[Overview of aerosol therapy- particle size, inspiratory flow, device resistance; trainers]

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Faculty Disclosures

Maureen George

- **Relevant financial relationships with a commercial interest:**

Teva	Ad Board; Speaker's Bureau; Consultant
Vernalis	Ad Board

Device selection

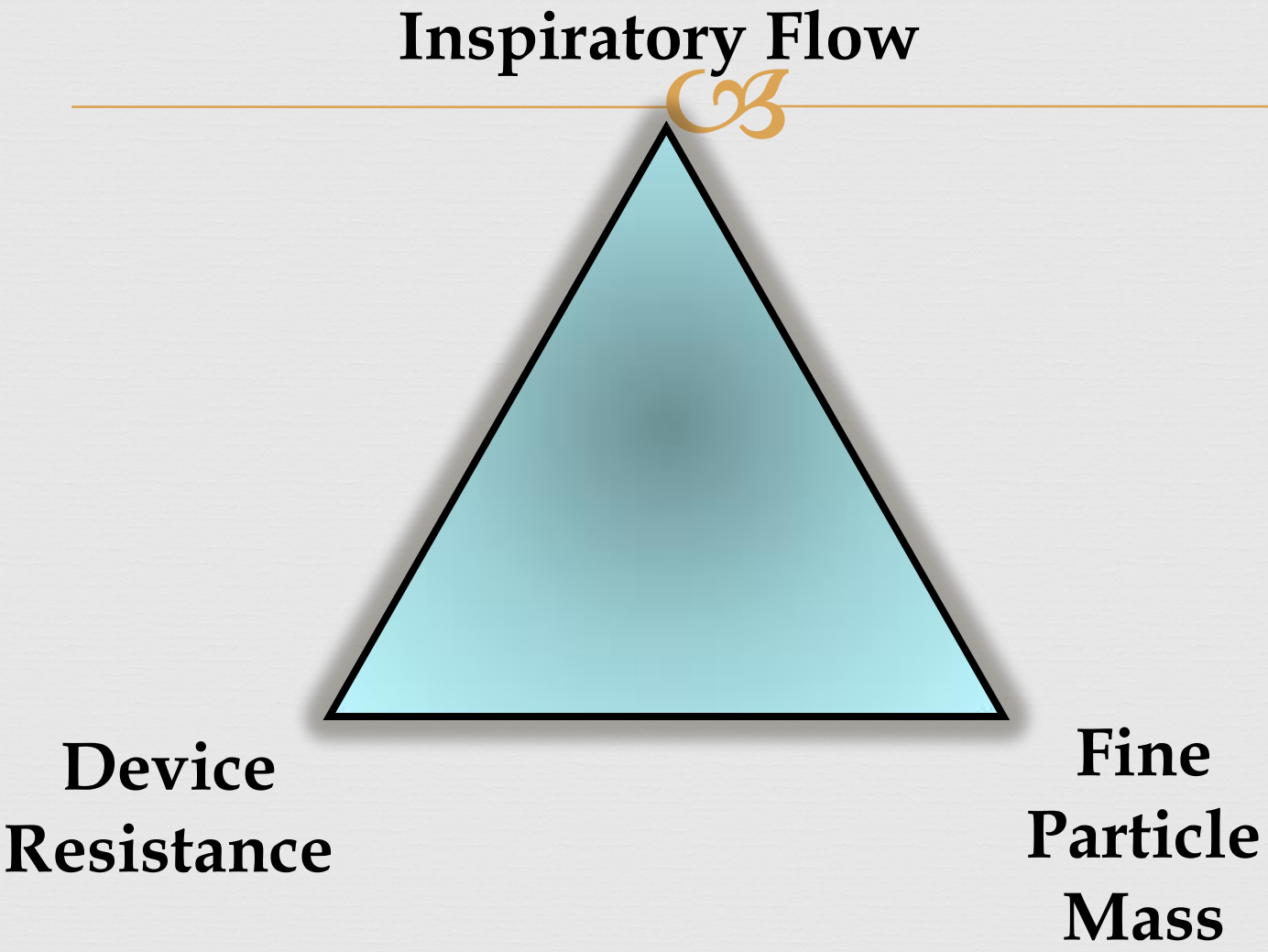
- Nebulizers do not offer any advantages over MDIs when the MDI technique is correct
- For asthma or COPD either DPIs or MDIs are appropriate
  - **Dolovich, Hess, Dhand & Smaldone (2005) Device selection and outcomes of aerosol therapy: Evidence-based guidelines. Chest, 127, 335-371.**
- *Consider age, lung function, visual acuity, presence of tremors in making selection*

Asthma Device Learning Lab

Why are there problems ?

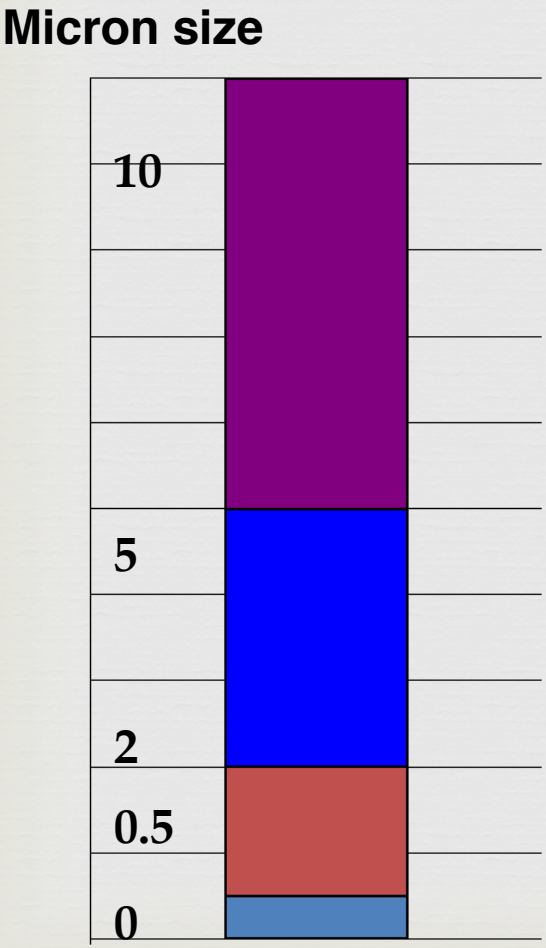
- Design of inhalers vary
  - Formulation of drug
  - Mechanical activation (passive MDI vs active DPI)
  - Internal resistance to airflow
- Patients vary
  - Pulmonary performance- acute illness vs. Disease severity
  - Ability to learn / be taught the correct technique
  - Effort varies from dose to dose

Evaluating Medication Delivery



Particles exhaled if <0.5 micron

Particle Size

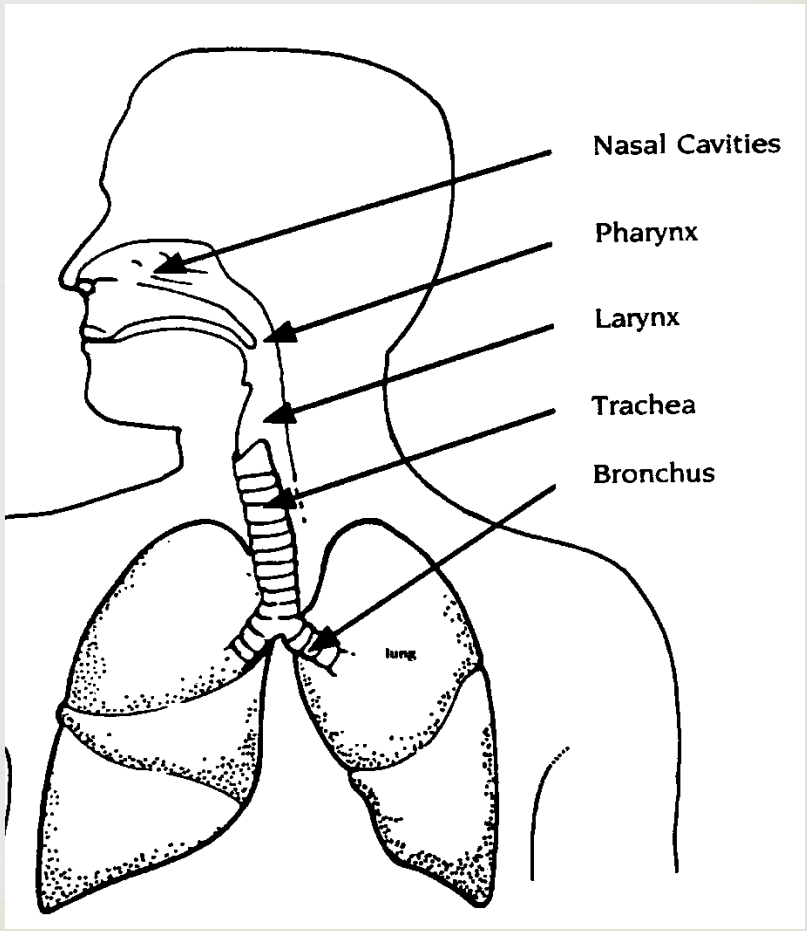


Deposition

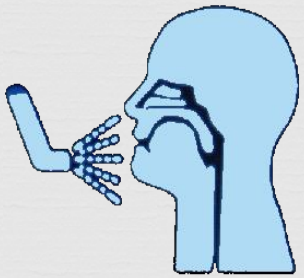
Pharynx, larynx & Upper respiratory tract

Optimal tracheobronchial deposition

Optimal alveolar deposition

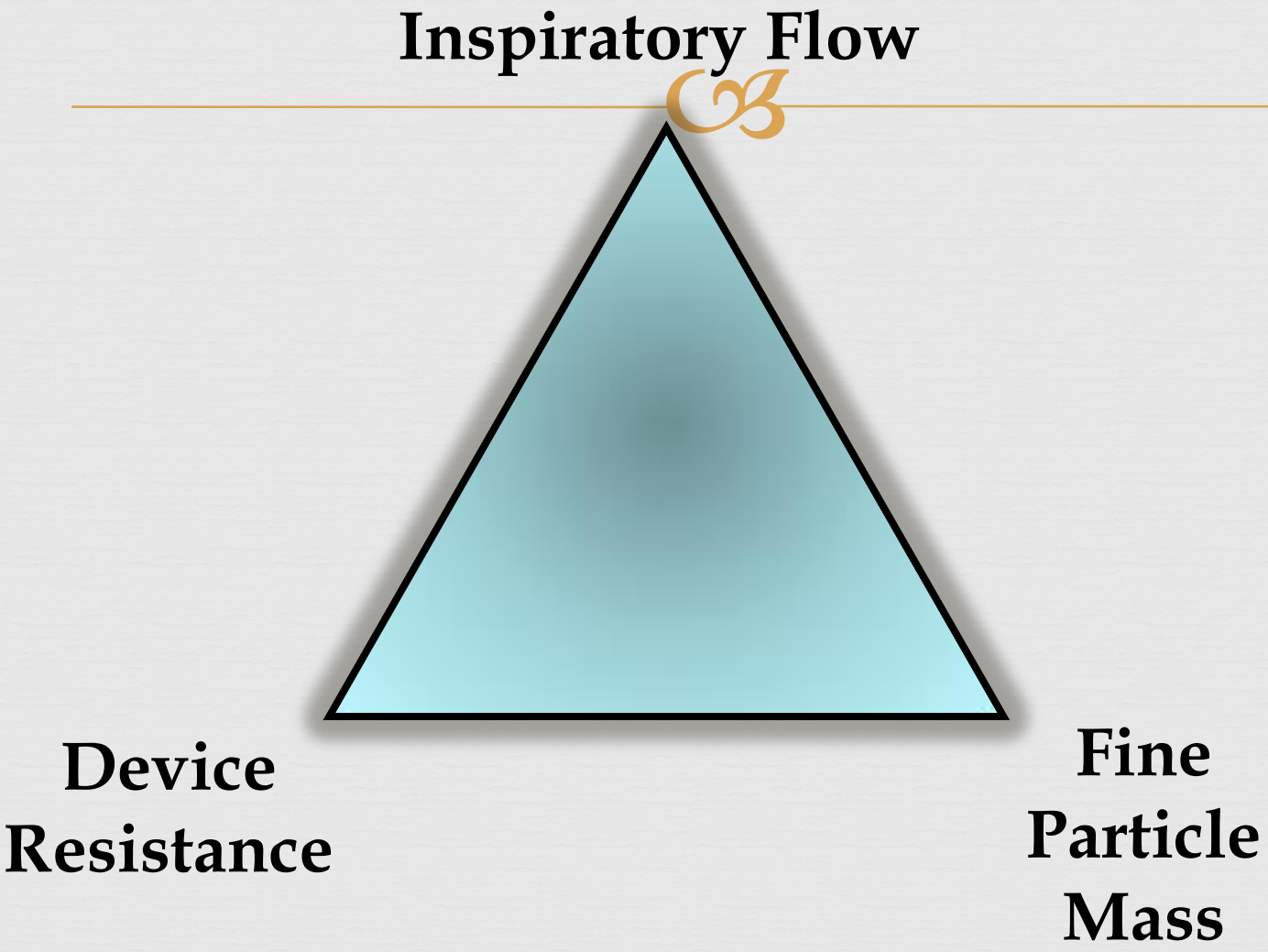


Particle Size and Airway Deposition



Particle Size	Result
> 5 microns	No clinical benefit Systemic absorption if swallowed
2-5 microns	Optimal size for clinical benefit
< 2 microns	Clinical benefit debated Potential for systemic absorption

Evaluating Medication Delivery



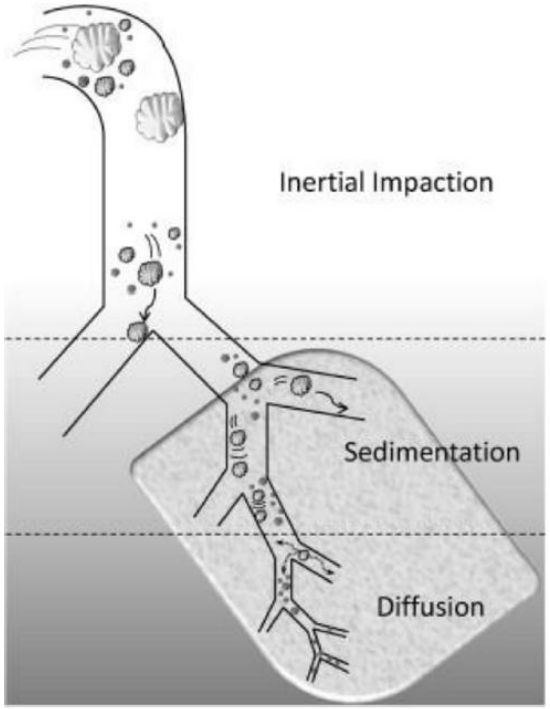
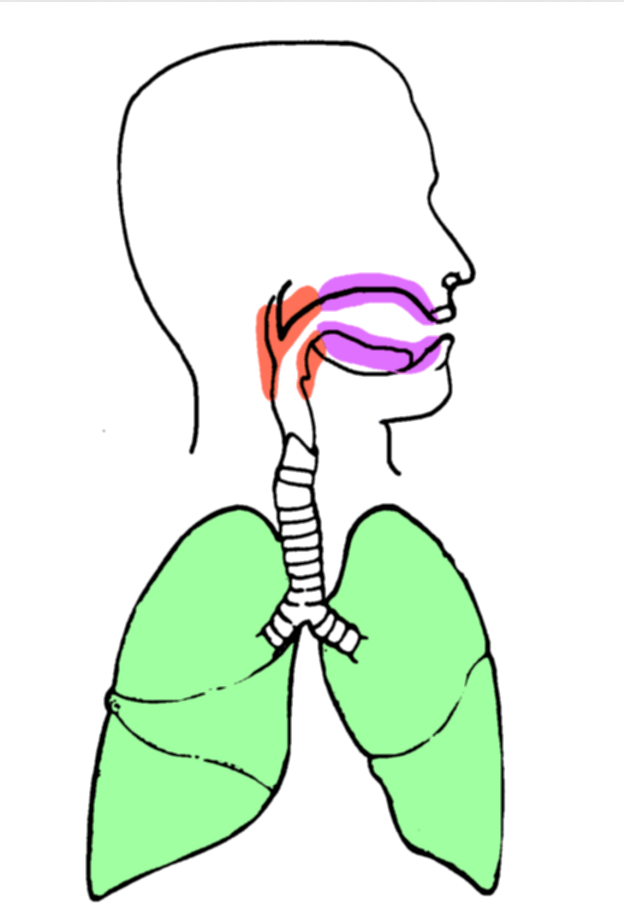


Figure 2. Deposition mechanisms of aerosols (reprinted with permission-Elsevier, Carvalho T, Int J Pharm 2011)

Inspiratory Flow Influences Drug Deposition

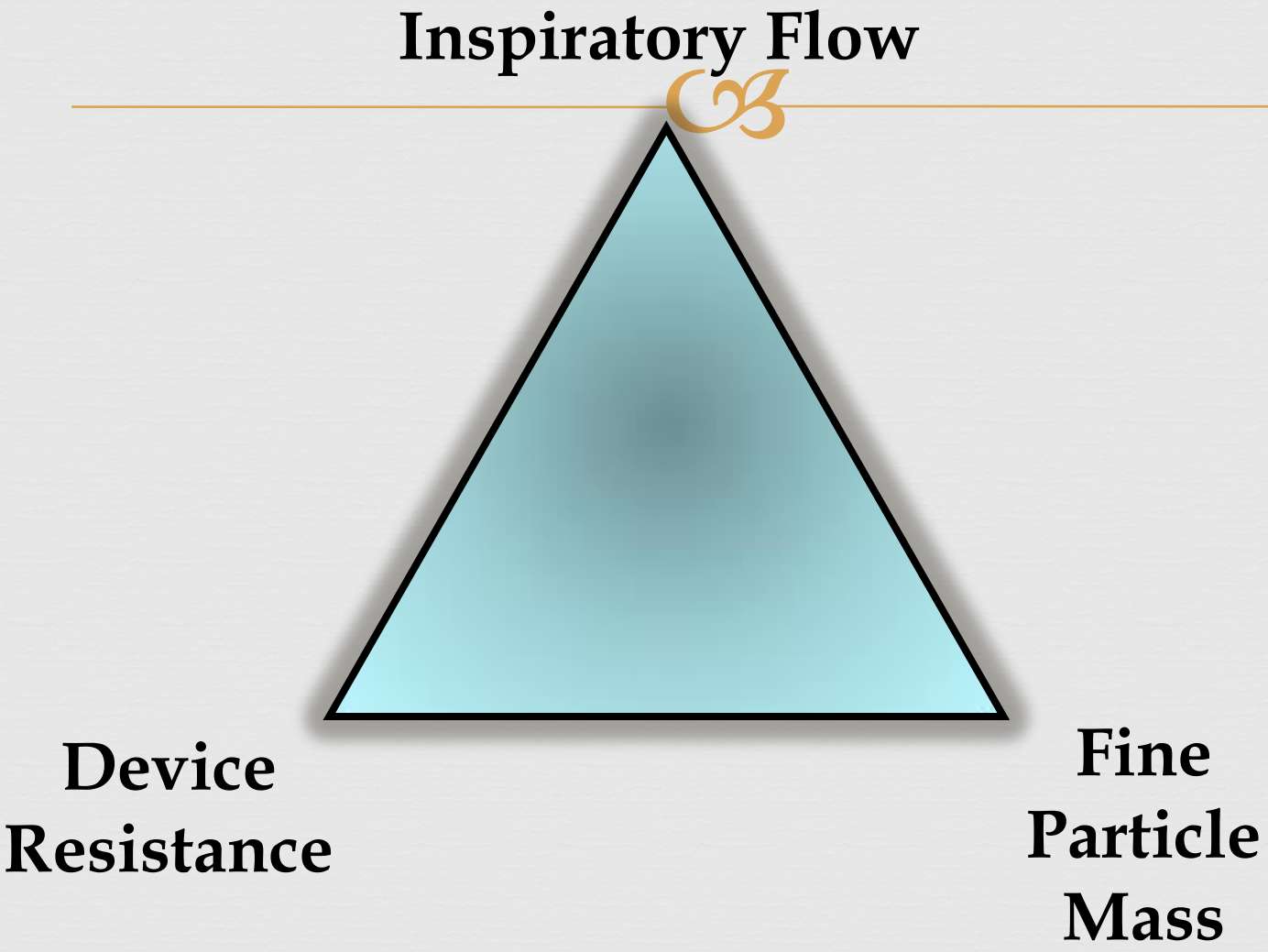
Inspiratory Flow	Drug Deposition	
Too Slow	Mouth	
Too Fast	Throat	
Correct Speed	Lungs	



Peak inspiratory flow

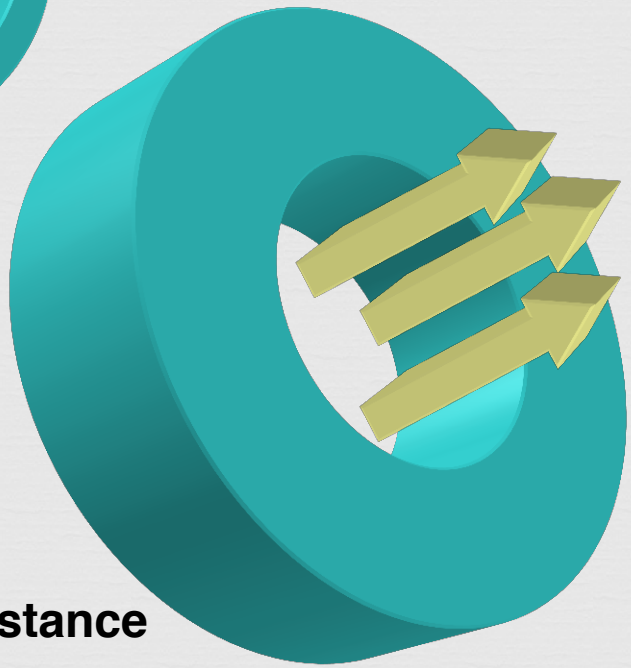
- Effort
- Chest muscle strength
- Airway resistance
- Disease morbidity
- Functional capacity
- Age
- Training and experience

Evaluating Medication Delivery

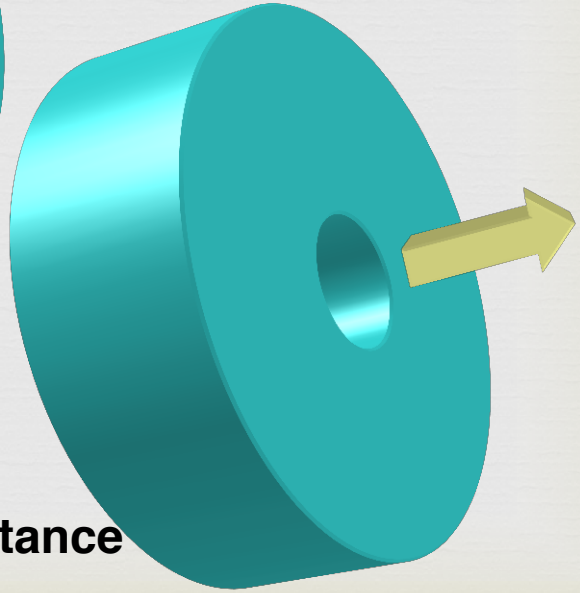


For the same inspiratory effort, the lower the resistance, the higher the flow

Low Resistance

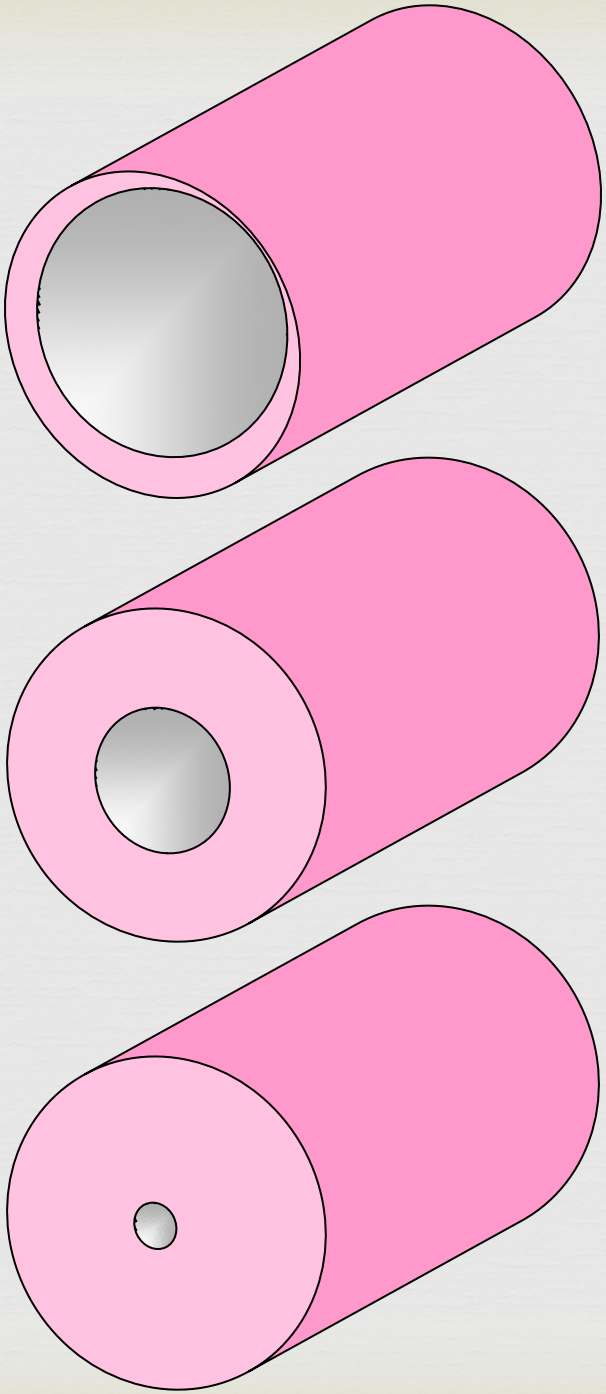


Medium Resistance

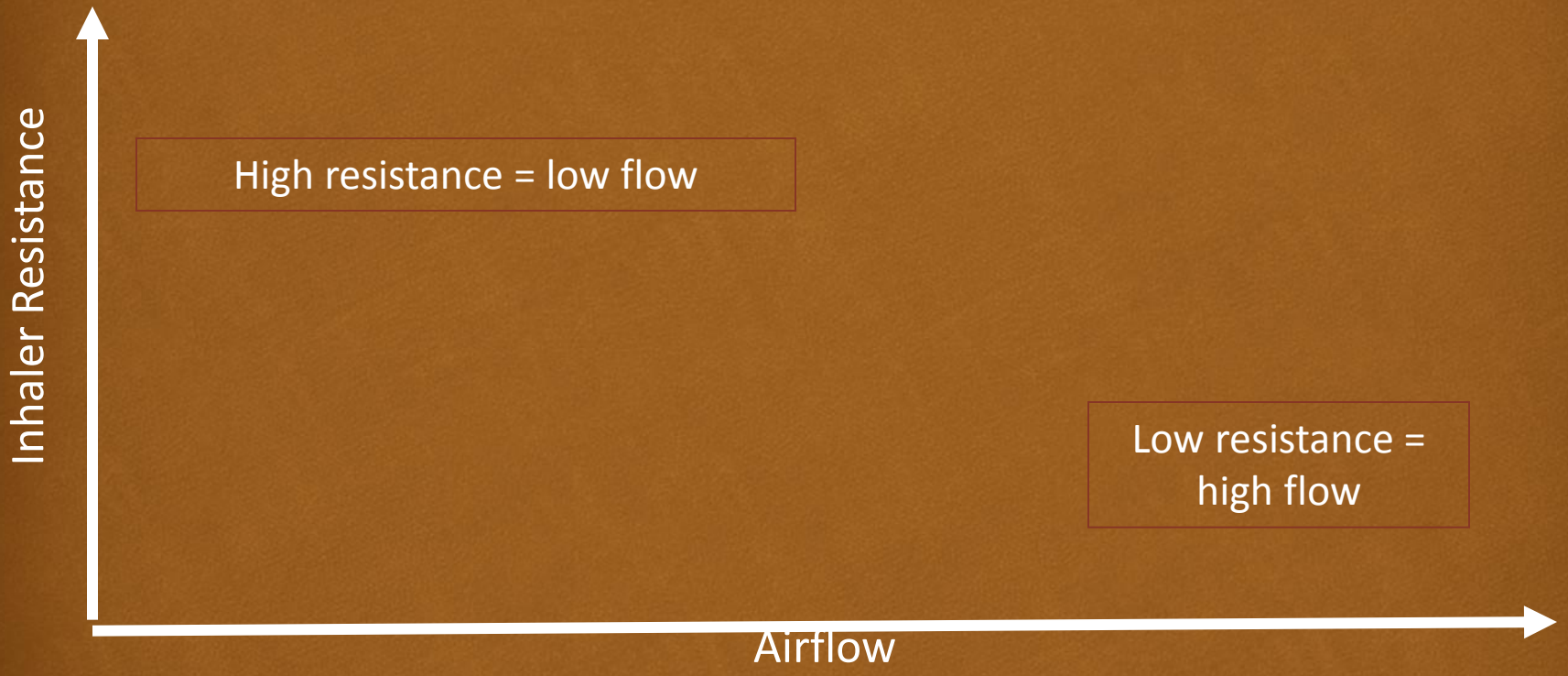


High Resistance

Imagine the effect when drinking through a straw…….

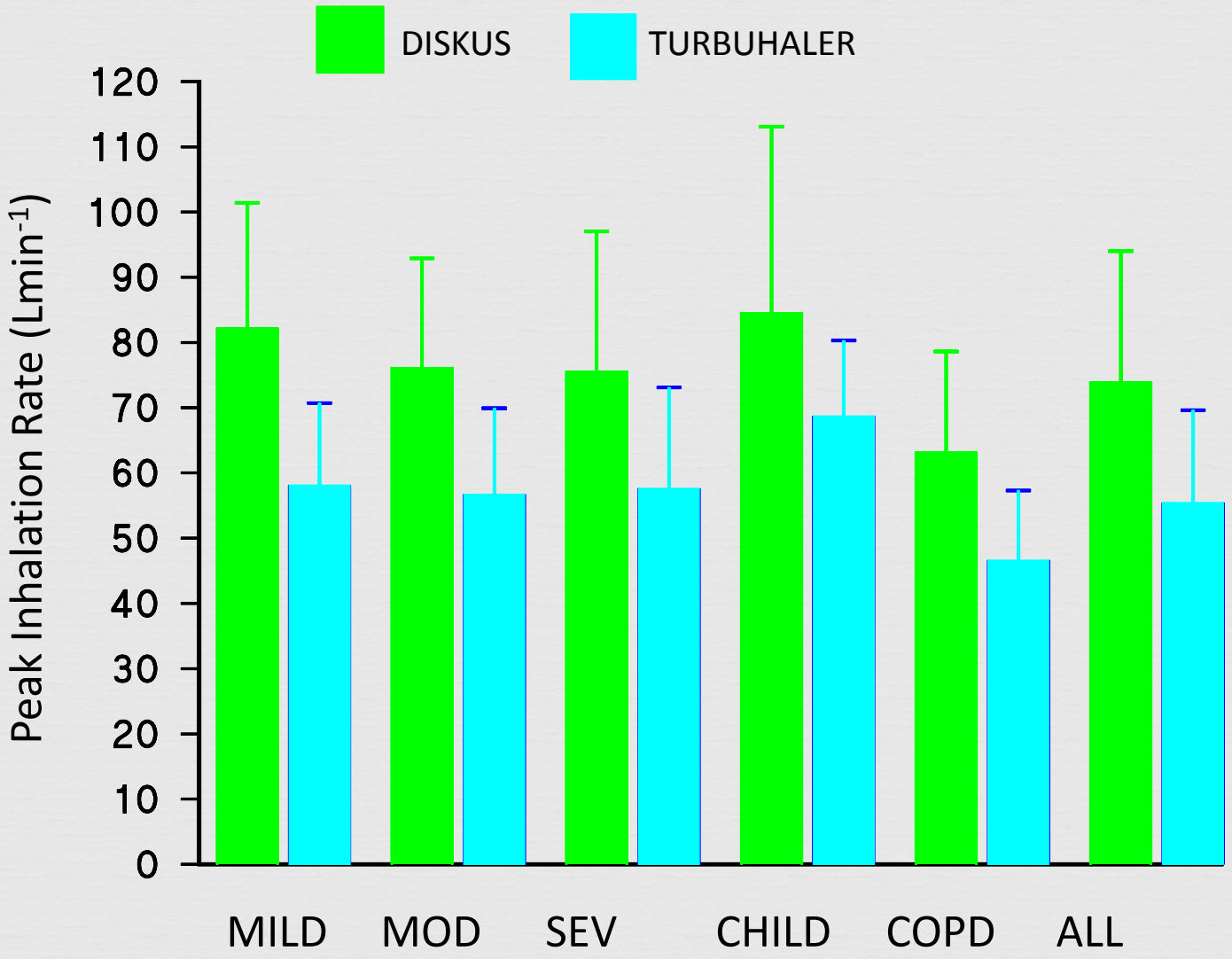


Inhaler Resistance



Clark AR, Hollingworth AM The relationship between powder inhaler resistance and peak inspiratory conditions in healthy volunteers – implications for in vitro testing *J Aerosol* Med 1993:6;(2) 99-110

Mean(SD) inhalation rates using two different resistance DPIs



Ref: Chrystyn, University of Bradford

Characteristics of 'ideal' inhaler

Safe

- Minimal oropharyngeal and gastrointestinal deposition
- No harmful additives (for patient and environment)
- Recyclable

Miscellaneous

- Simple
- Control mechanism that ensures optimal flow, correct technique and provides feedback
- Dose counter
- Easy to care for
- Meets patient's preferences

- ***Easy to use***
  - Portable
  - Discrete
  - Multiple dose
  - Minimal coordination required
- ***Effective***
  - Predictable and consistent lung deposition
  - Suitable for acute and chronic asthma
  - Unaffected by environment
- ***Inexpensive***

Why are there problems ?

- Design of inhalers vary
  - Formulation of drug
  - Mechanical activation (passive MDI vs active DPI)
  - Internal resistance to airflow
- Patients vary
  - Pulmonary performance- acute illness vs. Disease severity
  - Ability to learn / be taught the correct technique
  - Effort varies from dose to dose

Metered-dose inhaler

- Most patients use inhalers incorrectly
- Many health care professionals who teach inhaler technique do not know correct technique
- Patients do not know when to change canisters
  - Tail-off phenomenon
  - Desiccants
  - Float canisters

Asthma Device Learning Lab

Advantages and Disadvantages of MDIs

- Advantages
  - Everyone uses a MDI for rescue
- Disadvantages
  - Not all have dose counter
  - Each require different priming and care
  - More difficult coordination required than with DPIs
  - Dose uniformity problems

Asthma Device Learning Lab

Factors Affecting Dose Uniformity with MDI

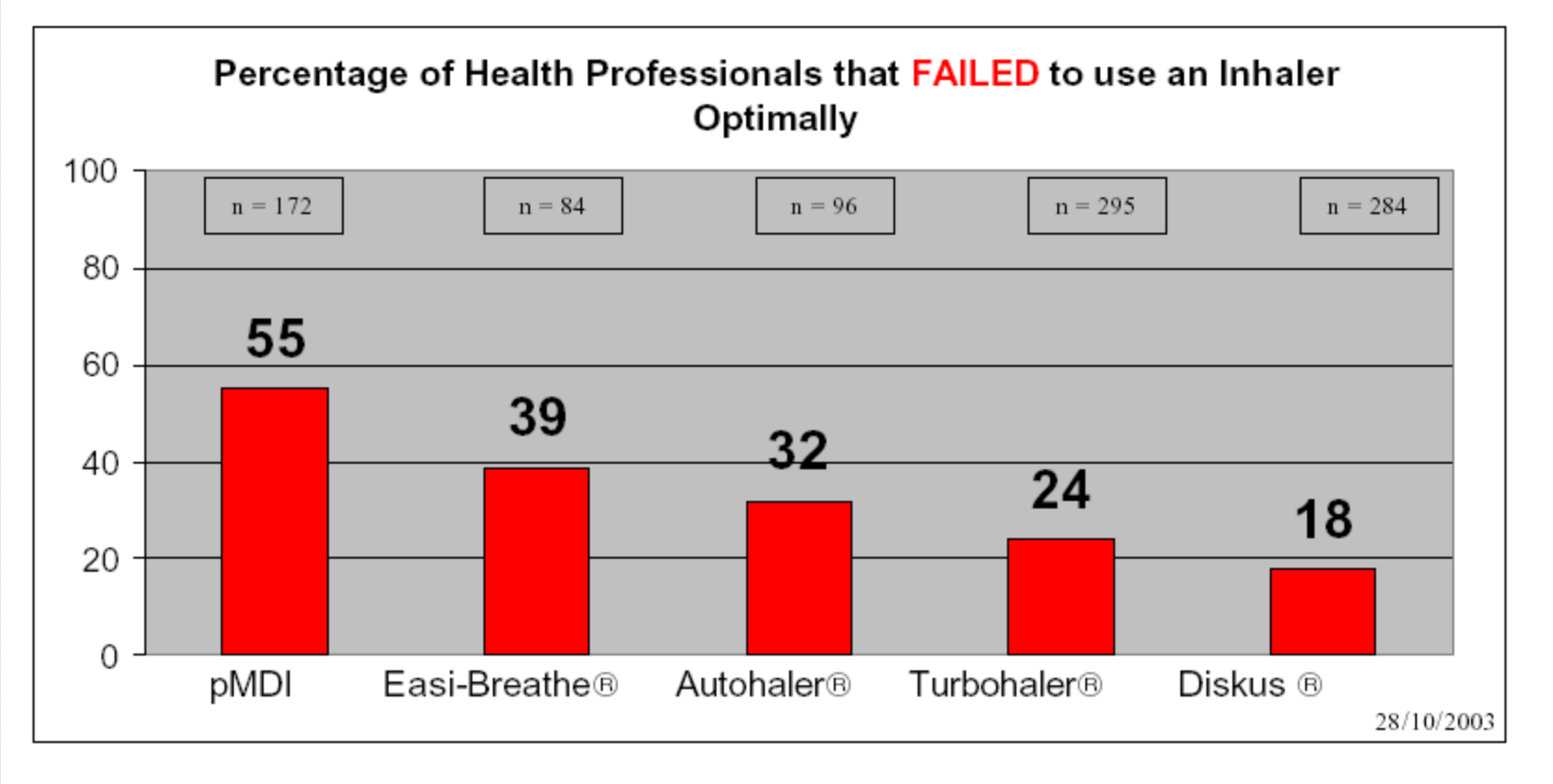
- Loss of Prime
  - Problem: After period of none use, first dose may be reduced or absent.
  - Cause: Propellant drained from metering chamber.
- Loss of Dose
  - Dose diminishes, but is unnoticed because propellant remains the same.
  - Cause: Active ingredient creams or settles
- Tailing off
  - Erratic drug delivery after labeled number of doses.
  - Cause: Metering chamber fills with vapor rather than propellant

Table 2 Errors observed during the various steps of the pMDI inhalation manoeuvre[a].

Step where error occurs	Patients demonstrating errors (%)	Range (%)
Remove the cap	0,[27] 2,[17] 3,[23] 5[24]	0–5
Shake the inhaler	7,[27] 15,[23,26] 20,[25] 26,[20] 27,[22] 32,[17] 34,[28] 57[24]	7–57
Hold inhaler upright	0,[23] 2,[20,24] 6,[22] 10[17]	0–10
Breathe out	30,[28] 34,[22] 42,[25] 46,[23] 66[24]	30–66
Place inhaler between lips	6,[22] 12,[25] 16[17]	6–16
Fire inhaler while breathing in slowly	10,[20,26] 16,[18] 19,[27] 24,[22] 26,[28] 34,[23] 37,[17] 43,[25] 47,[21] 68[24]	10–68
Continue to inhale	26,[20] 30,[23] 34,[27] 39,[21] 41,[22] 42,[25] 58[17]	26–58
Breath holding (5–10 s)	24,[21,22] 34,[20] 37,[23] 44,[27] 53,[24] 56,[17,25] 77[18]	24–77
Patients whose technique is adequate overall (%)	11,[17] 21,[23] 24,[28] 25,[21] 38,[18] 56,[22] 70[19]	
	Weighted average (1317 patients) = 34.3	
Patients whose technique is poor overall (%)	16,[18] 19,[23] 25,[17] 28,[28] 30,[19] 33[27]	
	Weighted average (5117 patients) = 31.8	
Poor coordination	33% of 3955 patients,[27] 43% of 746 patients,[25] and 26% of 556 patients[28]	

[a] Numbers show percentages of subjects making errors at each step of the manoeuvre in the cited studies. These studies were not homogeneous in design, disallowing statistical analysis, but the comparison nevertheless provides a general impression of the amount of difficulty and highlights the most difficult parts of the manoeuvre. Superscript numbers refer to references listed at the end of the paper. pMDIs: pressurised metered-dose inhalers.

Nearly 400 delegates attended the Clement Clarke stand and had their inhaler technique checked. Optimum Inspiratory Flow was identified from reference data, consistent with that provided with an In-Check DIAL.



Data on file, Clement Clarke International Ltd, 2003

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To reduce these mistakes

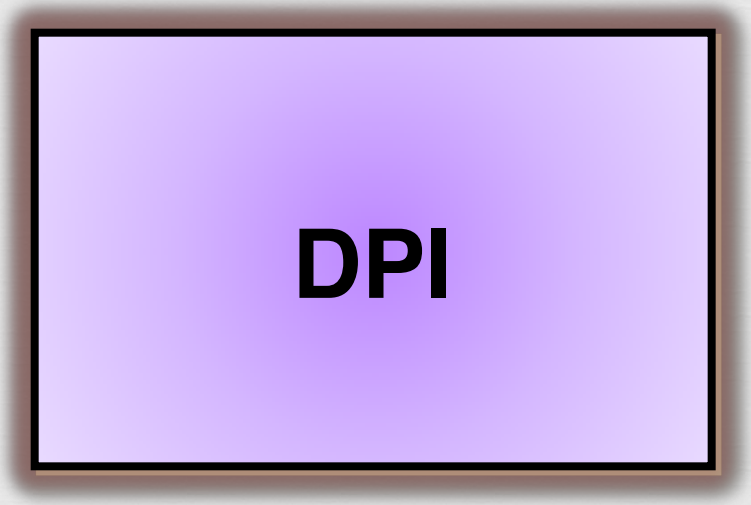
- The patient should be asked to demonstrate technique at each visit to the provider
- Use a spacer
- Dispense inhalers that are easy to use or similar to ones already being used
- Objective assessment of inspiratory flow is more accurate than observation (n.b. simulate resistance)
  - Use a training aide

Practical implications in prescribing MDIs

- Speed of inhalation
- Breath holding
- Priming and cleaning
- Dose counting

Evaluating Dry Powder Inhalers (DPIs)

DRUG & DEVICE



DEPOSITION

DELIVERY

Asthma Device Learning Lab

Advantages and Disadvantages of DPIs

- Advantages
  - Easier to use
  - All require in-mouth technique
  - All have method of assessing number of doses remaining
- Disadvantages
  - Still need to learn MDI technique for rescue
  - Each require different priming and care
  - Some are moisture sensitive
  - Each have different requirement for inspiratory flow

Table 4 Errors in inhalation manoeuvres observed with DPIs[a].

	Turbuhaler®	Diskus®/Accuhaler®	Rotahaler®	Diskhaler®/Rotadisk®	Aerolizer®/Cyclohaler®	All DPIs[24]
Inhaler positioning	7,[50] 18,[28] 29,[26] 31,[51] 31[53]	7[28]	32,[56] 3,[26] 37[53]	15[50]	0,[56] 9[26]	–
Priming	0,[53] 2,[56] 2,[26] 15,[28] 33[52]	3[28]	0,[53] 2,[56] 3[26]	2,[56] 3,[26] 4,[53]	1,[26] 4,[28] 10[56]	14
Breathe out and away	10,[51] 14,[50] 30,[28] 38,[56] 65 (out),[50] 50 (away)[50]	30 (out),[28] 6 (away)[28]	9[56], 66 (out),[53] 44 (away)[53]	0,[50] 28,[56] 44 (out),[53] 22 (away)[53]	40,[56] 33 (out),[28] 7 (away)[28]	66
Mouthpiece between lips	0,[51] 8,[56] 13,[52] 15,[50] 28[53]	2[28]	4,[56] 29[53]	4,[53] 7,[56] 15[50]	0,[56] 1[28]	4
Forceful, deep inspiration	2,[26] 6,[53] 8,[56] 23,[50] 48,[52] 55[51]	-	1,[26] 7,[56] 10[53]	2,[56] 23,[50] 37[50]	0,[26] 0[56]	19
Breath holding (5–10 s)	8,[56] 14,[54] 23,[50] 25,[28] 41,[53] 45,[51] 68[52]	26[28]	34,[56] 54[53]	2,[56] 23,[50] 37[53]	28,[28] 30[56]	53
Essential/critical errors	4,[19] 10,[55] 13,[53] >29,[56] 32,[28] 35[42]	6,[55] 11,[28] 27[42]	21,[19] >32[56]	4,[53] >9,[56] 19[19]	0,[56] 6,[55] 12,[28] 9[42]	14–19

DPI: dry powder inhaler.

[a] Numbers correspond to percentages of patients observed to make each particular error in each study included. Superscript numbers refer to references listed at the end of the paper. Essential or critical errors were those that were felt to significantly impede delivery of the drug to the patient's respiratory tract. Given the diversity of the studies included no attempt has been made to amalgamate data from each individual study.

TABLE 3.—*DPIs: Summary of Patient Preference Studies*

Study	Age	Attribute	Aerolizer, %	Diskhaler, %	Diskus, %	Turbuhaler, %
Boulet[39]	Adult	Ease of use		15	73	
Burdon[40]	Adult	Patients liked it			98	72
Eliraz[17]	Adult	Used correctly	98			86
Gioulekas[41]	Adult	Preferred treatment		16		44
Mahajan[42]	Adult	Preferred treatment		25	61	
		Satisfaction		72	87	
		Comfort		79	85	
Pieters[43]	Adult	Preferred treatment		35	65	
Schlaeppi[12]	Adult	Preferred treatment			65	35
		Doses			77	6
		Attached cover			63	18
		Shape			60	31
		Size			24	50
Serra-Batlles[44]	Adult	Correct use			92.6	89.8
		Preferred treatment			60	40
van der Palen[45]	Adult	No errors in use			92	74
Williams[46]	Pediatric	Liked device			85	58

Sheth, George & Kelley (2002)Dry powder inhalers in the treatment of asthma. Meniscus Ltd

Practical implications in prescribing DPIs

- Training
- Speed of inhalation
- Breath holding
- Priming and cleaning
- Dose counting
- Storage

EPR-3 Specifies IFR and IFT

- IFR= inspiratory flow rate
- IFT= inspiratory flow time

- MDI – 30 LPM for 3-5 seconds (p. 250)
- DPI – 60 LPM for 2-3 seconds (p. 249)

How do you measure IFR & IFT?

Optimum Inspiratory Flow

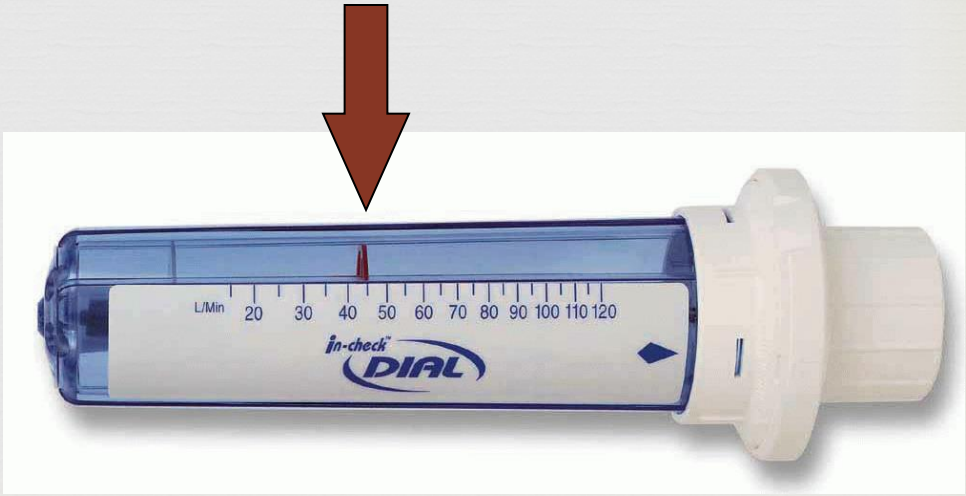
- Delivery of medication to the lungs is dependant on inspiratory airflow and medication device resistance.
- Resistance to airflow differs between devices therefore inspiratory flow requirements vary
- A device used to measure inspiratory airflow is the In-Check Dial

Device	Optimum Inspiratory Flow
Diskus	30 to 90 L/min
Flexhaler	60 to 90 L/min
Autohaler	30 to 60 L/min
MDI	25 to 60 L/min
Aerolizer	25 to 90 L/min
Twisthaler	30 to 60 L/min
Handihaler	20 to 90 L/min

To measure PIF (inhaler)

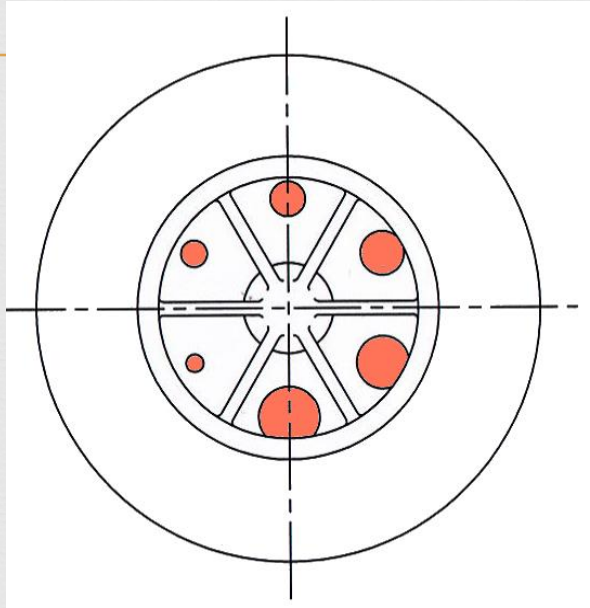
1. Inhale through the meter as if using inhaler

2. Read value from Red Pointer against scale (L/min)



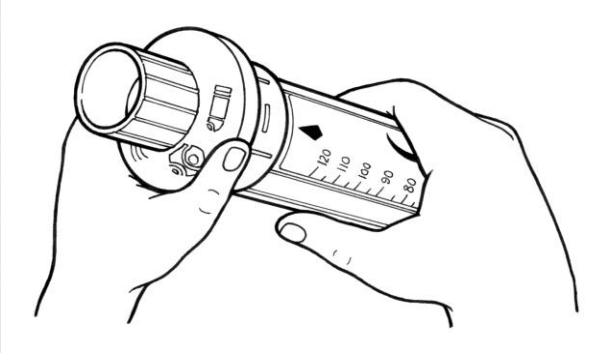
To select an inhaler's resistance

Turn the DIAL to select the Inhaler



Simulation of resistance of up to six different inhalers

Turn the DIAL to select the inhaler resistance



(Diskus / Accuhaler)

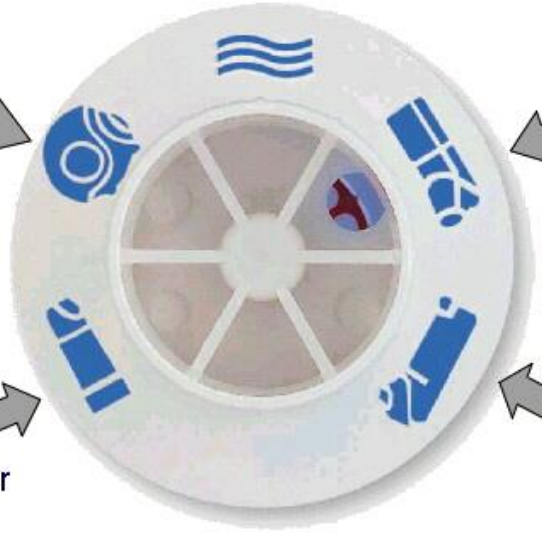
Multiple-dose powder inhaler

(Common pMDI)

Metered Dose Inhaler and MDI spacers with low resistance (e.g. AbleSpacer)

(Easibreathe)

Automatic pMDI



(Turbuhaler)

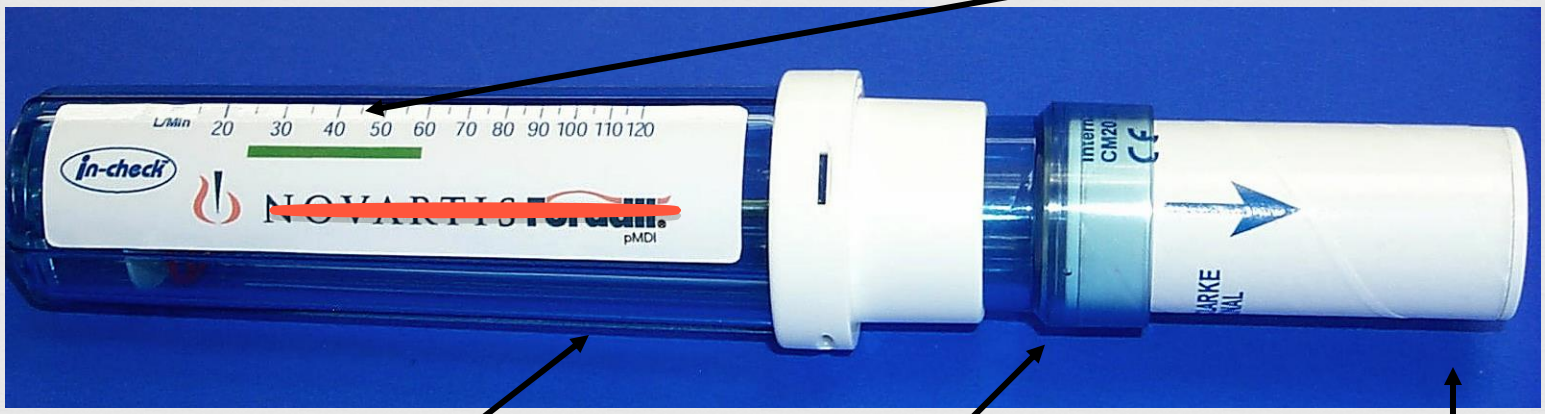
Turbulent flow inhaler

(Autohaler)

Automatic pMDI

Trainer

Optimum Inspiratory Flow range in green (pMDI = 25 to 60 L/min)



Inspiratory flow meter
(15 to 120 l/min)

Resistance to simulate
newer devices

Disposable
One-Way Mouthpiece
(keeps meter clean)

In-Check DIAL
What about cross-infection ?

The In-Check DIAL is an inhalation meter – air is inhaled by the patient through the device, so no exhaled air enters the meter in normal use. However, some patients may exhale into the device if not instructed correctly, and Clement Clarke can now offer a "One-Way" Disposable Mouthpiece, to reduce the risk of contamination for the patient and the In-Check DIAL.

The In-Check DIAL can be disinfected between clinic use by using standard water-based chlorine disinfection solutions – instructions are available from Clement Clarke.

Mouthpieces

Clement Clarke now offer two types of mouthpieces – standard cardboard disposable (tubes) and one-way cardboard disposables (with valves).

One-Way Mouthpieces

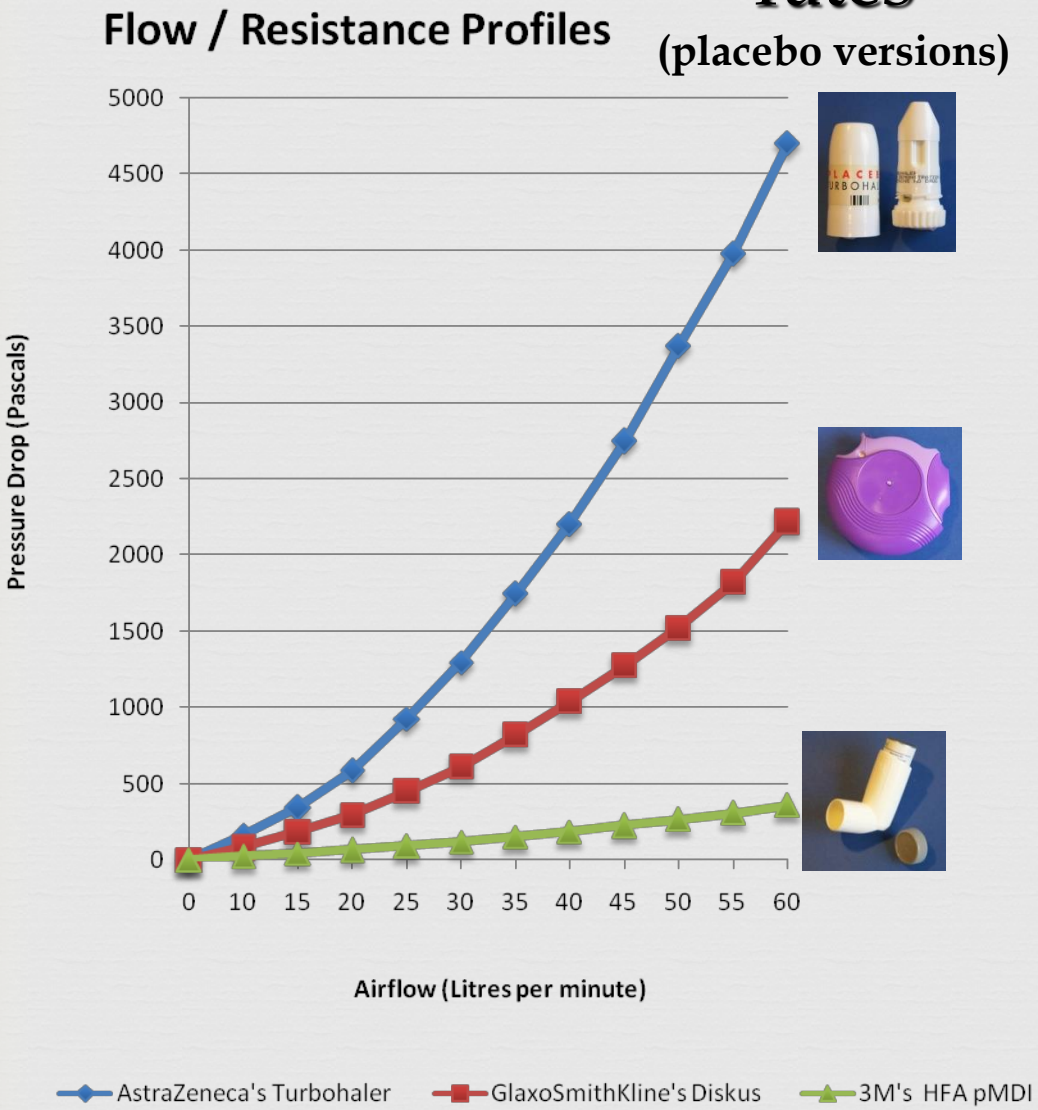
Two types are available – one designed for use with In-Check DIAL (inspiratory only - blue), and the other for use with peak flow meters and spirometers (exhalation only - red). Less expensive than filters, they are very low resistance, and the check valve only opens when air travels in the right direction.

in-check DIAL

Measure, then compare the inspiratory flow achieved with the optimum recommended for that device

in-check DIAL		Optimum Inspiratory Flow Range (l/min) 10 20 30 40 50 60 70 80 90 100 110
Multiple-dose powder inhaler **Diskus®**		
Turbulent flow inhaler (old style) **Turbuhaler®**		
Turbulent flow inhaler [redacted] **Turbuhaler®**		
Auto inhaler **Autohaler®**		
Auto inhaler **Easi-Breathe®**		
Multiple-dose powder inhaler **Clickhaler®**		
Low-resistance aerosol **pMDI**		

Resistance of 3 Common Inhalers at different flow rates

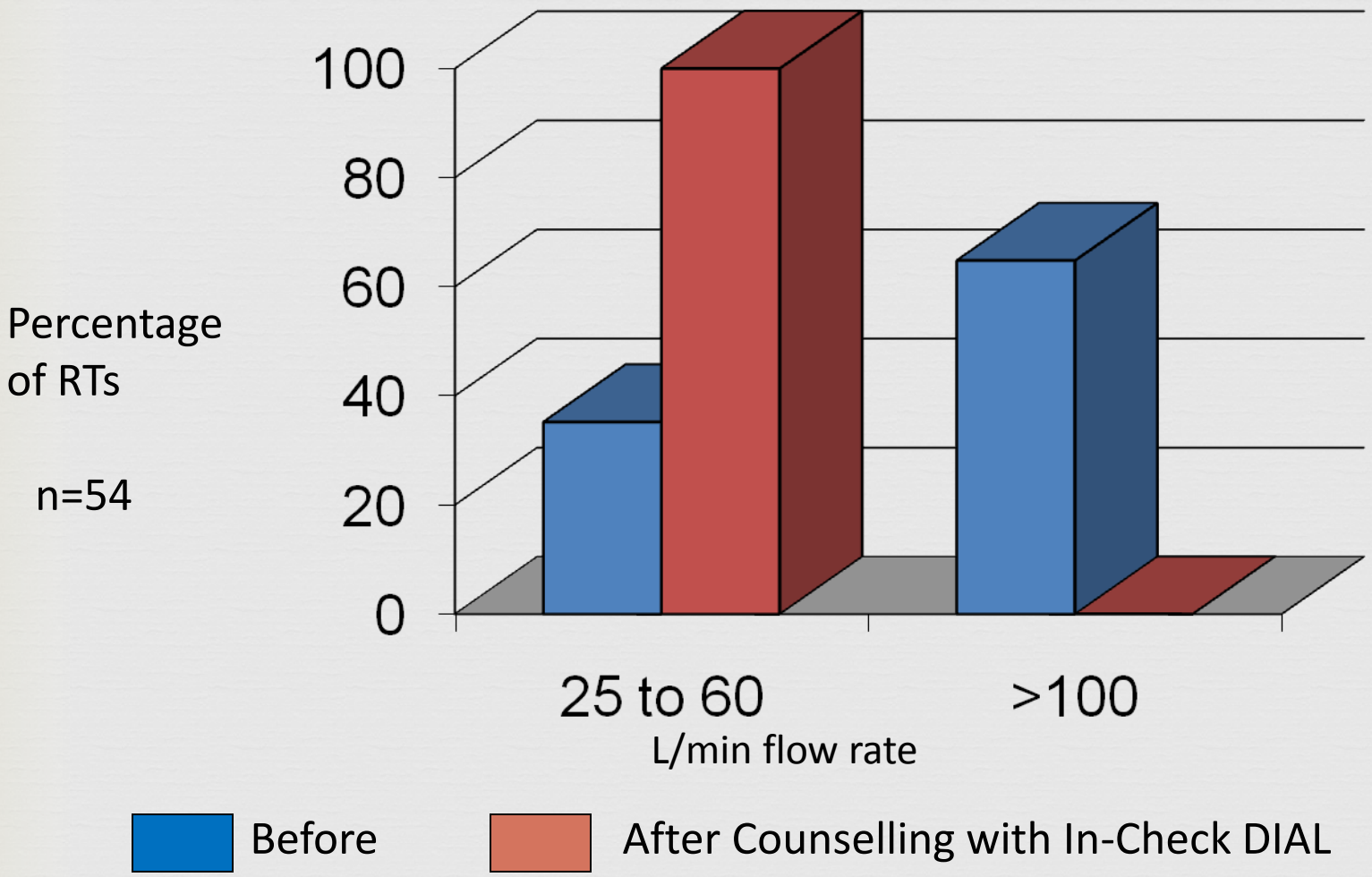


Dry powder device

pMDI aerosol "puffer"

Ref: J Bell 2004, data on file: jon@canday.freeserve.co.uk

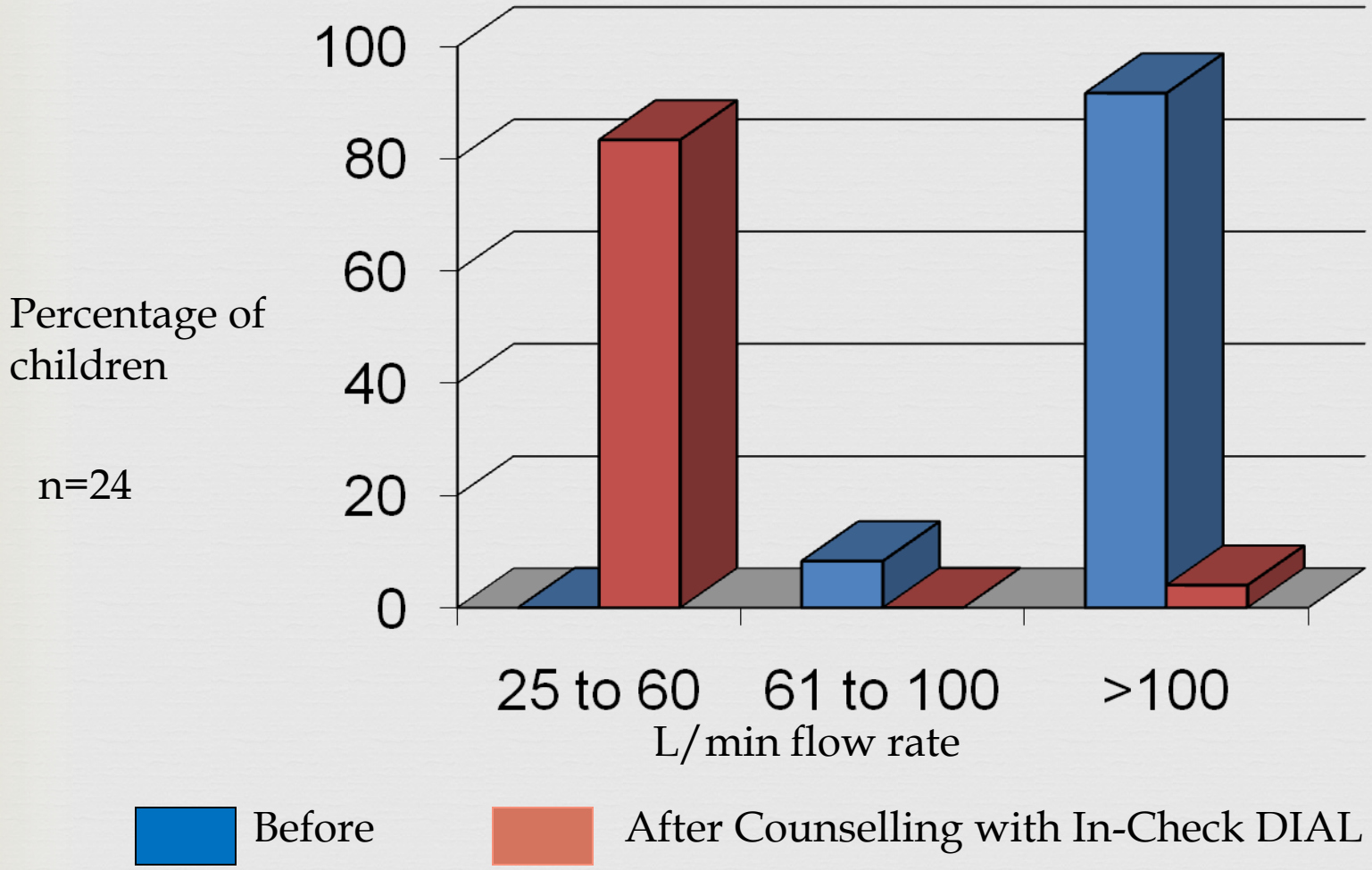
PIF through a pMDI – Respiratory Therapists



N.B. Recommended inspiratory flow is 25 to 60 l/min for a pMDI

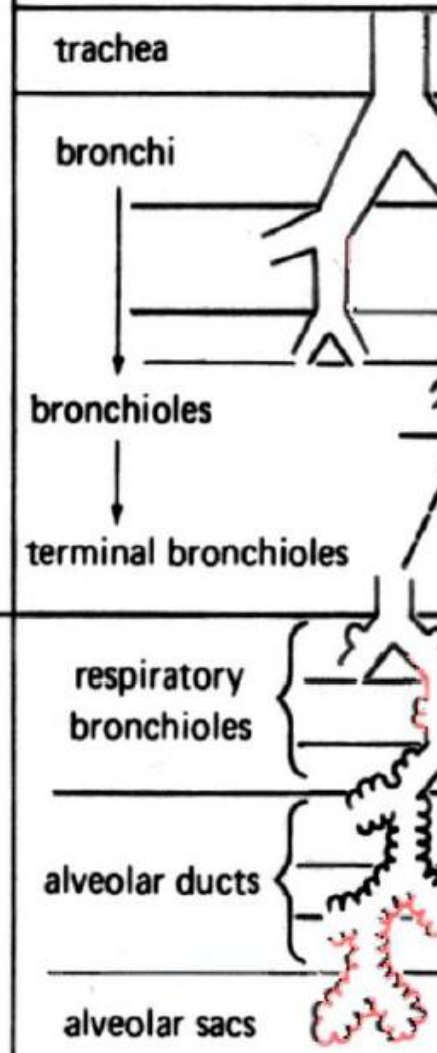
Conlin, T. Respiratory Care, November 2004, vol 49, No 11 p1425

In-Check Training (pMDI) – PIF in Children aged 7 to 11



N.B. Recommended inspiratory flow is 25 to 60 l/min for a pMDI

Conlin, T. NAEPP National Conference on Asthma 2003 P82



	Generation		Diameter, cm	Length, cm	Number	Total cross-sectional area, cm^2
conducting zone	trachea	0	1.80	12.0	1	2.54
	bronchi	1	1.22	4.8	2	2.33
		2	0.83	1.9	4	2.13
		3	0.56	0.8	8	2.00
	bronchioles	4	0.45	1.3	16	2.48
	terminal bronchioles	5 ↓ 16	0.35 ↓ 0.06	1.07 ↓ 0.17	32 ↓ 6×10^4	3.11 ↓ 180.0
transitional and respiratory zones	respiratory bronchioles	17	↓	↓	↓	↓
		18				
		19	0.05	0.10	5×10^5	10^3
	alveolar ducts	T_3 20	↓	↓	↓	↓
		T_2 21				
		T_1 22				
	alveolar sacs	T 23	0.04	0.05	8×10^6	10^4

Particle size	Fate
9 - 30 μm	visual pollution
5.5 - 9 μm	settle in nose/throat
3.3 - 5.5 μm	lodge in main breathing passages
2 - 3.3 μm	lodge in small breathing passages
1 - 2 μm	lodge in bronchi
0.3 - 1 μm	penetrate to bronchioles and alveoli
0.1 - 0.3 μm	penetrate to bronchioles and alveoli