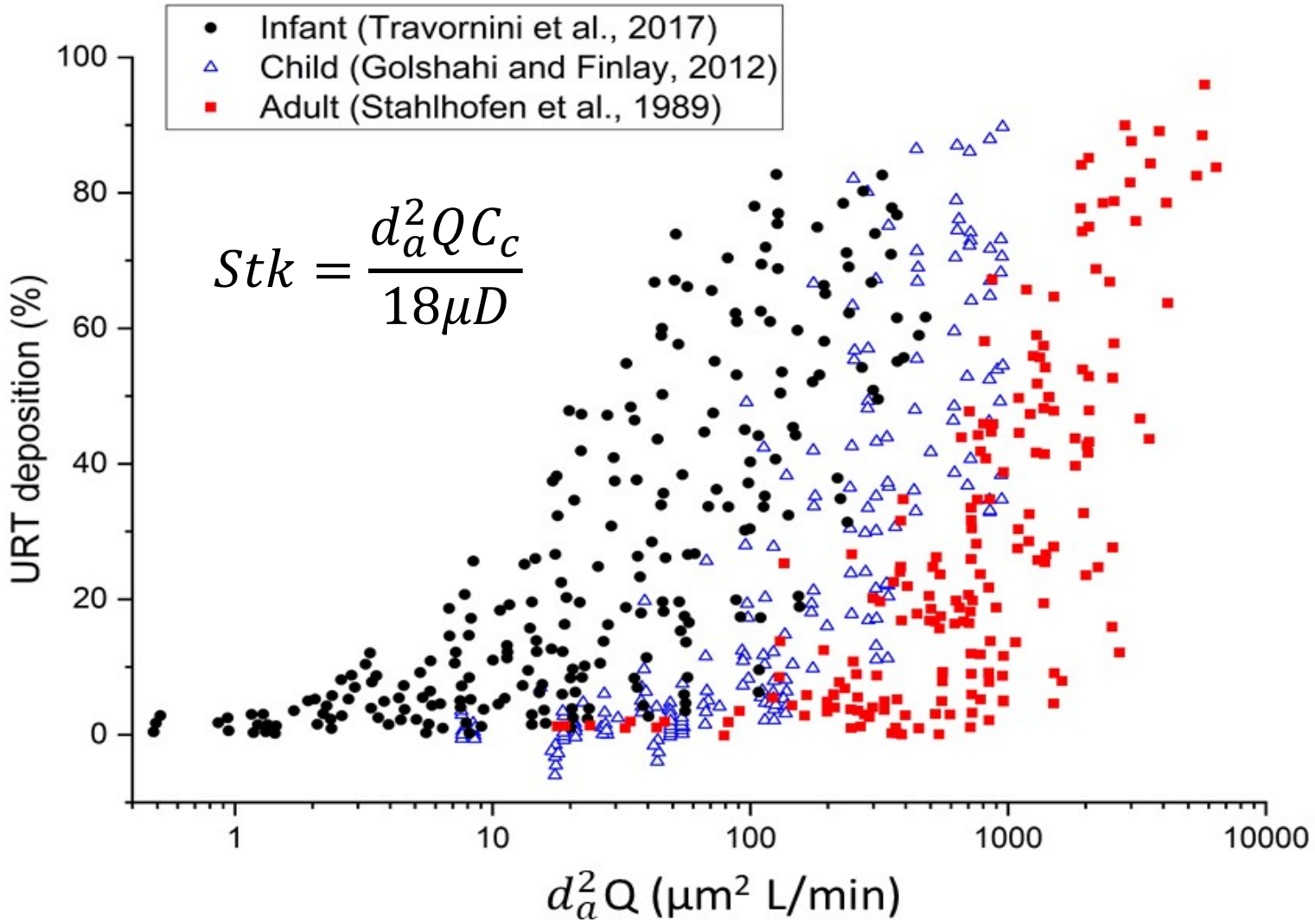
Bypassing deposition in the URT of children and infants requires drug/device combinations with smaller impaction parameters



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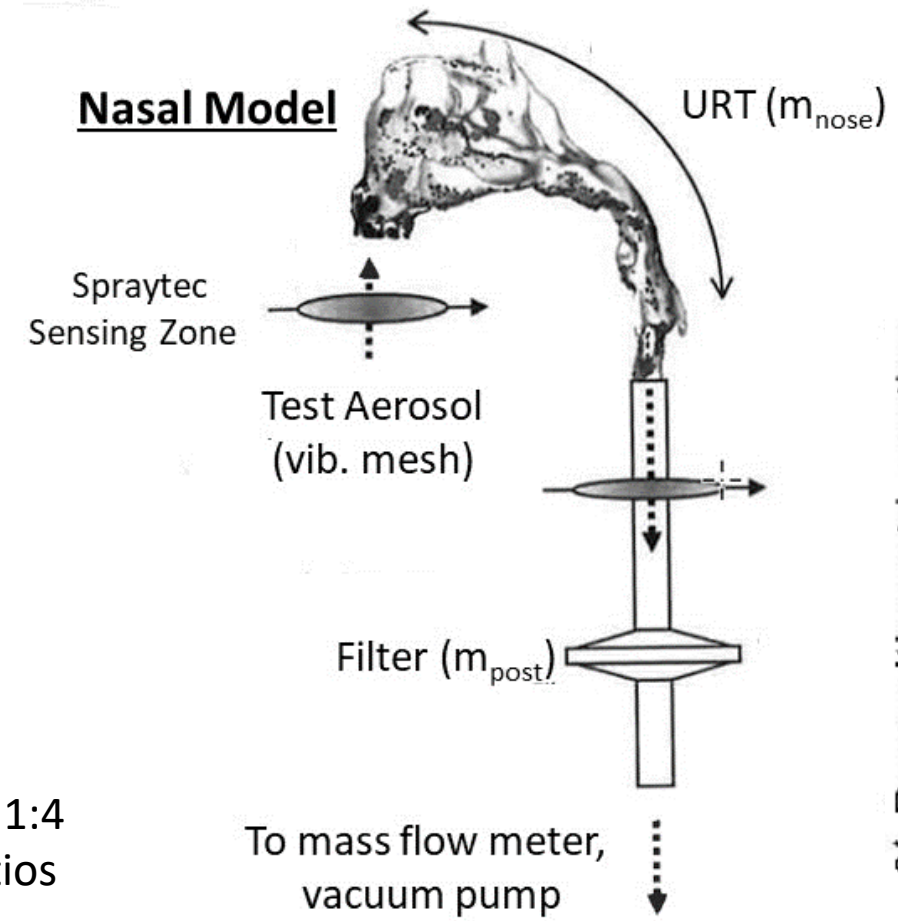
Aerosol delivery of ‘surfactant’ to neonates using nasal CPAP may seem impossible…

Breathing cycles – 1:3 or 1:4 inhalation:exhalation ratios



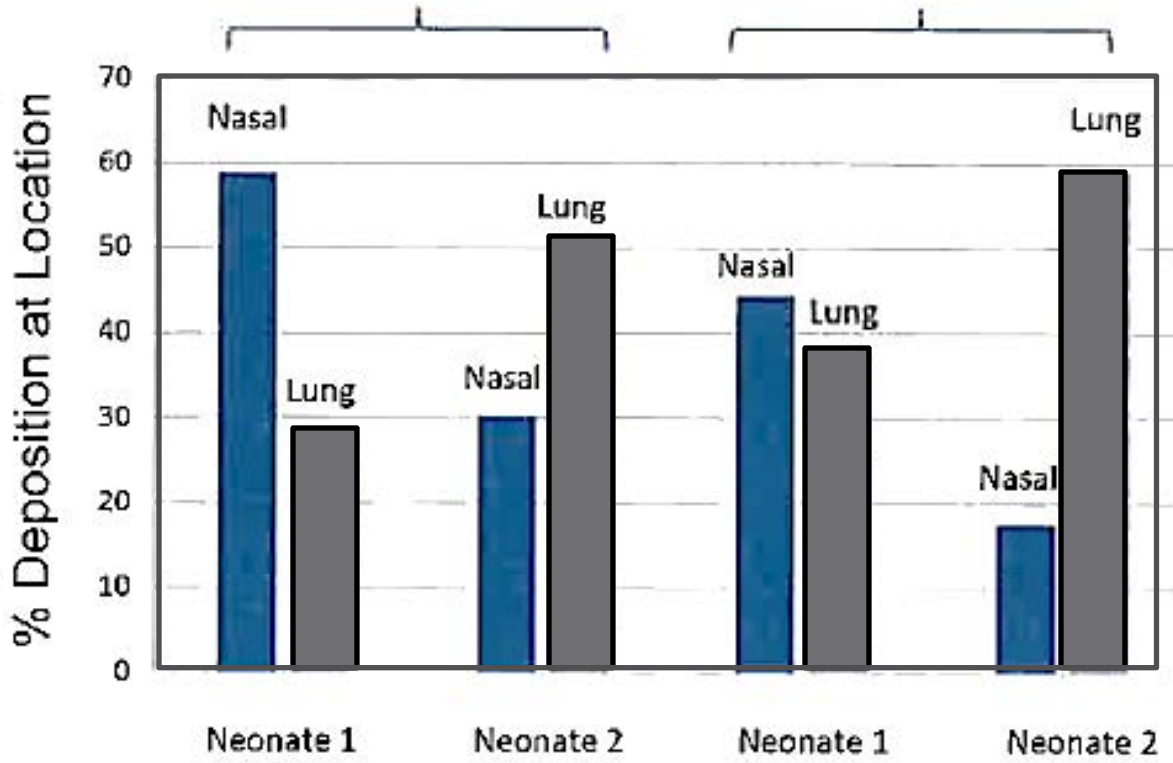
$Q = 1.9\ L/min$

$d_a^2 Q = 17.1$

3 µm MMAD

$d_a^2 Q = 7.6$

2 µm MMAD



Source: Clark AR et al: Aerosol delivery in term and preterm infants: The final frontier. Respiratory Drug Delivery 2018, pp 159-167.

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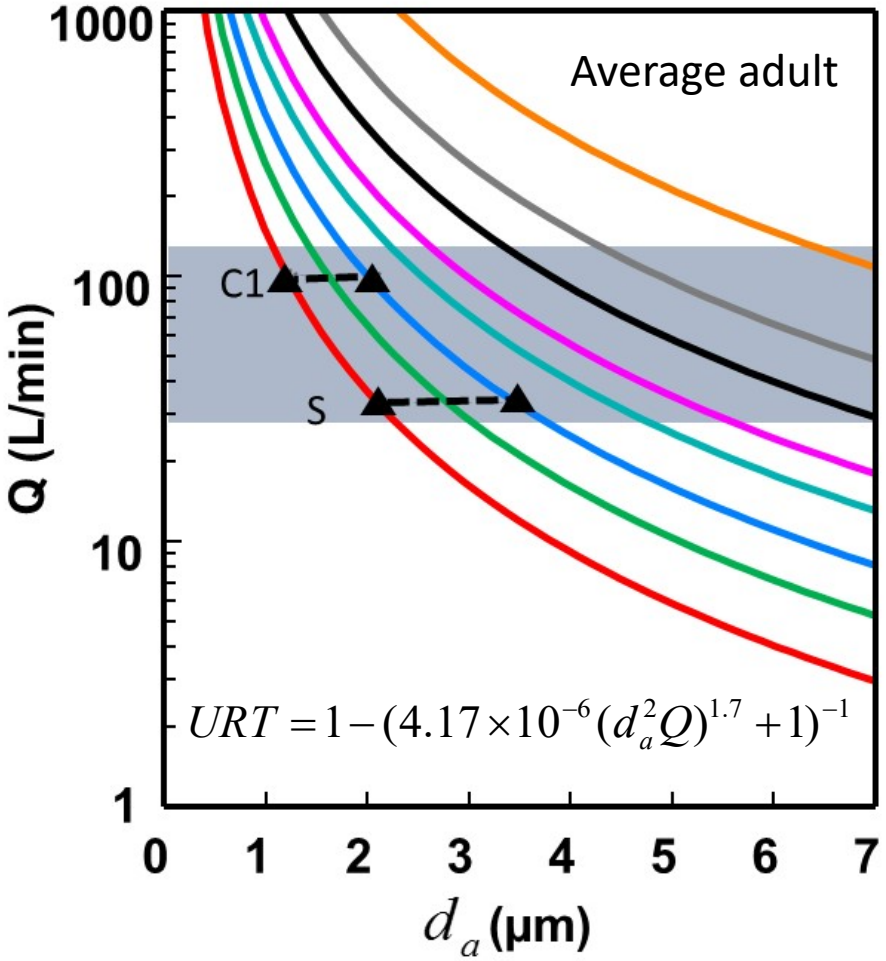
Bypassing deposition in the URT of adults requires that particles have an impaction parameter < 150 µm² L/min



URT	d_a^2Q
0.90	5286
0.70	2388
0.50	1452
0.30	882
0.20	642
0.10	396
0.05	258
0.02	146

Concept1

R = 0.06

Higher resistance device may enable high TLD with less risk of exhaled particles

Source: Stahlhofen W, Rudolf G, James AC: Intercomparison of regional deposition data. J Aerosol Med. 1989, 2:285-308.

Source: Ung K, Weers J, Huang D, Rao R, Son Y-J: Targeted delivery of spray-dried formulations to the lungs. WO 2017 / 042696 A1.

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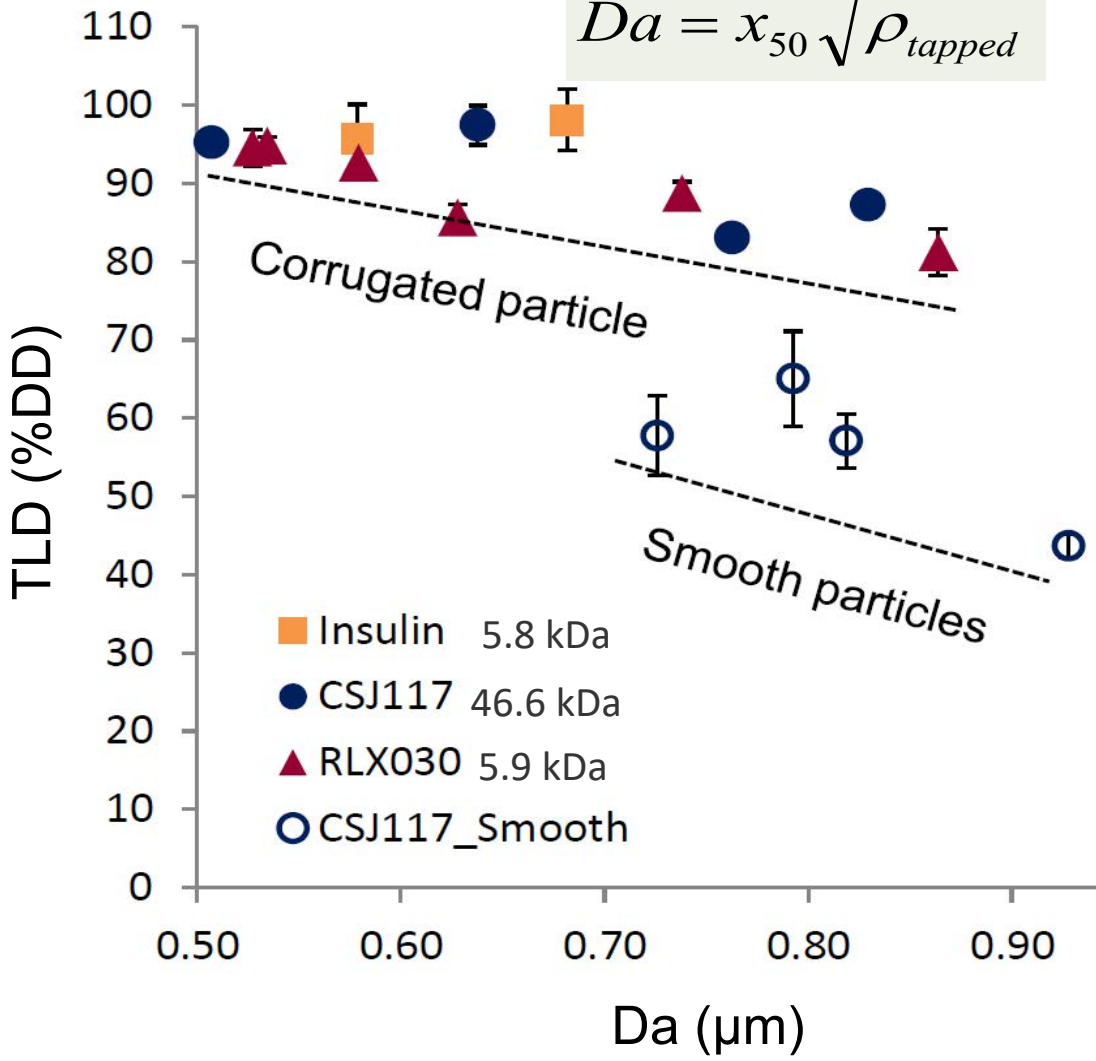
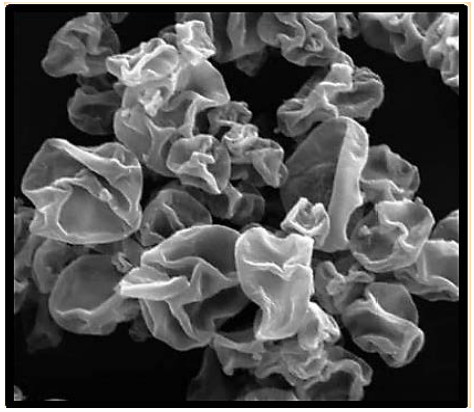
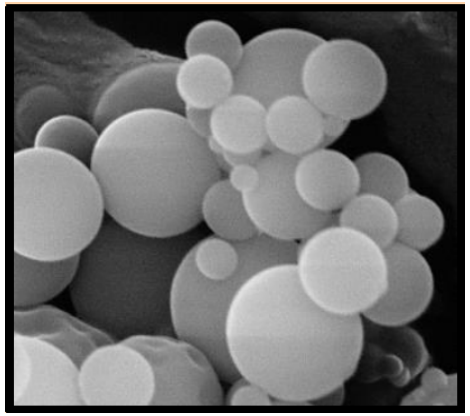
Extrafine corrugated particles with median aerodynamic diameters less than ~0.7 µm enable total lung doses > 90%

$$Da = x_{50}\sqrt{\rho_{tapped}}$$







Dry powder inhalers never fully disperse dry powders

Dispersed particles and their agglomerates must be respirable to bypass deposition in the URT

Source: Ung K, Weers J, Huang D, Rao R, Son Y-J: Targeted delivery of spray-dried formulations to the lungs. WO 2017 / 042696 A1.

Source: Weers J et al: Idealhalers versus realhalers: is it possible to bypass deposition in the upper respiratory tract? J Aerosol Med Pulm Drug Deliv. 2019,32:55-69.

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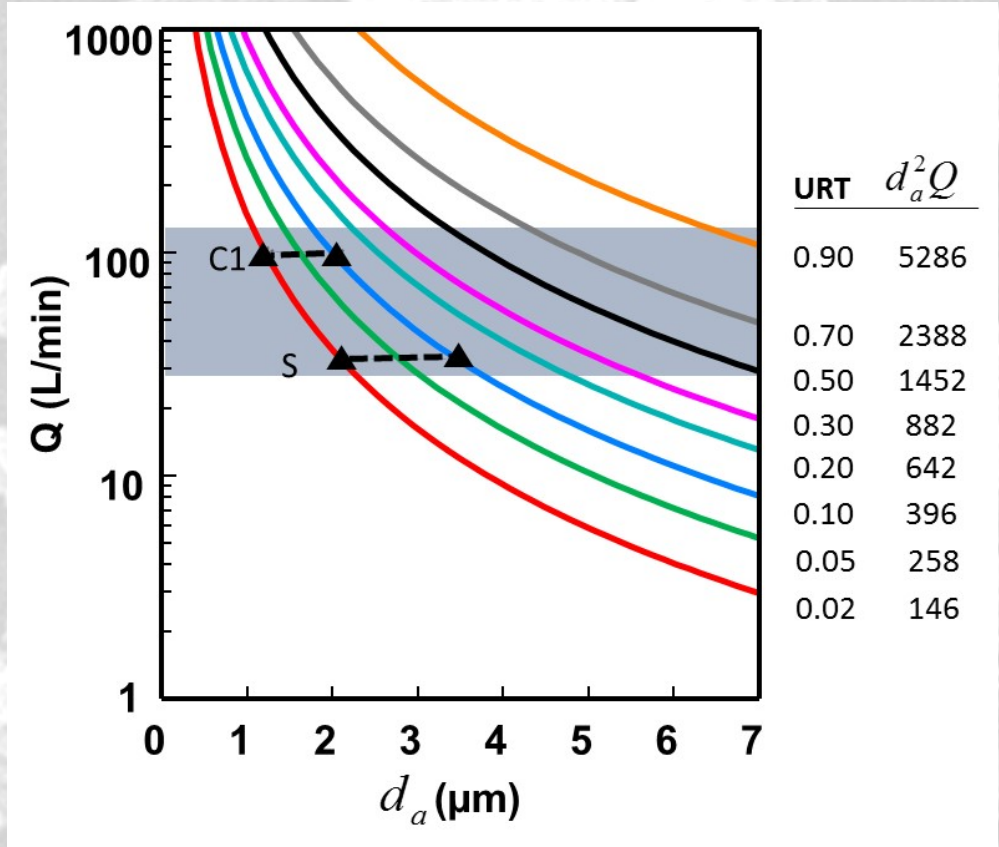
URT deposition of extrafine corrugated insulin particles is consistent with Stahlhofen's empirical equation

Simoon Inhaler: ΔP = 4 kPa (polydisperse particles)

Attribute	Method	Lot A	Lot B
x50 (µm)	Laser diffraction	1.40	1.76
Bulk density (g cm^{-3})	Uniaxial compaction	0.17	0.15
Da (µm)	Calculated	0.58	0.68
MMAD (µm)	NGI	1.78	2.02
d_a^2Q (µm² L/min)	Calculated	105	135
URT deposition (%DD)	AIT	2	5



Source: Ung K, Rao N, Weers J, Huang D, Chan H-K: Design of spray-dried insulin microparticles to bypass deposition in the extrathoracic region and maximize total lung dose. Int J Pharm. 2016, 511:1070-1079.

Source: Weers JG et al: Idealhalers versus realhalers: Is it possible to bypass deposition in the upper respiratory tract? J Aerosol Med Pulm Drug Deliv. 2019, 32:55-69.

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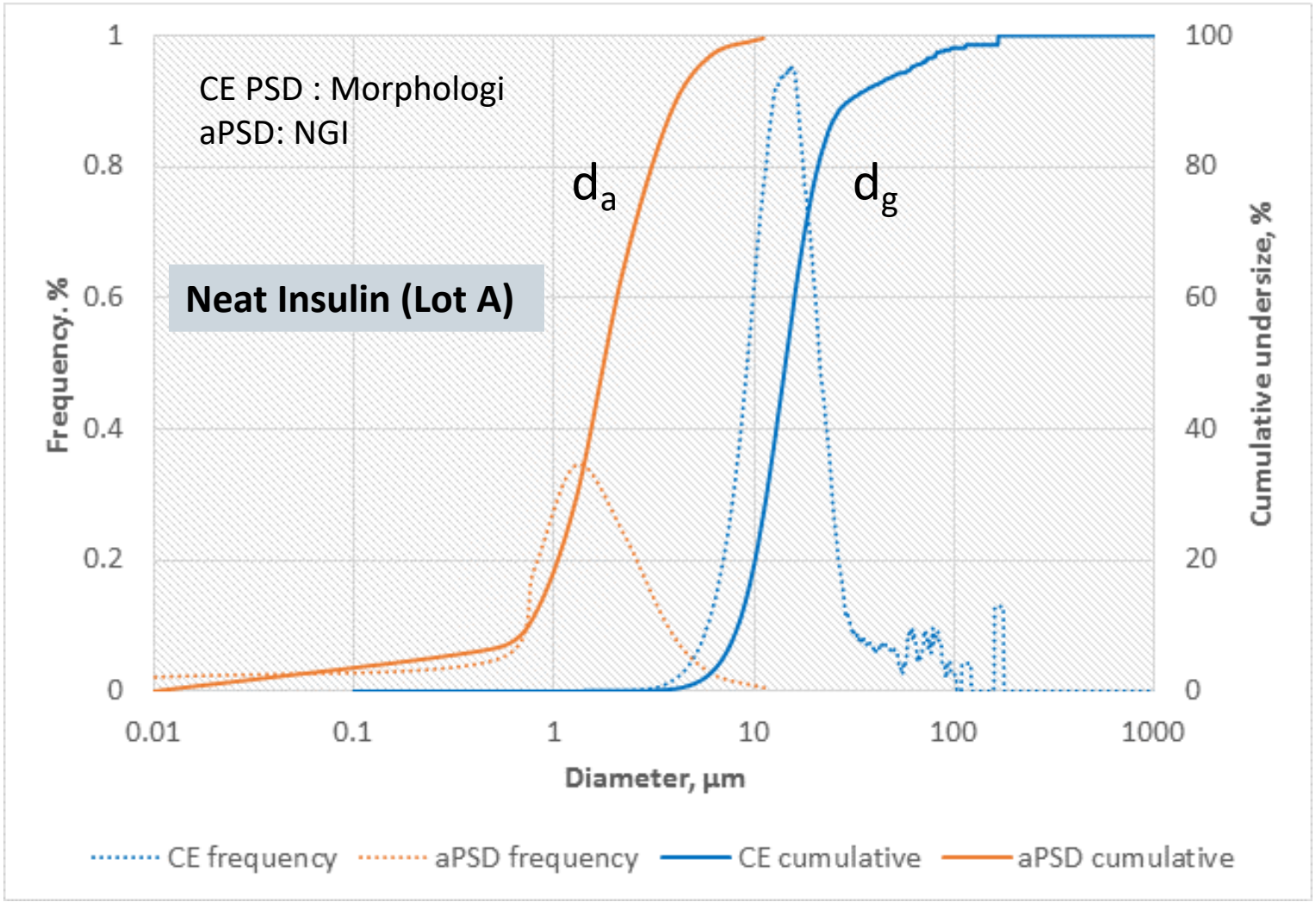
Dry powder aerosols of PP are comprised of ‘large porous agglomerates’



$$d_a^{agg} = d_g^{agg}\sqrt{\rho_{agg}}$$

$$\rho_{agg} = \left[\frac{1.78}{12}\right]^2 = 0.02 g \cdot cm^{-3}$$

Morphologi G3 (Malvern)

Source: Weers J et al: Idealhalers versus realhalers: is it possible to bypass deposition in the upper respiratory tract? J Aerosol Med Pulm Drug Deliv. 2019, 32:55-69.

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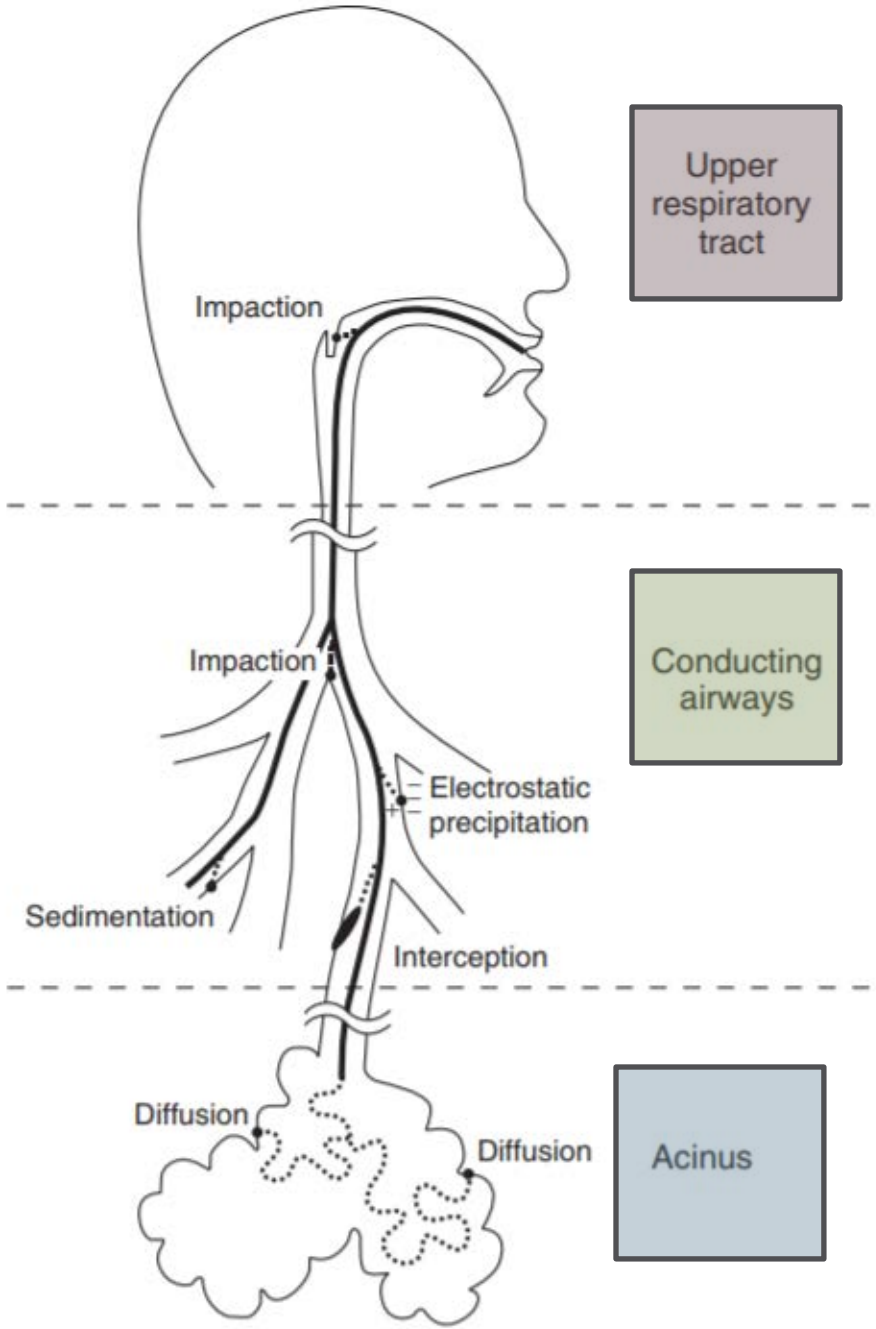
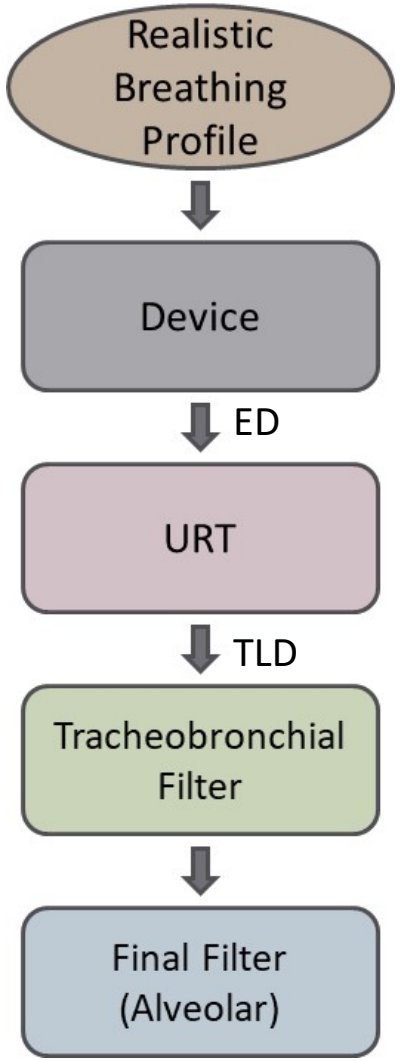
Misconceptions driven by focus on aerodynamic size

- **APSDs measured in an impactor are representative of the APSDs of the drug product**
- **A constant particle size with variations in flow rate leads to flow rate independence *in vivo***
  - Active devices that create the same APSD independent of Q provide flow rate independence
- **'Extrafine' particles are needed for effective delivery to the lung periphery**
- **Regional targeting within the respiratory tract can be achieved with monodisperse particles**
- **DPIs are inherently flow rate dependent, and the youngest and oldest of patients cannot effectively use a DPI**
  - Many asthma and COPD patients cannot generate sufficient airflow with a high resistance DPI to achieve effective dose delivery

Should we continue to measure size or do we really care more about regional deposition?





Source: Tavernini S, Kiaee M, Farina D, Martin A, Finlay W: Development of a filter that mimics tracheobronchial deposition of respirable aerosols in humans. Aerosol Sci Technol. 2019, doi.org/10.1080/02786826.2019.1606414.

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" I have seen a medicine

that's able to breathe life into a stone "

William Shakespeare – All's Well That Ends Well - Act II, Scene 1

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