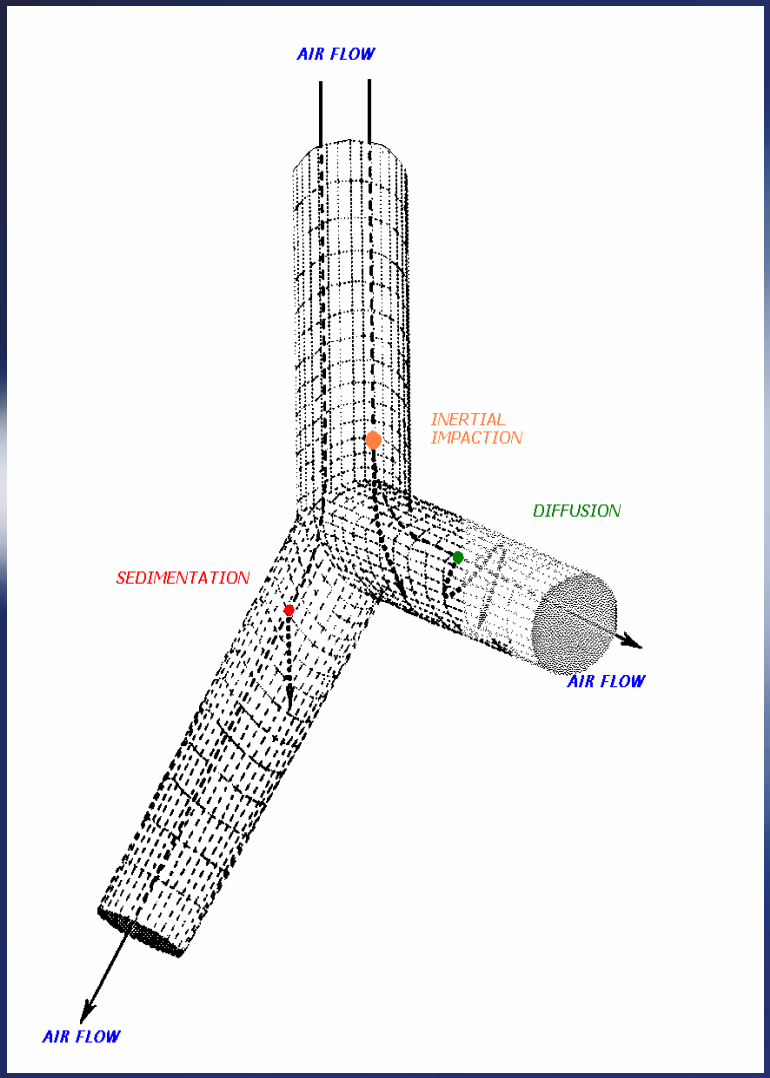
binomio farmaco-erogatore nell'aerosolterapia delle patologie flogistiche delle vie respiratorie

A. Kantar


Device
Farmaco
Paziente

Lung Deposition



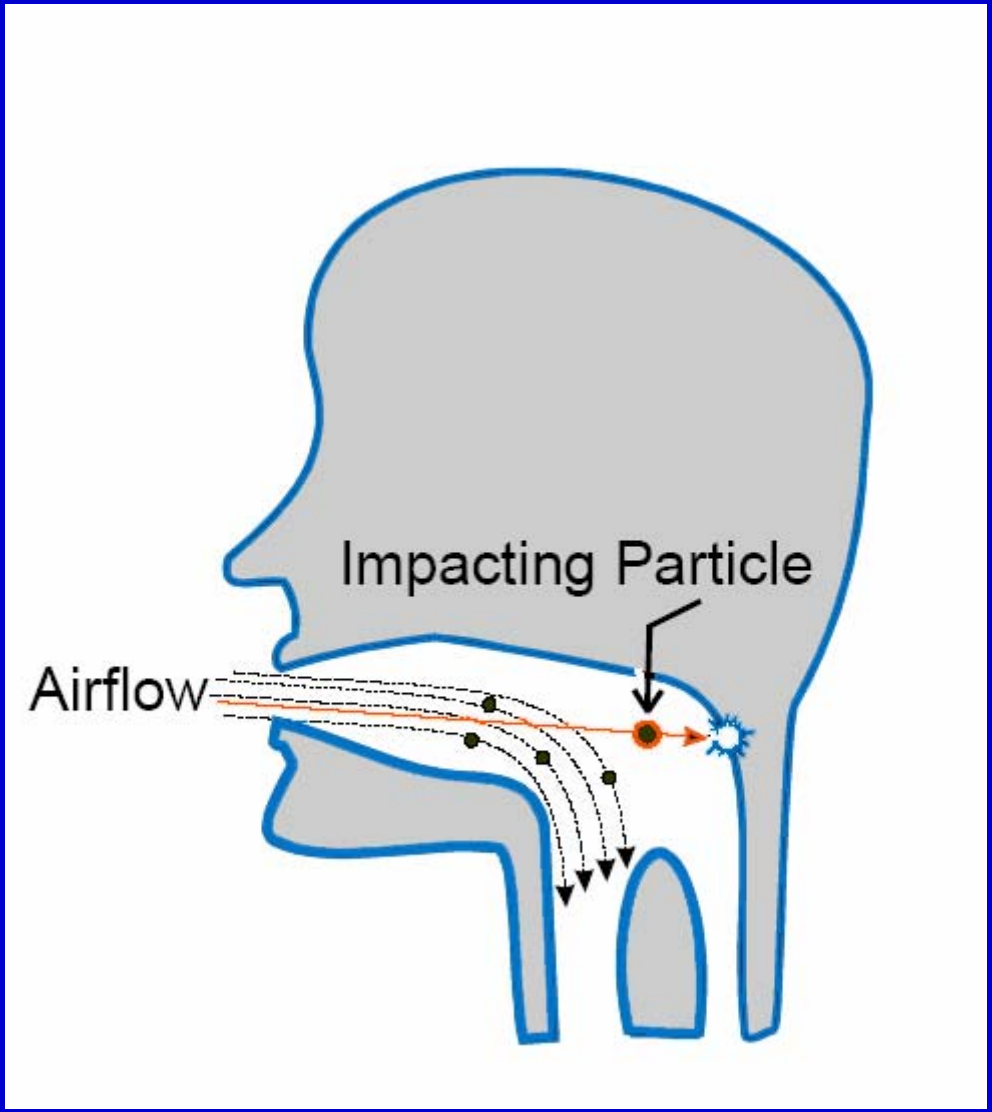
- lung deposition is related to particle size
- cut off < 4.3 um is appropriate for delineating between lung and extra-pulmonary deposition

DIAMETRO AERODINAMICO MEDIANO DELLA MASSA (DAMM)
MASS MEDIAN AERODYNAMIC DIAMETER (MMAD)

Diametro che divide la massa totale (la quantità totale dell' erogato o del farmaco) in due parti uguali, di cui una composta di diametro inferiore al MMAD e l'altra di diametro superiore

es. in un aerosol (eterodisperso) con MMAD=4,3μm, il 50% delle particelle presenta un diametro <4,3μm e il restante 50%>4,3μm.

Factors predecting lung deposition


Impacting Particle
Airflow

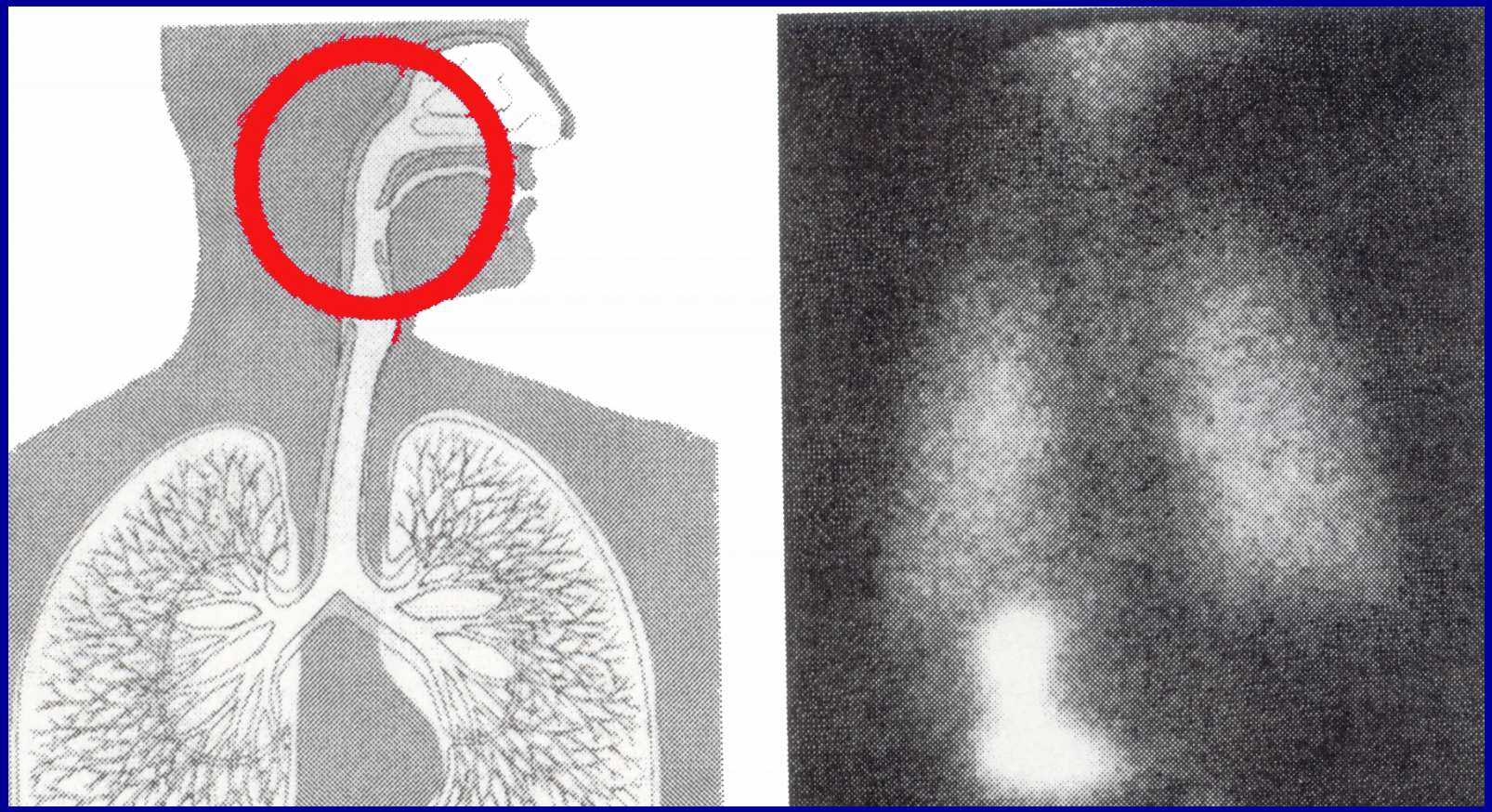
L'impatto inerziale avviene quando una particella è troppo veloce o troppo grande per compiere un cambio improvviso di direzione

Impatto inerziale

stokes number = *T*U/d

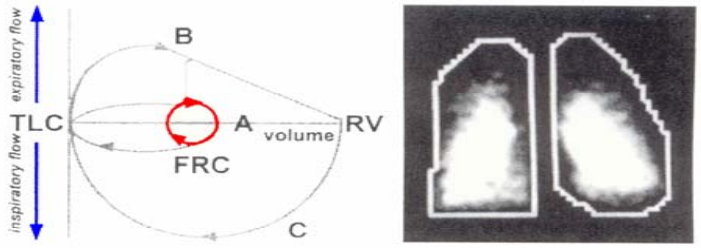
***T* componenti della massa**
***U* velocità**
***d* geometria locale**

Deposition pattern of nebulized radiolabeled Pulmozyme (MMAD 3.0 *u*m) in a 9-year-old-child. Approximately 60% of the deposition was to stomach, representing oropharyngeal deposition.

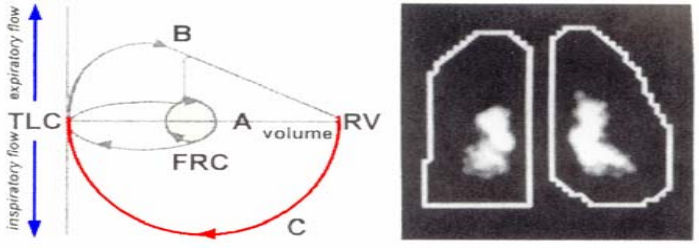


Diot Am J Respir Crit Care Med 1997

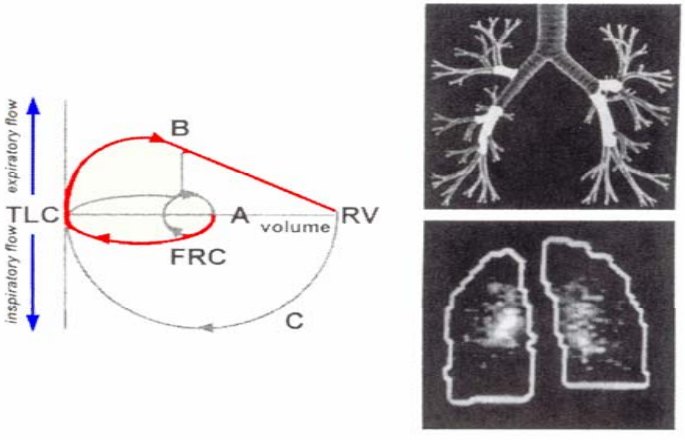
The relationship of the lung deposition to breathing pattern.
(monodisperse aerosol of 1.5 *u*m)



Quiet tidal breathing



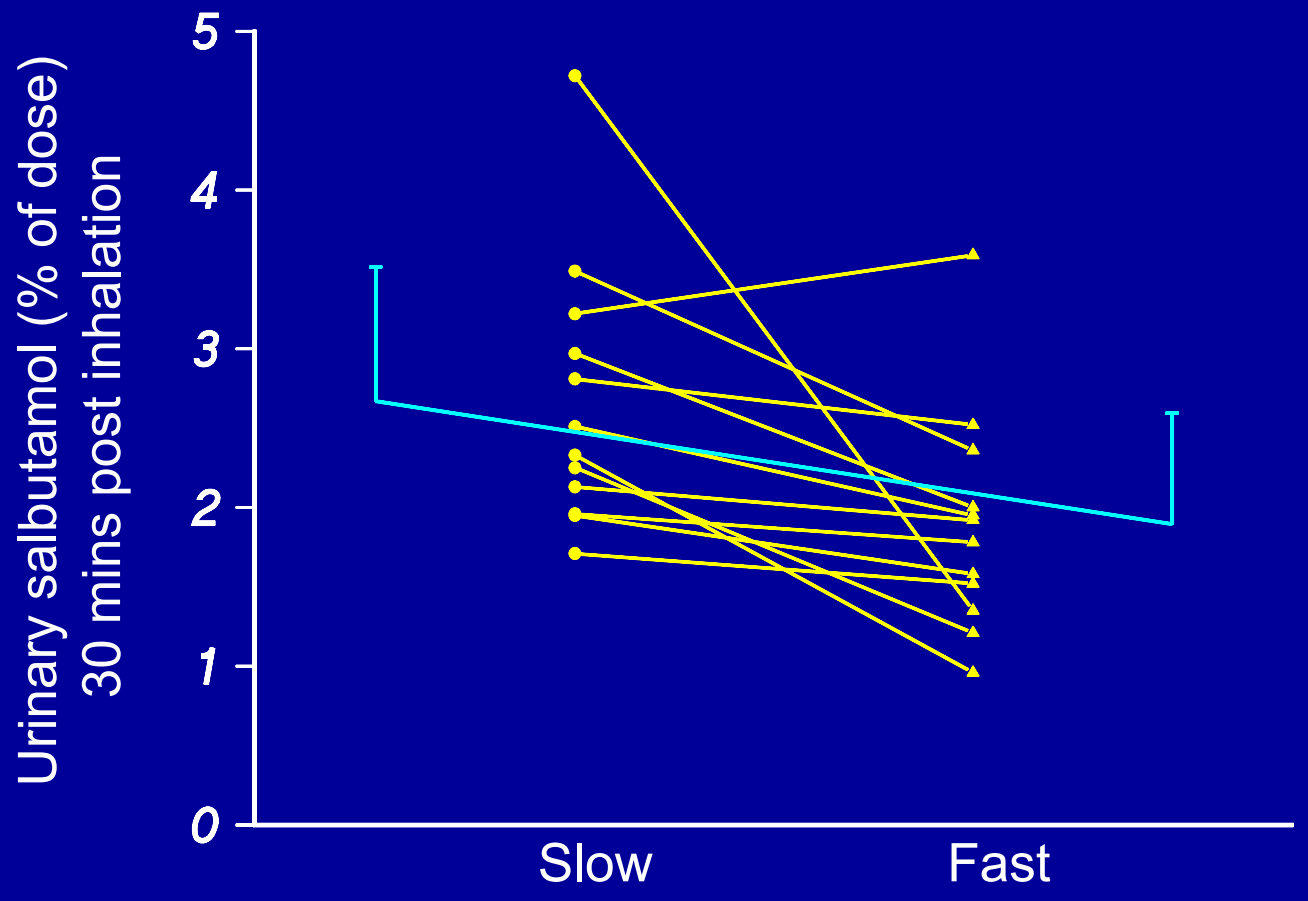
Forced inspiration



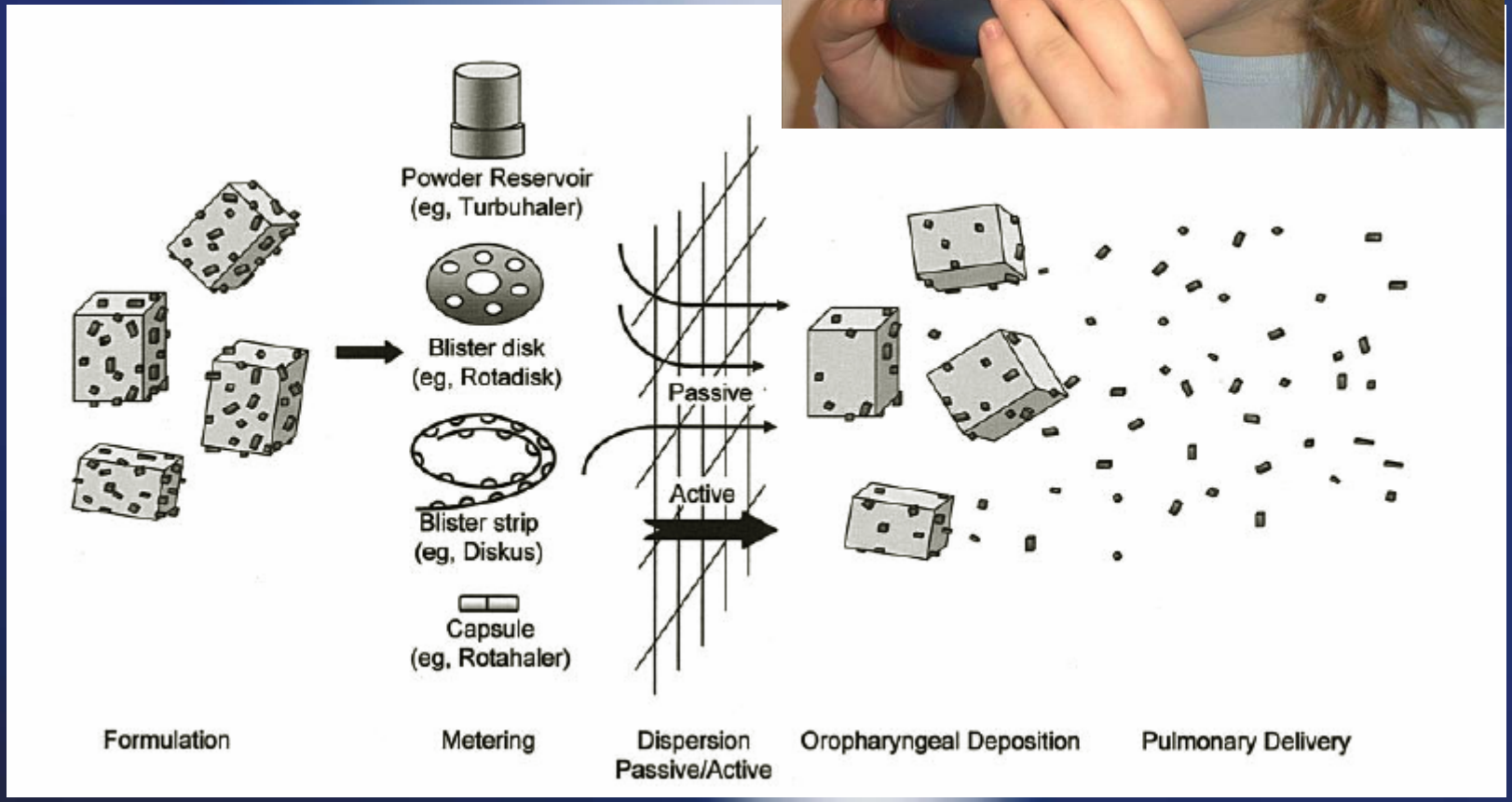
Tidal inspiration and forced expiration

Smaldone Respir Care 2002

Slow v's fast inhalation rate with a MDI

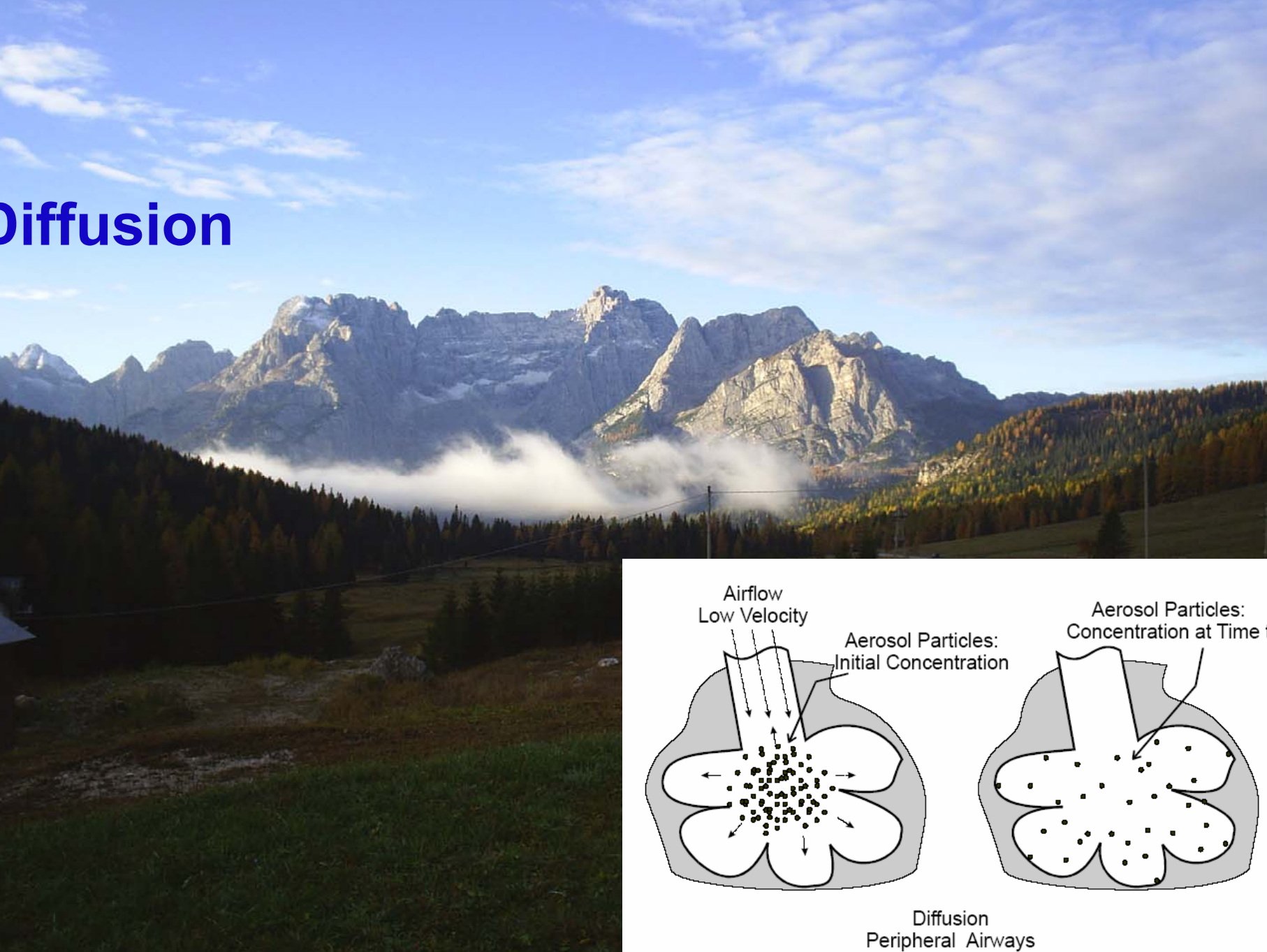


Tomlinson Brit J Clin Pharmacol 2005


Powder Reservoir
(eg, Turbuhaler)
Blister disk
(eg, Rotadisk)
Blister strip
(eg, Diskus)
Capsule
(eg, Rotahaler)
Passive
Active
Formulation
Metering
Dispersion
Passive/Active
Oropharyngeal Deposition
Pulmonary Delivery

Sedimentation

Diffusion


Airflow
Low Velocity
Aerosol Particles:
Initial Concentration
Aerosol Particles:
Concentration at Time
Diffusion
Peripheral Airways

Velocity

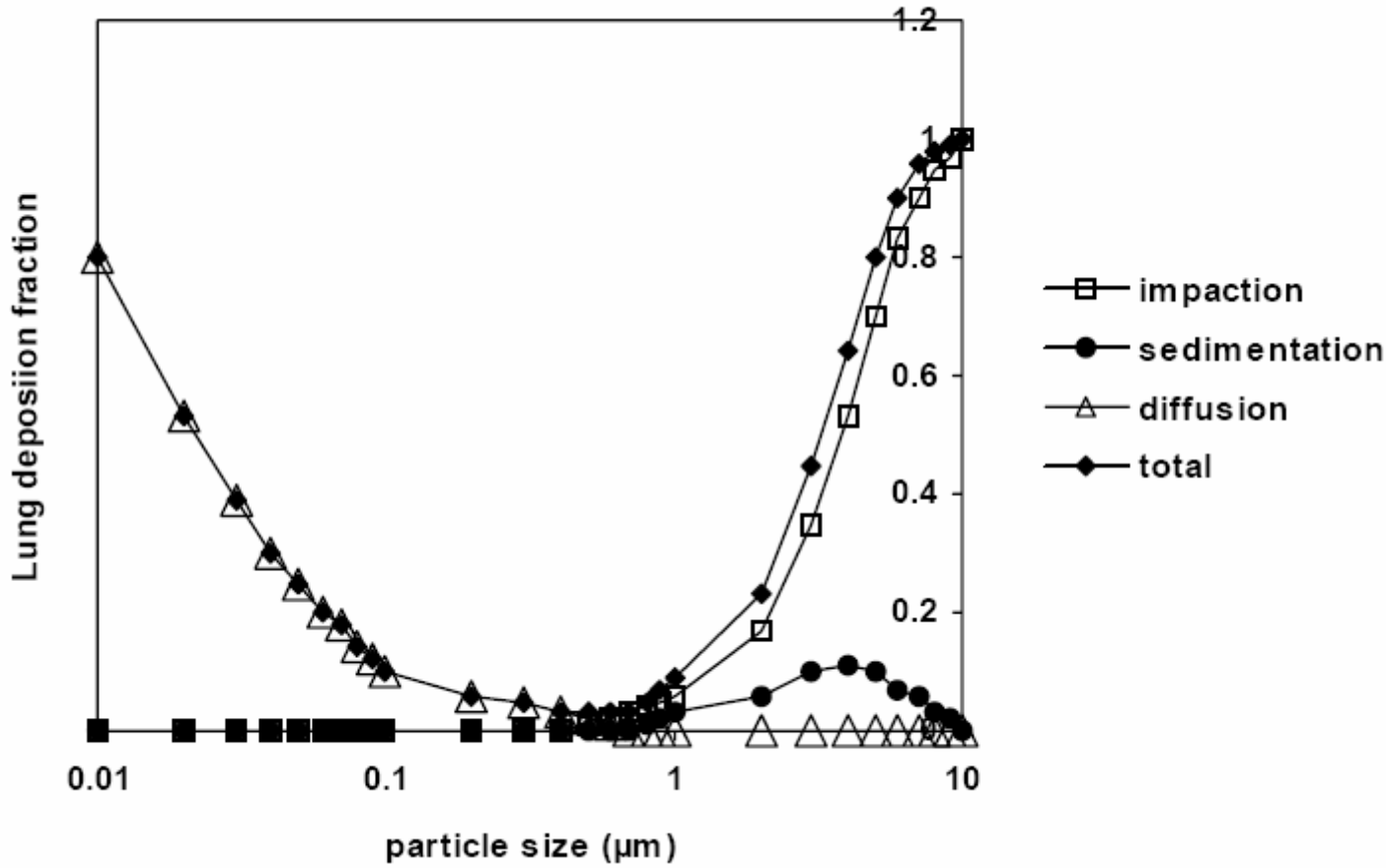
Device-Patient

Seize

Device-Drug

IMPACTION
SEDIMENTATION
DIFFUSION

site of deposition

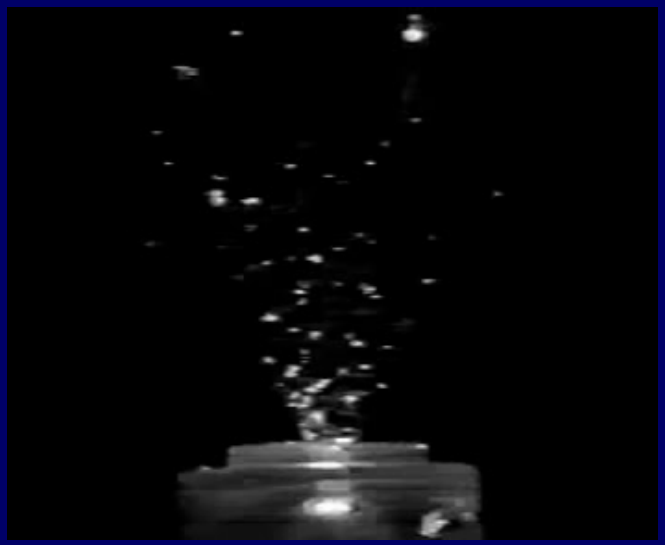

Lung deposiion fraction
1.2
1
0.8
0.6
0.4
0.2
0.01
0.1
1
10
particle size (µm)
impaction
sedimentation
diffusion
total

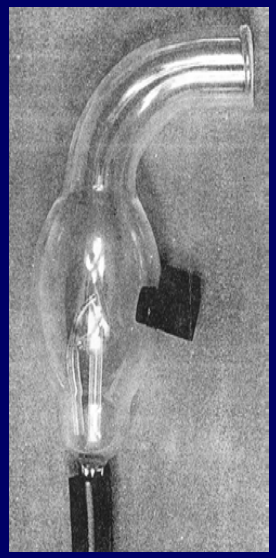
Il miglior modo per ottimizzare il passaggio dell'aerosol nell'oro-faringe e vie centrali ed aumentare la deposizione polmonare, è di inalare lentamente il farmaco erogato in particelle piccole.

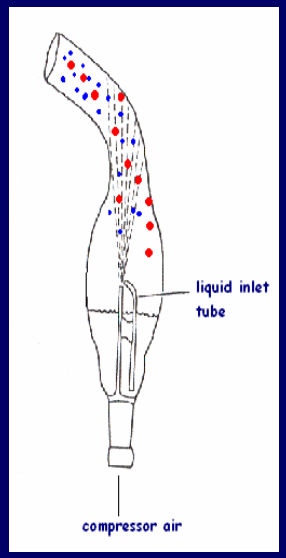
"small and slow"

Nebulization: The device

il gas di spinta passa attraverso un piccolo orifizio noto come Venturi. A questo punto la velocità del gas aumenta con conseguente caduta della pressione. Come risultato della caduta di pressione, la miscela del farmaco è risucchiata e frantumata in tante goccioline di aerosol

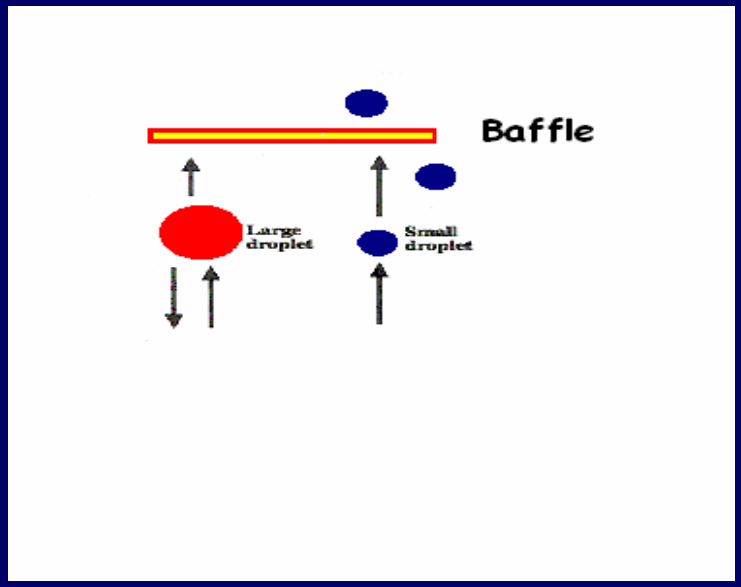






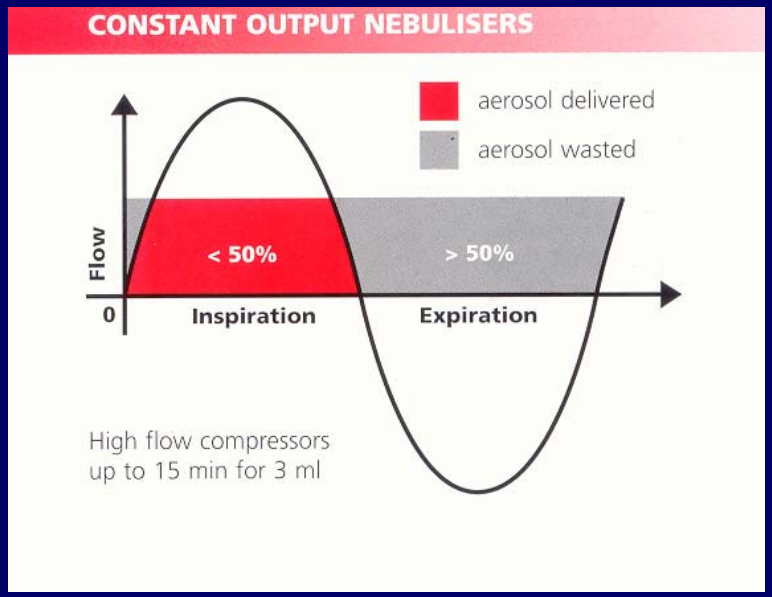
Atomizzazione

Il deflettore



Solo il 0,5% delle goccioline lasciano il nebulizzatore direttamente, il rimanente 99,5% impatta sul deflettore e sulle pareti della ampolla e vengono riciclati.

Nebulizzatore convenzionale



Nebulizzatore convenzionale

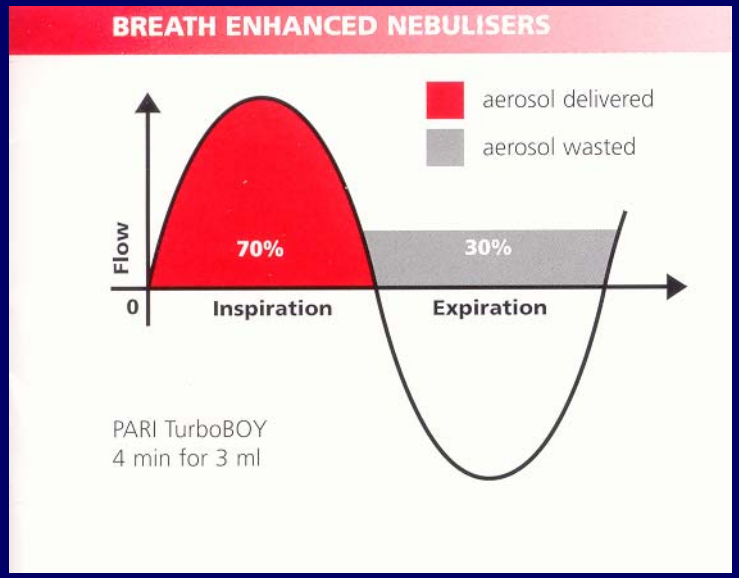
Dispersione del farmaco

Tempo di nebulizzazione lungo

Open-vent

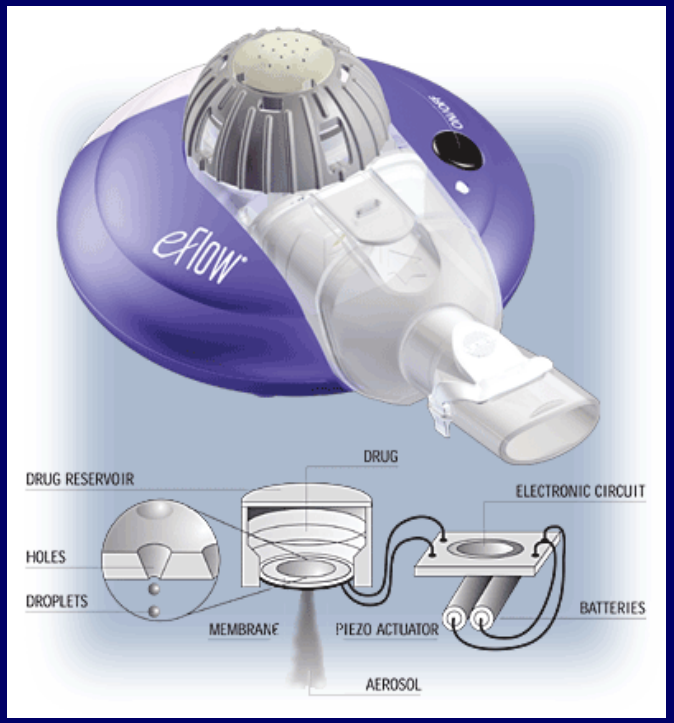
Ridotto tempo di nebulizzazione
Favorite le particelle piccole

Breath-enhanced open vent



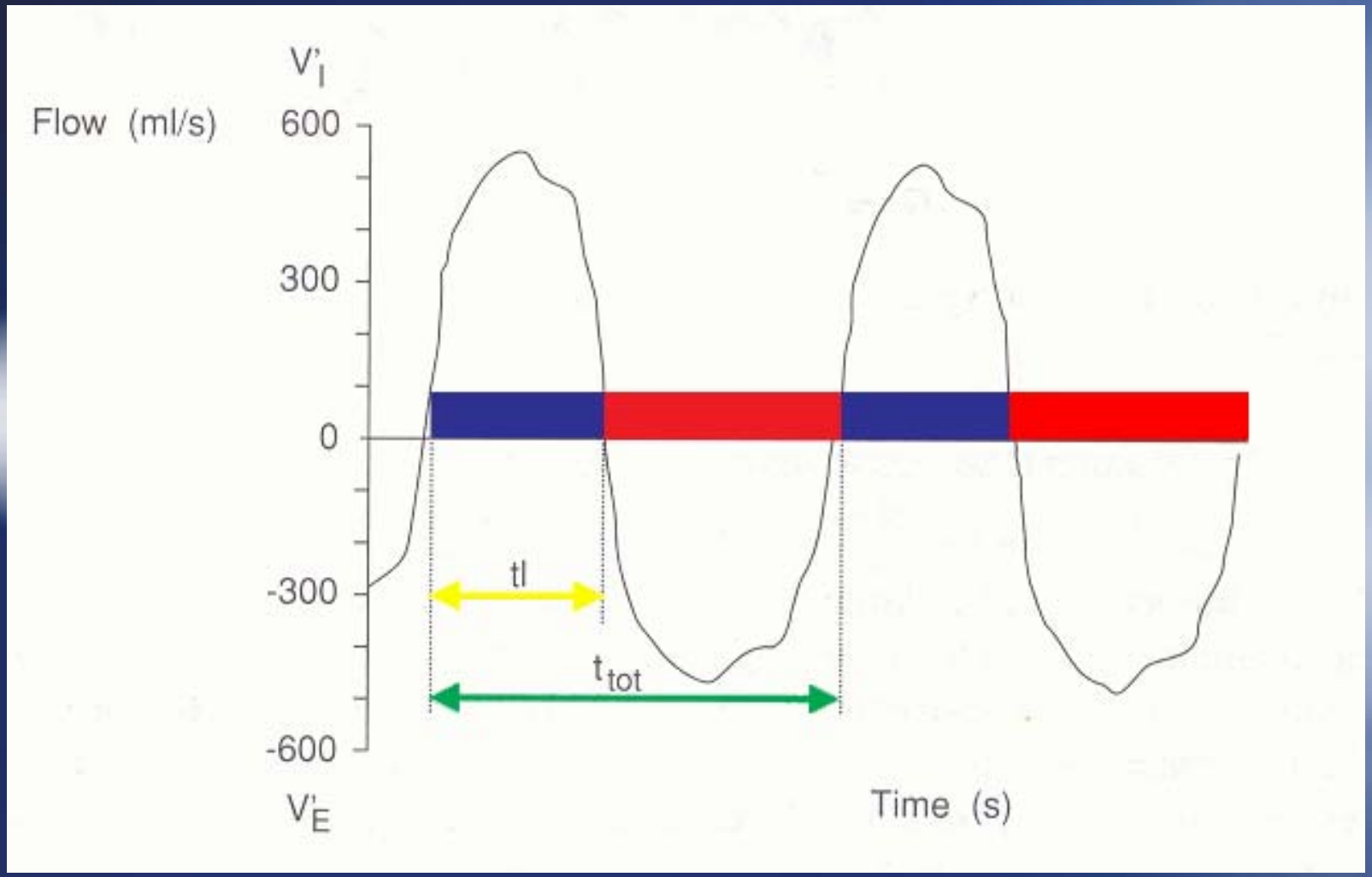
Breath activated open vent
AEROECLIPSE
(drug delivery during inspiration)

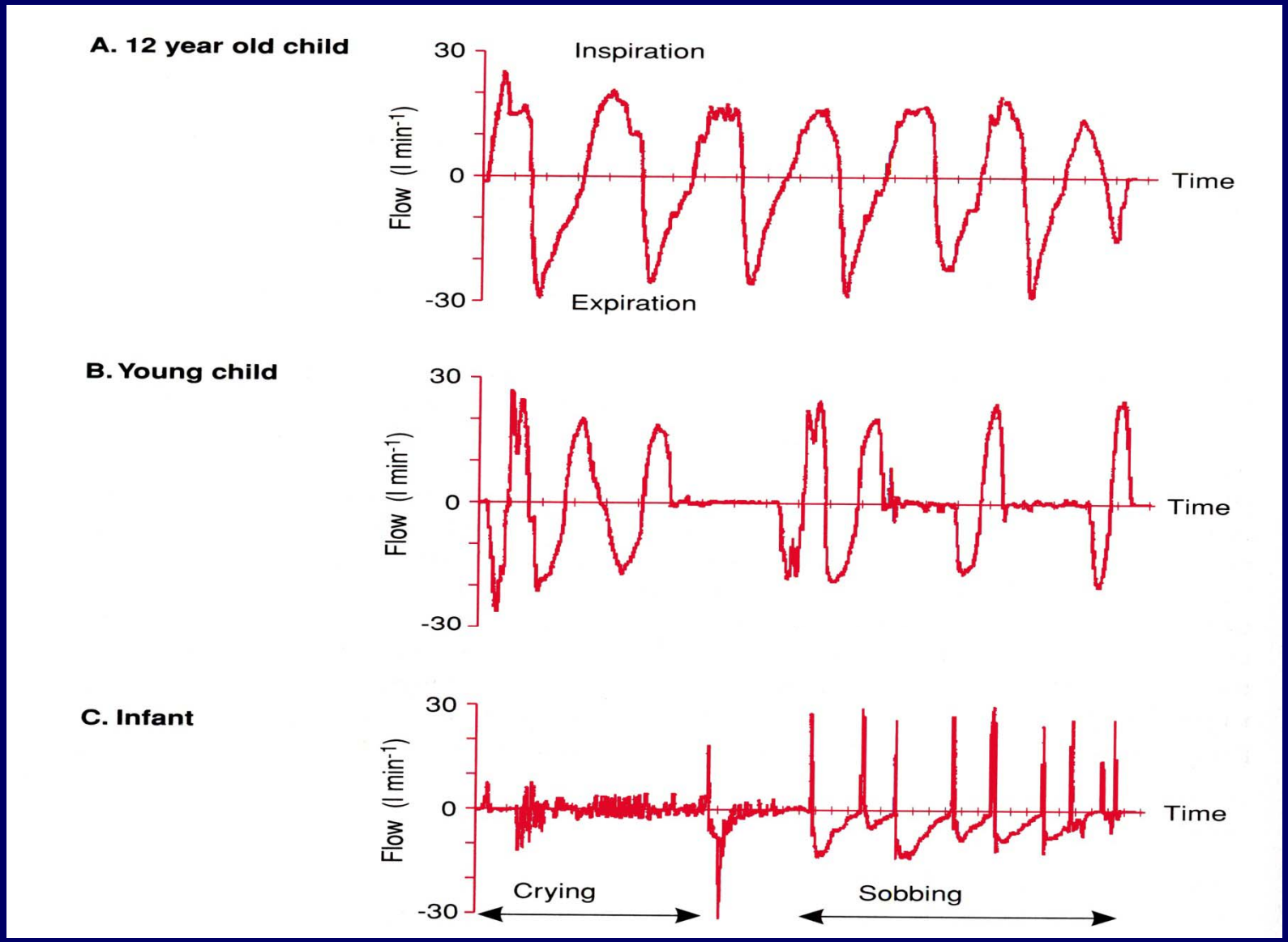
Mesch
e-Flow



I nebulizzatori erogano aerosol "nuvola" a <u>velocità contenuta</u> e il pattern respiratorio del paziente determina la velocità

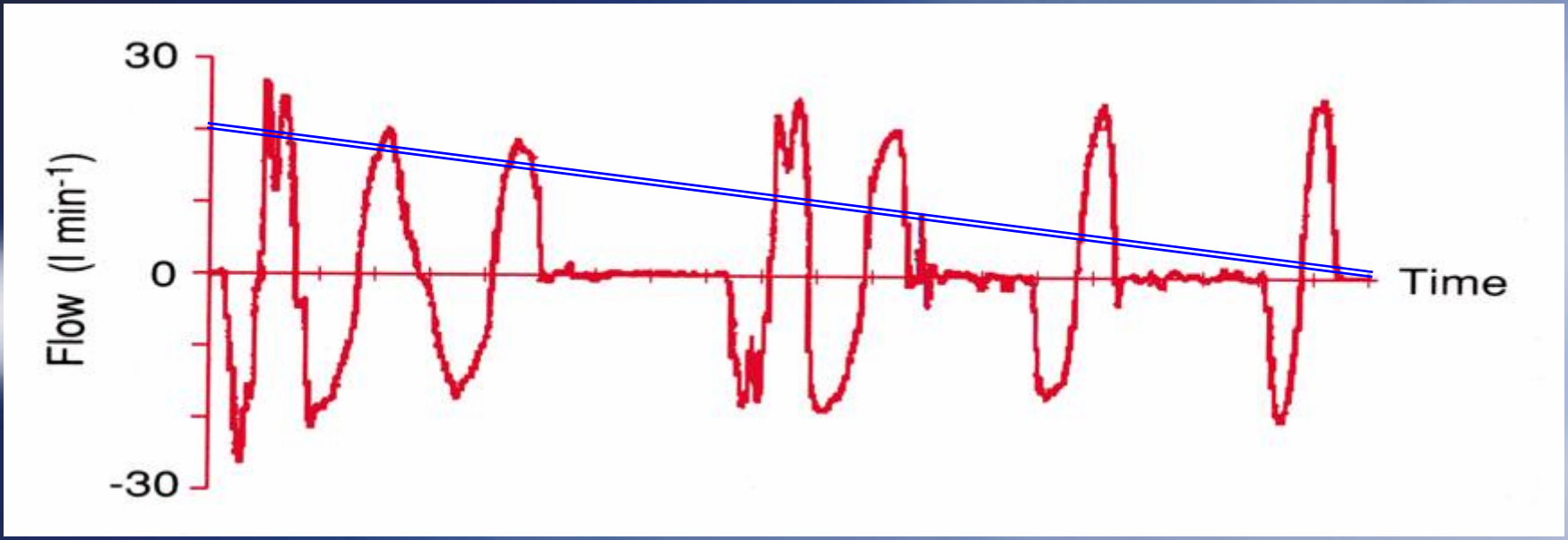
L'importanza del ciclo di rendimento (duty cycle)



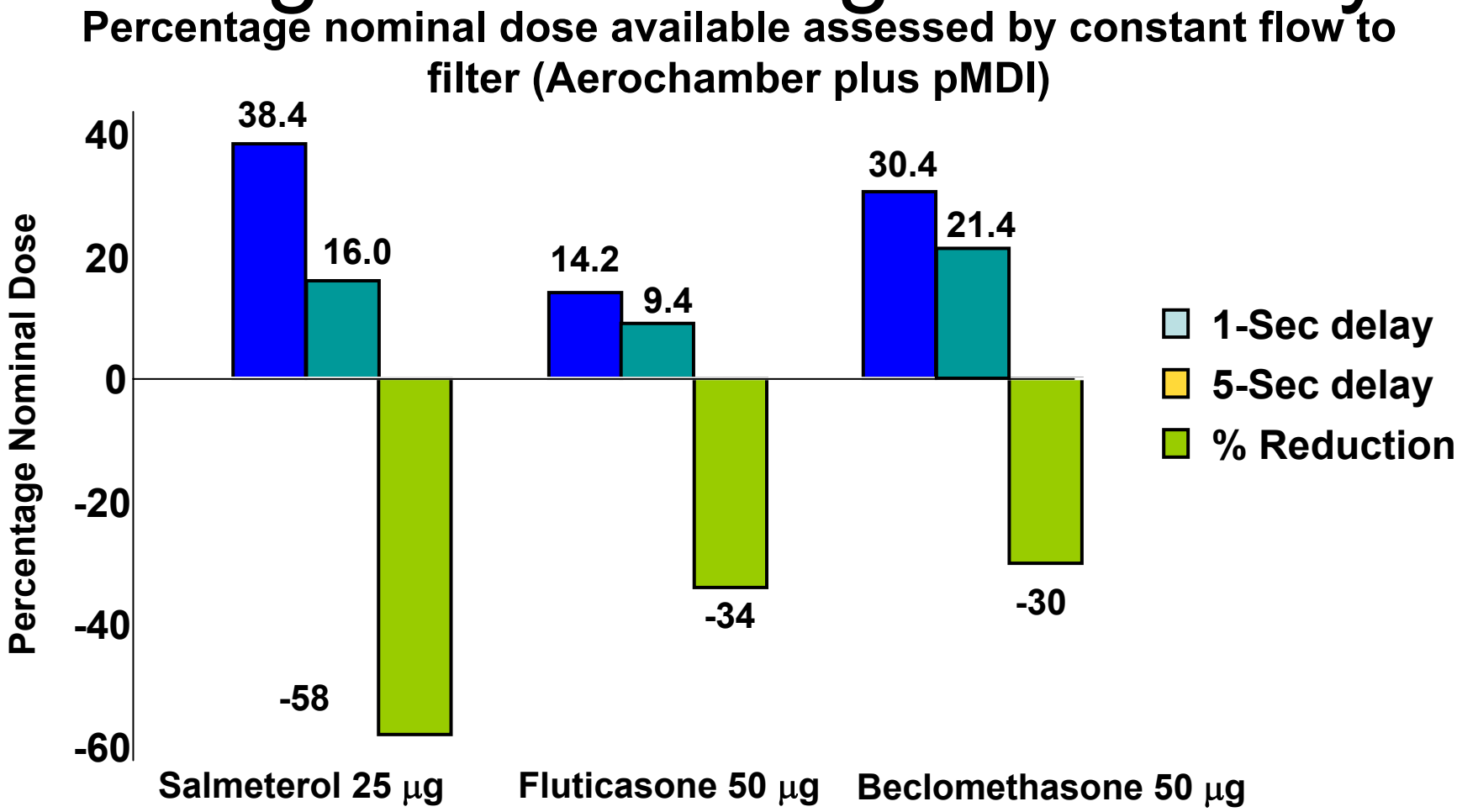


Pattern respiratorio nel bambino

PMDI

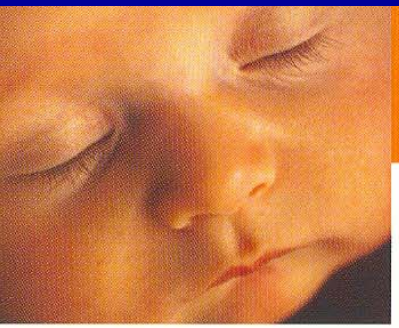


Appropriate Inhalation: Timing Affects Drug Availability

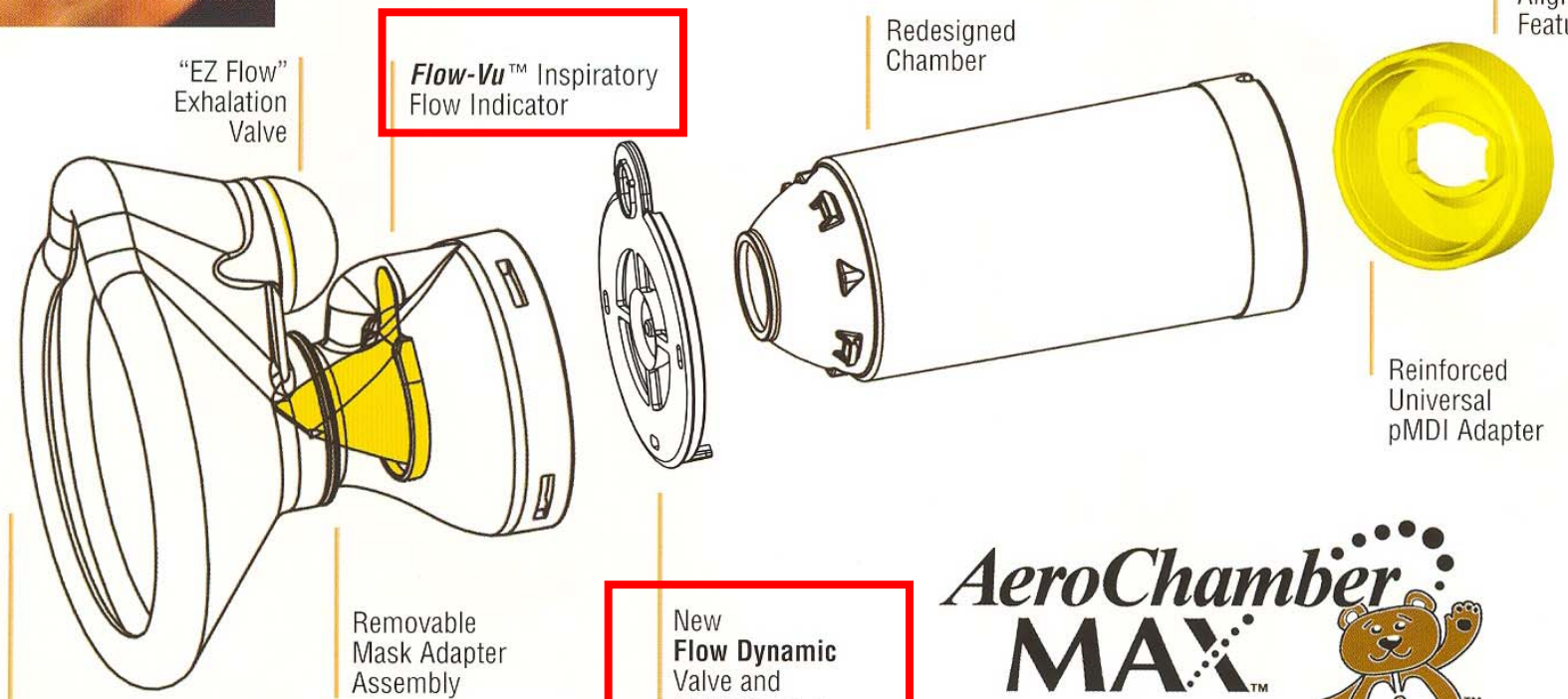


Barry et al. *Br J Clin Pharm.* 1999.

SPACERS



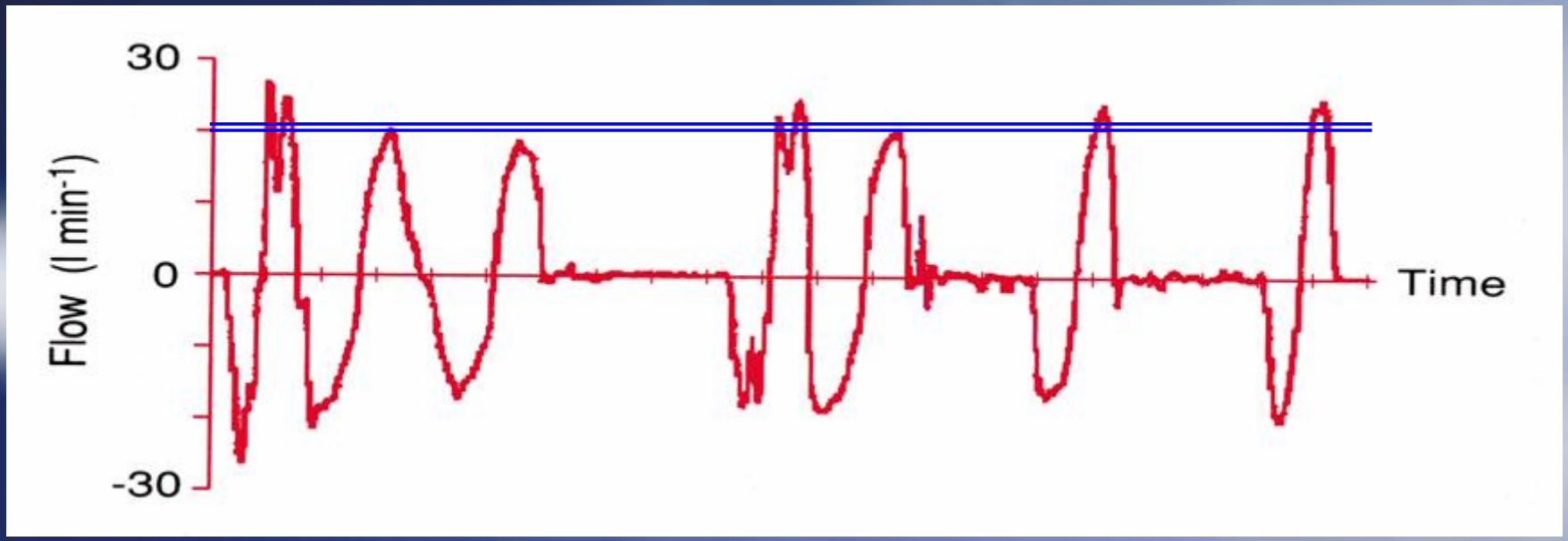
Designed specifically for the smallest patients.



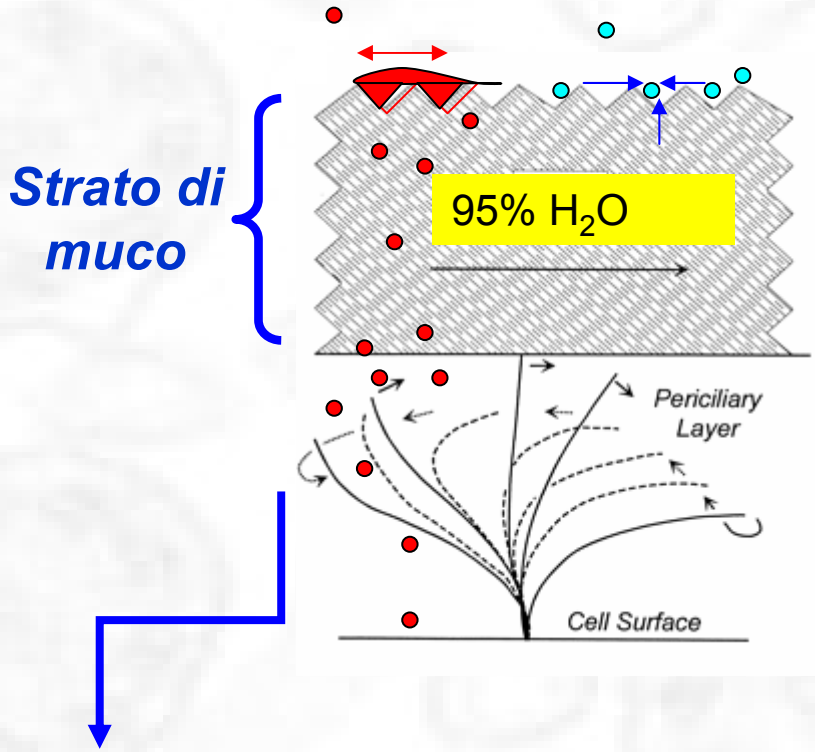
AeroChamber MAX™

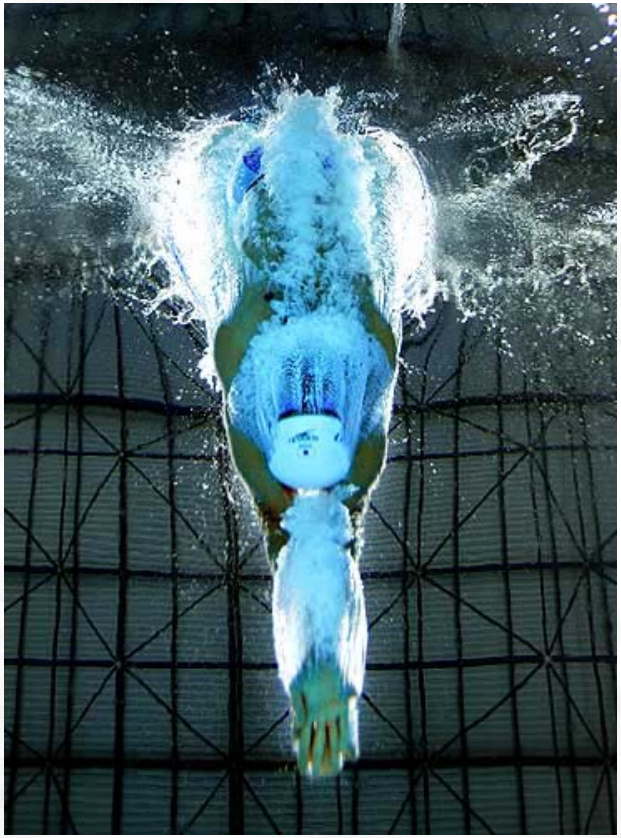
Inspiration pure and simple!

Nebulizer



Particolarità della nebulizzazione	*Azione*
Erogazione del farmaco a velocità contenuta	Riduzione dell'impatto inerziale nelle vie aeree
Periodo di erogazione prolungato	Riduzione dell'effetto negativo dell'irregolare pattern respiratorio
Erogazione con minimo impegno del paziente	Impiego nei bambini non collaboranti
Erogazione del farmaco in soluzione	Deposizione in ampia area polmonare per l'azione del "spreading forces"



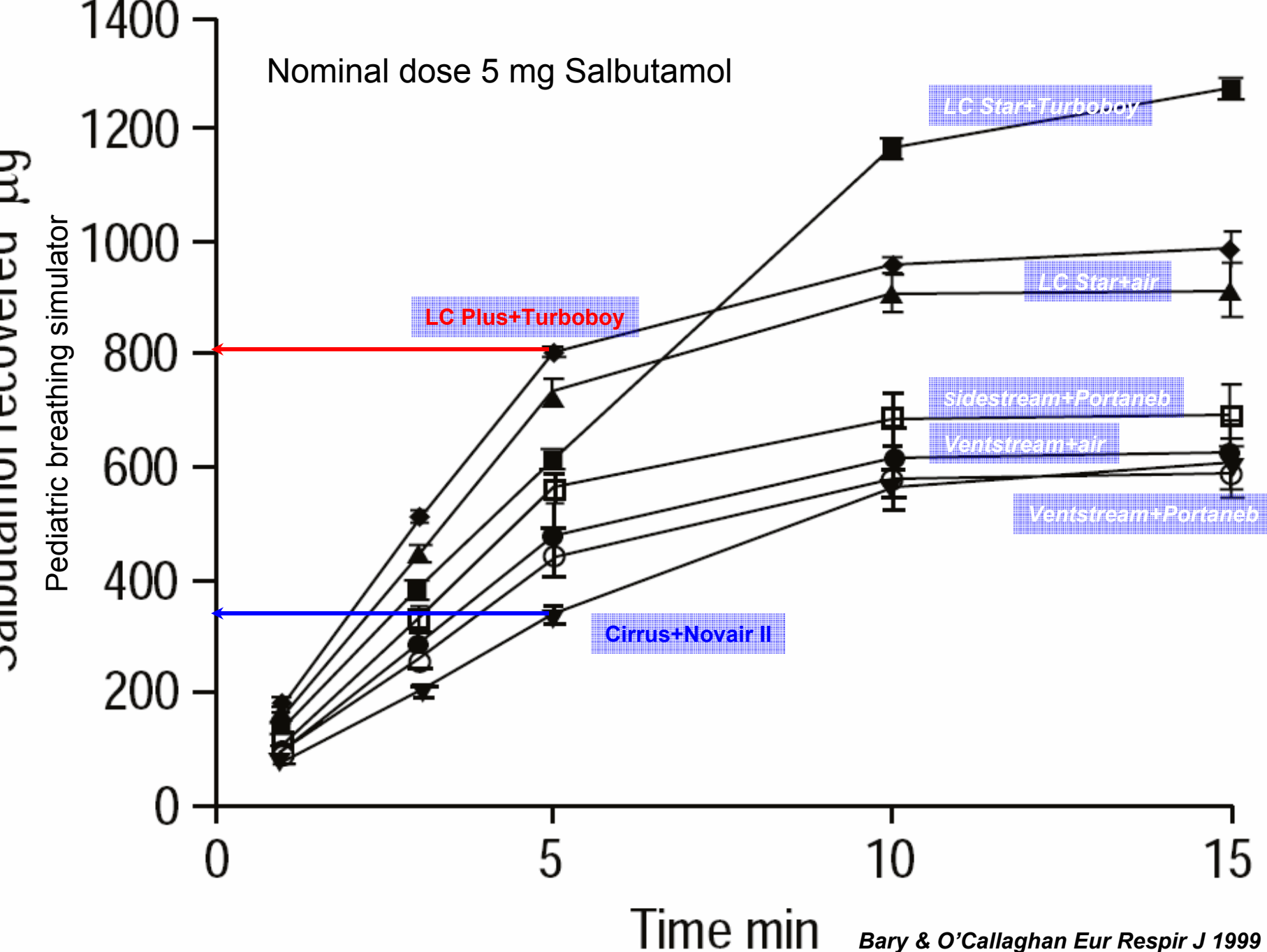


LPC
profondità 7-10 μm
ambiente fluido
separa e protegge le cellule epiteliali

- **Nelle vie aeree di piccolo calibro, lo strato di muco viene allontanato ad una velocità media di 1mm/min. Quest'ultima aumenta nelle vie aeree di calibro maggiore e raggiunge il valore di 2cm/min nella trachea**

- **"Spreading forces" soluzioni in grado di disperdersi in larga area**

Nebulization: Drug output



Bary & O'Callaghan Eur Respir J 1999

Drug out-put

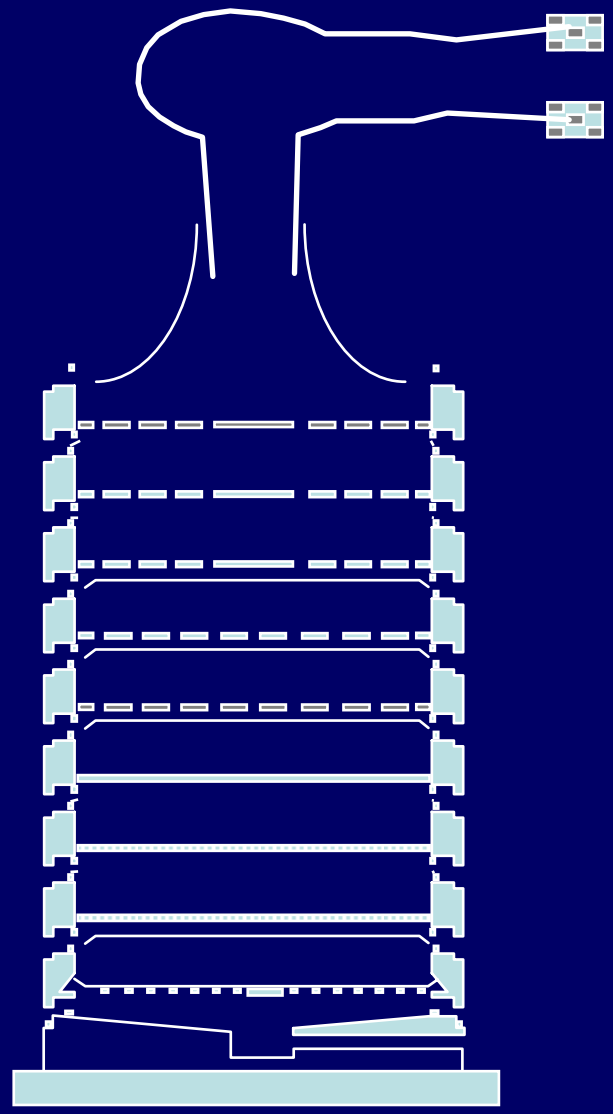
Nebula Plus

BimboNeb

- **FLU 600 µg** *(Lunibron A)* *in* 2ml di soluzione fisiologica
- **BDP 400ug/ml** (*Clenil* A) fiale da 2ml
- **BUD 0,25 mg/ml** (*Spirocort*) fiale da 2ml

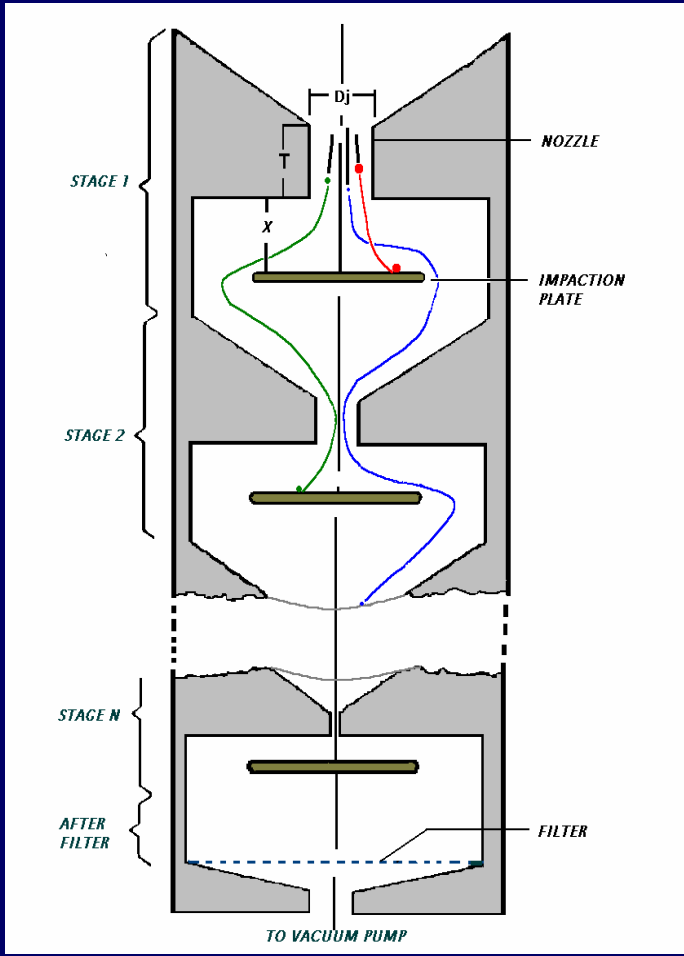
***O'Callaghan Riv Ital Pediatr 2000, J Pharm Pharmacol 2002 , J Pharm Pharmacol* 2005**

Glass Multistage Liquid Impinger



- ***4 stages***
- ***Flow 60L/min***
- ***calibrated with aerosol of known particle size distribution***
- ***cut off diameters for stages: 12.6 um, 10.1 um, 6.8 um and 4.3um.***
- ***nebuliser mouthpiece held at 2 cm away from MSLI***

Drug Collection and Assay



- Methanol was placed at each stage of the MSLI to dissolve the impacted drug
- Amount of drug collected was assayed by HPLC

	BUD (500µg)		FLU (600µg)		BDP (800µg)	
	Nebula	BimboNeb	Nebula	BimboNeb	Nebula	BimboNeb
MMAD	3,38 (0,38)	4,48 (0,44)	3,86 (0,21)	3,87 (0,14)	5.36 (0,16)	6,37 (0,36)
Erogated mass in part. <6,8 (mcg)	86,8 (4,0)	76,7 (3,5)	208,7 (14,4)	201 (10,4)	149,6 (21,4)	105,2 (6,3)
% of nominal dose in part. <6,8	17,4%	15.3%	34,6%	33,5%	18,6%	13,1%
Erogated mass in part. <4,3 (mcg)	67,0 (5,4)	53,5 (5,4)	154,18 (10,85)	148,53 (7,44)	91,53 (15,9)	57,26 (1,7)
% of nominal dose in part. <4,3	13,4%	10,7%	25,7%	24,7%	11,5%	7,2%

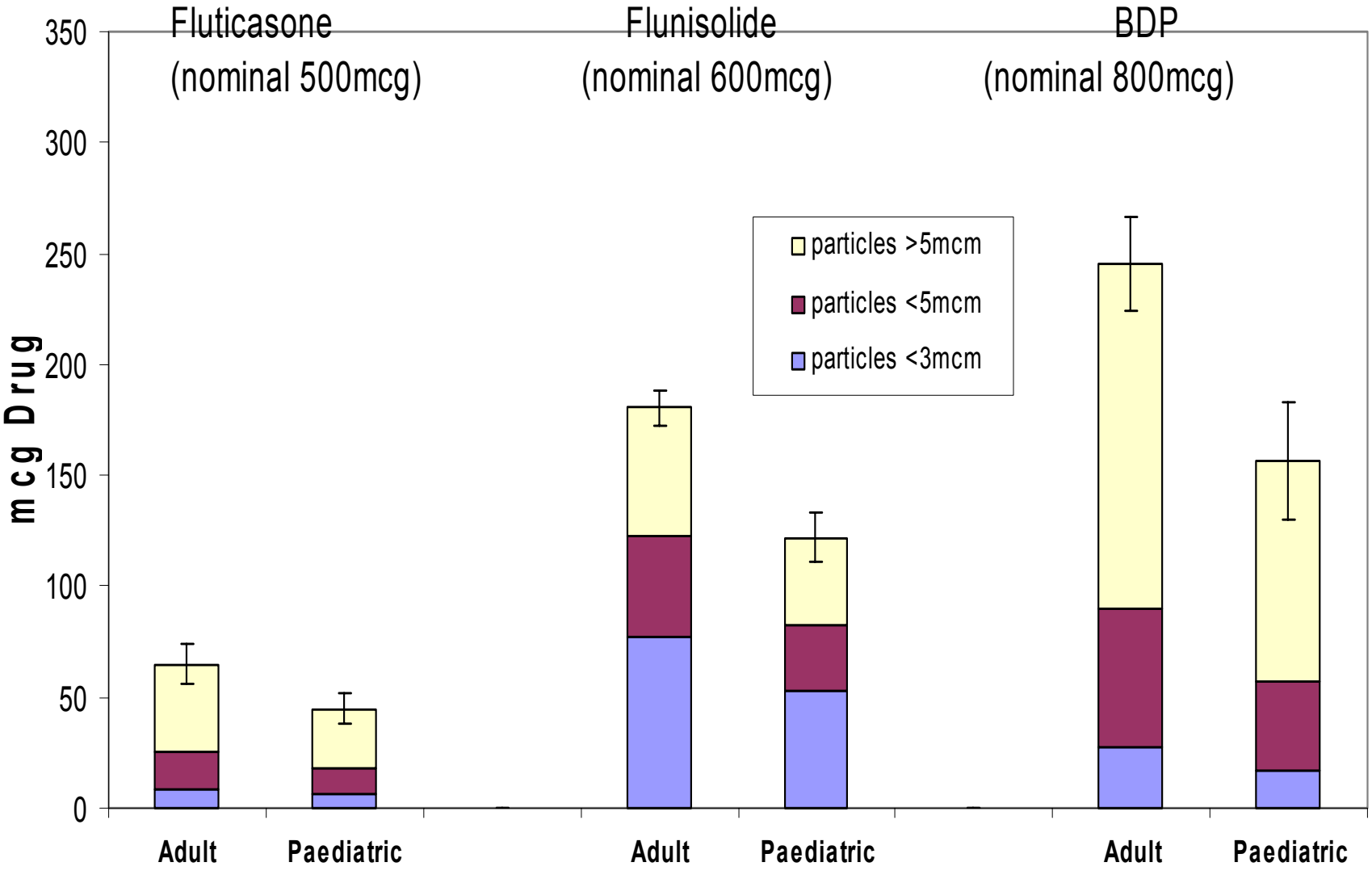
Drug out-put

in a 3 ml volume fill

- ***FP 500 µg***
- ***FLU 600 µg***
- ***BDP 800 µg***

	FP 500 µg	FL 600 µg	BDP 800 µg
Cloud µg % nominal dose	84.35 16.89	219.68 36.61	245.93 30.74
MMAD	5.30	3.36	5.48
% Particles <5µg in cloud	39.4	67.8	36.4
% Particles <3µg in cloud	13.3	42.9	11

Fig. 2 - Combined data showing the mass of Fluticasone propionate, Flunisolide and Beclomethasone dipropionate in particles <5mcm and <3mcm after 10min nebulisation using the Pari LC Plus and TurboBoyN compressor (Mean & 95% C.I.)



	Water solubility (ug/ml)	Dissolution time *(human bronchial fluid in vitro)*
BPD/BMP	0.13/15.5	>5h/-
Budesonide	16	6 min
Flunisolide	140	<2 min
Fluticasone	0.14	>8h

Rev Contemp Pharmacother 1998

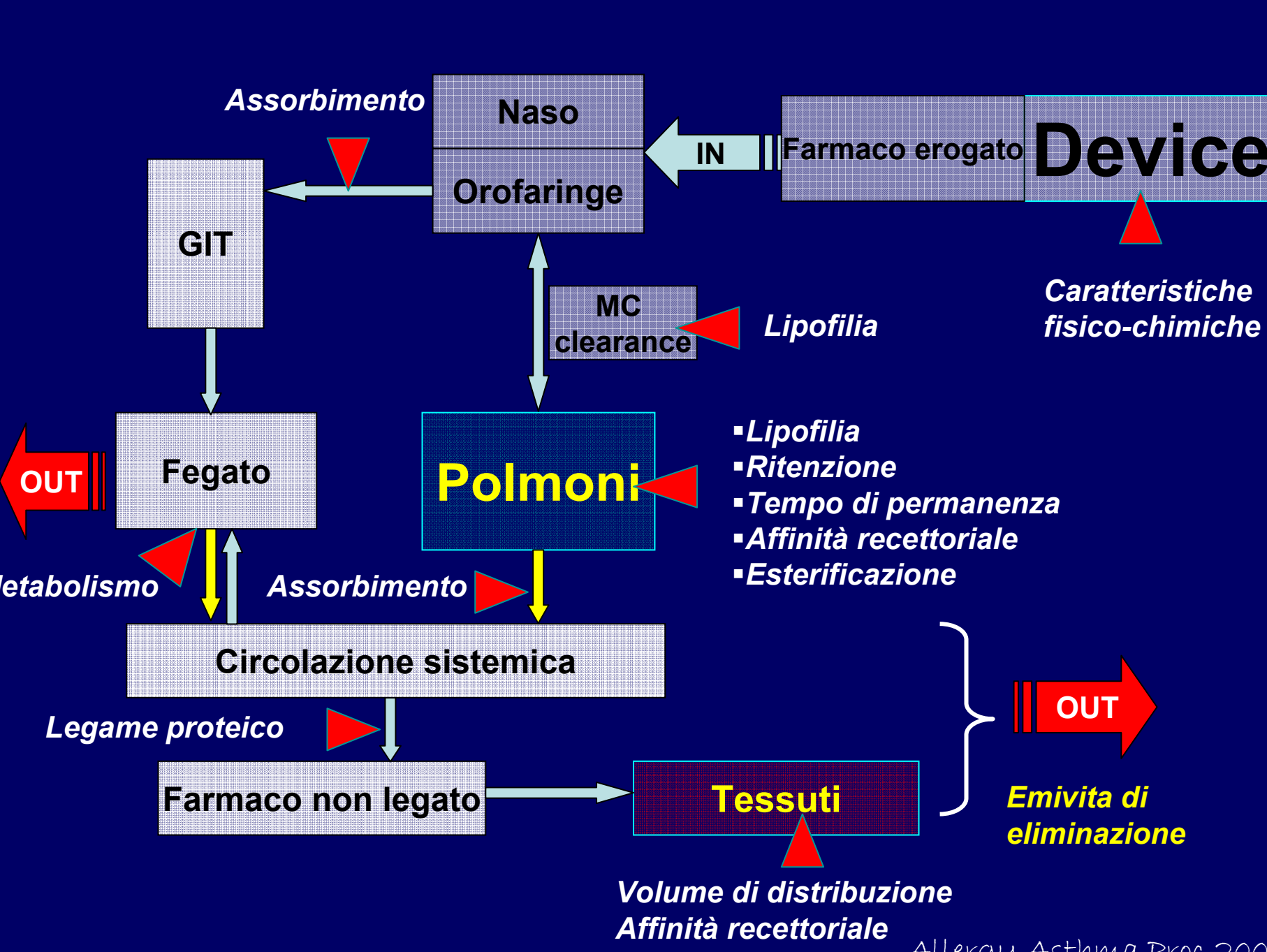
SOLUZIONE

Una soluzione consiste in una miscela di due o più componenti che formano *una dispersione molecolare omogenea in una sola fase fisica*.

SOSPENSIONE

Una sospensione consiste in una miscela di particelle insolubili disperse in un liquido.

***Le particelle di un farmaco in una sospensione si rivestono di una pellicola di liquido con un incremento significativo del loro diametro*.**


Assorbimento
Naso
Orofaringe
IN
Farmaco erogato
Device
GIT
MC clearance
Lipofilia
Caratteristiche fisico-chimiche
OUT
Fegato
Polmoni
▪Lipofilia
▪Ritenzione
▪Tempo di permanenza
▪Affinità recettoriale
▪Esterificazione
etabolismo
Assorbimento
Circolazione sistemica
OUT
Legame proteico
Farmaco non legato
Tessuti
Emivita di eliminazione
Volume di distribuzione
Affinità recettoriale

Devices used for the delivery of bronchodilators and steroids can be equally efficacious. It is important that patients can use the inhaled device they have been prescribed.

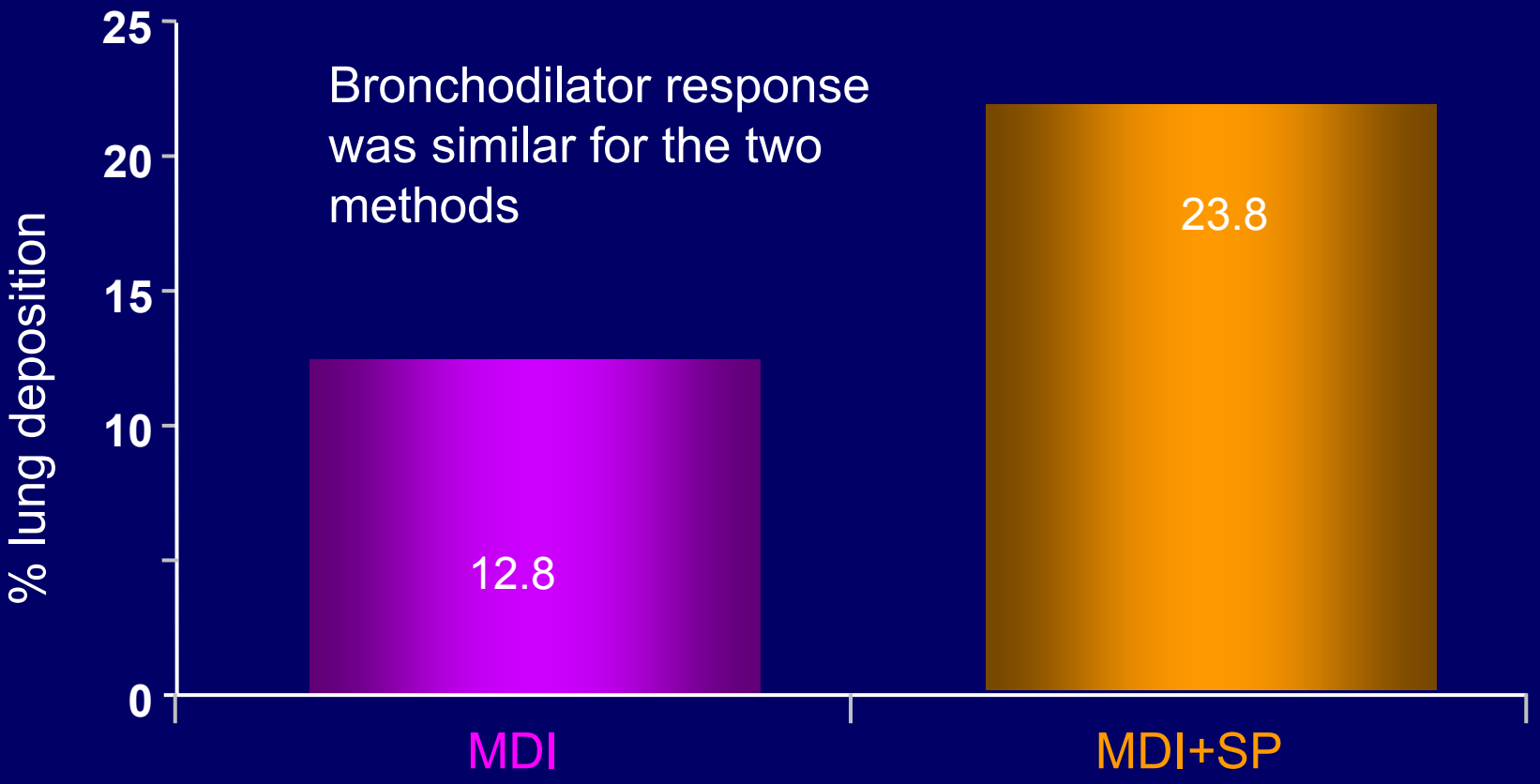
Dolovich et al. Device selection and outcomes of aerosol therapy: Evidence Based guidelines. Chest 2005

No difference in clinical effectiveness between nebulisers and alternative inhaler devices compared to a MDI and a MDI attached to a spacer

Brocklebank D et al. Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. Health Technology Assessment 2001

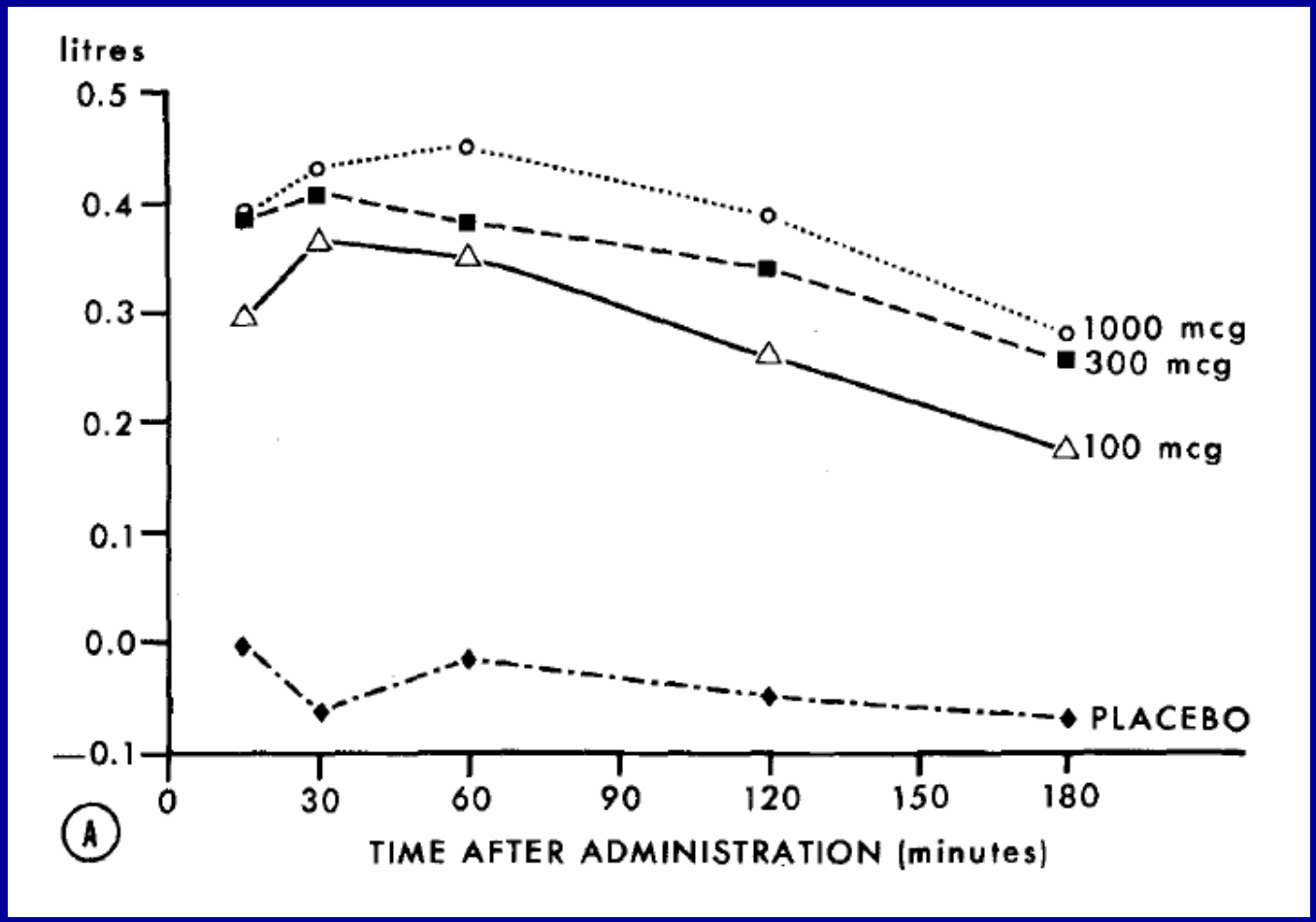
FOLLOW
GUIDE AIR LINES

100μg of salbutamol delivered from a Rondo Spacer compared to a MDI in 10 asthmatics



Newman et al Acta Therapeutica 1991

20 children with stable asthma (6-14 years)
comparison of 0, 100, 300, and 1000 ug of nebulized fenterol (jet nebulizer)



Mean increases in FEV1 from baseline up to three hours after completion of nebulization

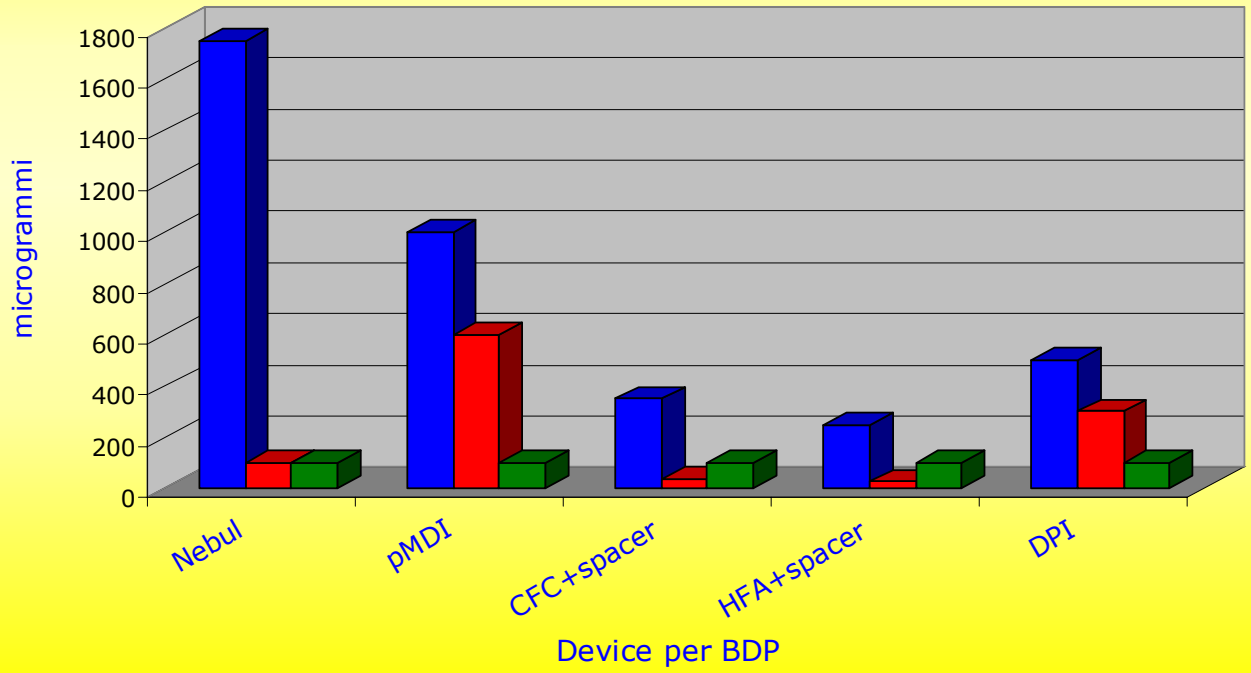
Reilly J Pediatr 1983

BDP per via inalatoria

Dosaggio "stimato" di BDP per assicurare la deposizione di 100 ug nei polmoni

Biodisponibilità sistemica "stimata" di origine extrapolmonare per assicurare la deposizione di 100 *ug* nei polmoni

deposizione polmonare



DRUG-DEVIVE MATCHING

✓The choice of a device depends on the drug to be delivered and on the patient

✓Much of this practice may not be evidence-based

✓Some present practice may be ineffective or even harmful

✓Many aerosol therapy represents an empirical mode of treatment without any precise data on the performance of the device, the appropriateness of device/drug combination, the dose of drug deposited in the lungs and its actual site of deposition

AEROSOL THERAPY

pulling surprises from our pockets