

# ■ ■ Inhalation & Nasal Device Overview

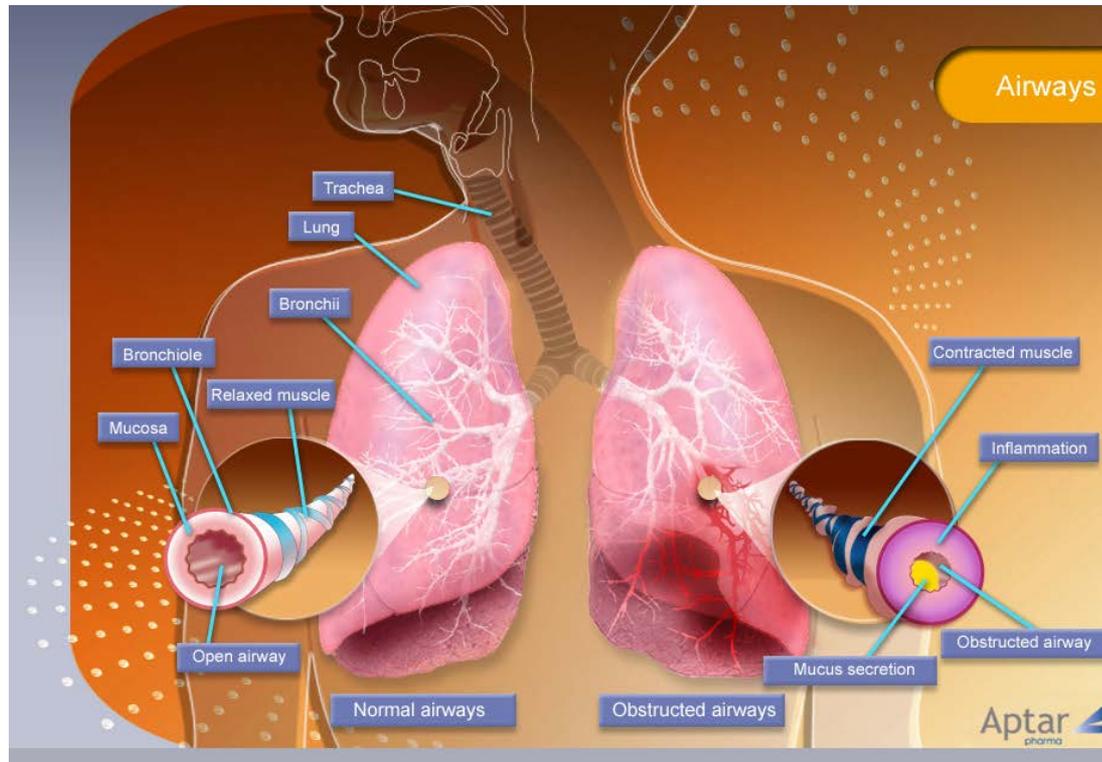
■ ■ September 29, 2015



## Learning Objectives

- ■ To understand rationale for nasal and pulmonary drug delivery
- ■ To differentiate between device attributes for inhalation and nasal platforms
- ■ To list the important components of a MDI
- ■ To describe the metering mechanisms for DPIs
- ■ To understand effects of formulation on nasal spray performance

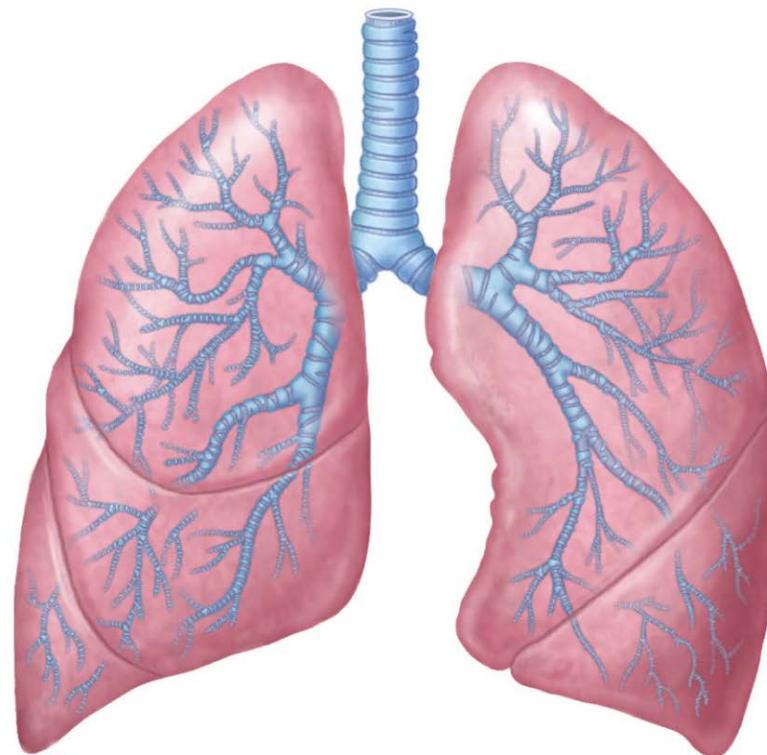
# Rationale for Pulmonary Drug Delivery



- Large surface area
- Gas exchange
- Blood supply
- Particle trapping and removal

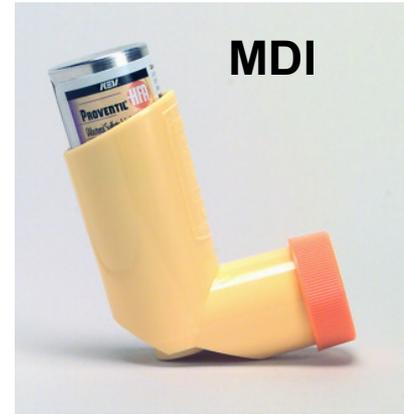
# Targeting the Lung

- Upper Respiratory Tract
  - Bronchodilators
  - Corticosteroids
  - Anti-infectives
- Lower Respiratory Tract
  - Surfactant Replacement
  - Systemic Drug Delivery
    - Insulin
- Size Matters!
  - Particle size



Aptar  
pharma  
**Inhalation  
Delivery Platforms**

- Metered Dose Inhalers (MDI)
- Soft Mist Inhalers (SMI)
- Nebulizers
- Dry Powder Inhalers (DPI)



**MDI**

**Pari LC Star**



ON

**Respimat (SMI)**



**E-Flow**



**Ellipta**



**Dreamboat**



**Twisthaler**



**HandiHaler**



**Diskus**

# Metered Dose Inhalers (MDIs)

- Solution or suspension
- Propellant (HFA-134a or HFA 227)
  - All US drug products will use HFA propellants
  - CFC's lagging in developing markets
- Excipients
  - Co-solvent (ethanol)
  - Surfactant
  - Taste masking
  - Moisture control



ProAir HFA

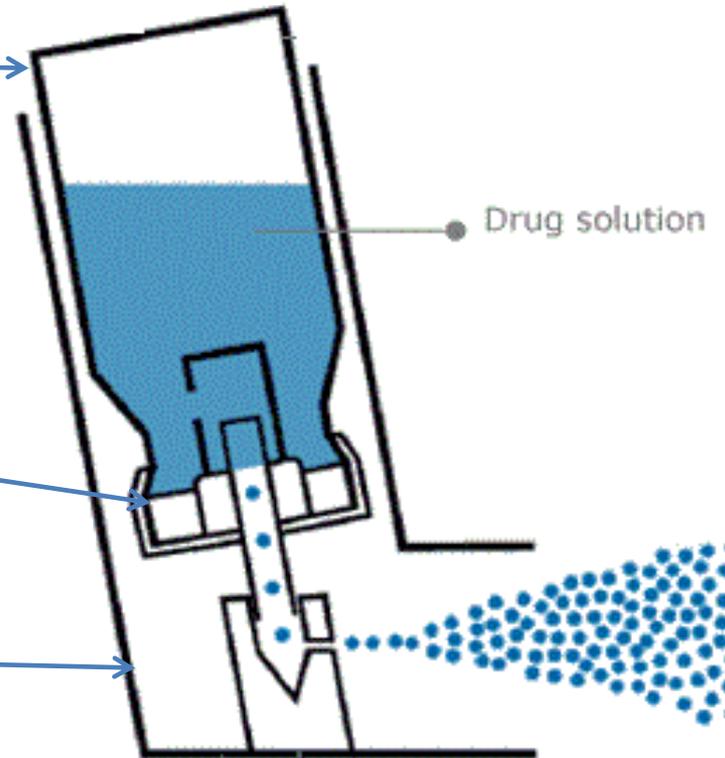


Ventolin HFA

## pMDI - Basic Design & Function

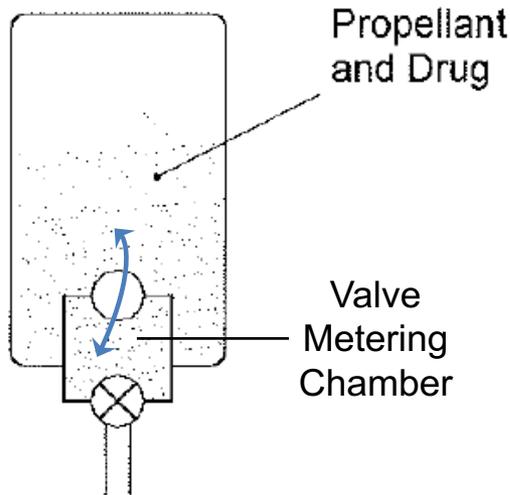
■ ■ Standard pMDIs include three fundamental components:

1. Canister
  - Single component
  - Contain and protect drug formulation
2. Valve
  - Multi-component
  - Multi-function
3. Actuator
  - Single component
  - Easy to hold in hand
  - Direct drug product spray to patient's mouth



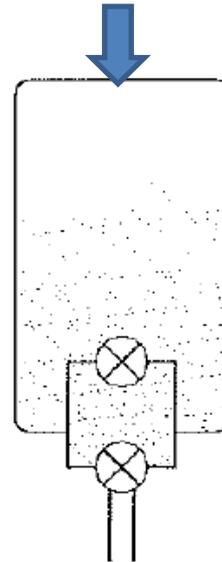
## Dose Delivery from the Valve

❖ Basic principle :



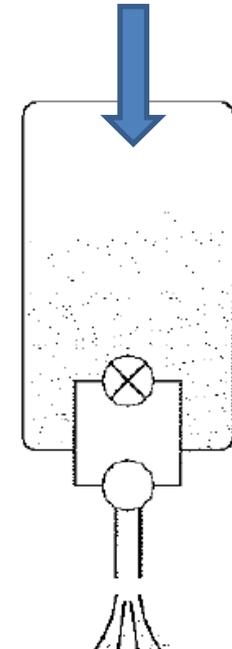
### At rest

Free flow of drug formulation between the bulk contents in the can and the Valve Metering Chamber. The drug product formulation is a pressurised liquid.



### Beginning of Actuation

The patient pushes on the bottom of the can. The Valve Stem is pushed into the Valve. The drug formulation in the Metering Chamber is isolated. This is the dose that will be delivered to the patient.



### End of actuation

The patient continues pushing until the Stem is fully pushed into the Valve. The drug formulation in the Metering Chamber is exposed to exterior (ambient) pressure and changes from liquid to gas vapour. The vapour exits the Valve.

## MDI Features

- Dose counters\*
  - New drug products in US must utilize dose counters
  
- Spacers
  - Add on device
  - Marketed separately from MDI
  - Common use in pediatric and geriatric populations
  - Sometimes specified or listed in product labeling in US
    - Required to be described and tested in EU



Landmark Dose Counter courtesy Aptar Pharma

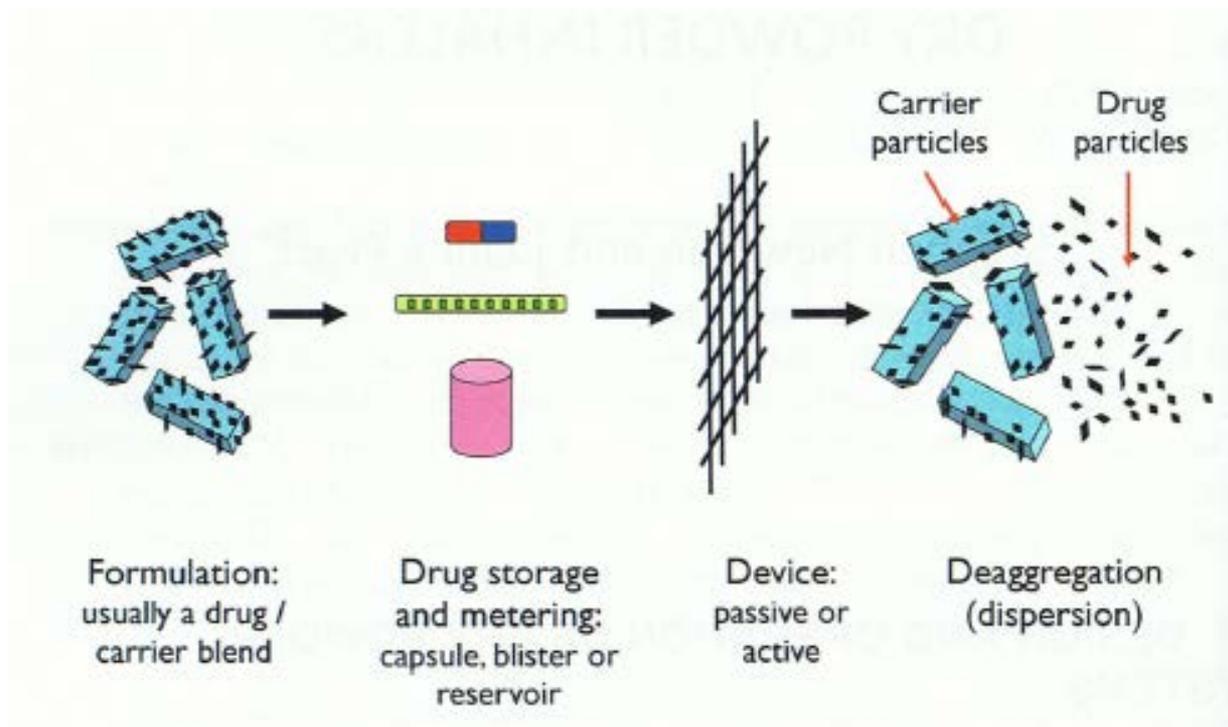


# Dry Powder Inhalers (DPIs)

- ❑ Drug
  - Micronized or spray dried
- ❑ Carrier
  - Lactose
- ❑ Additional excipients
  - Taste masking
  - Stability
- ❑ Dose counter often present



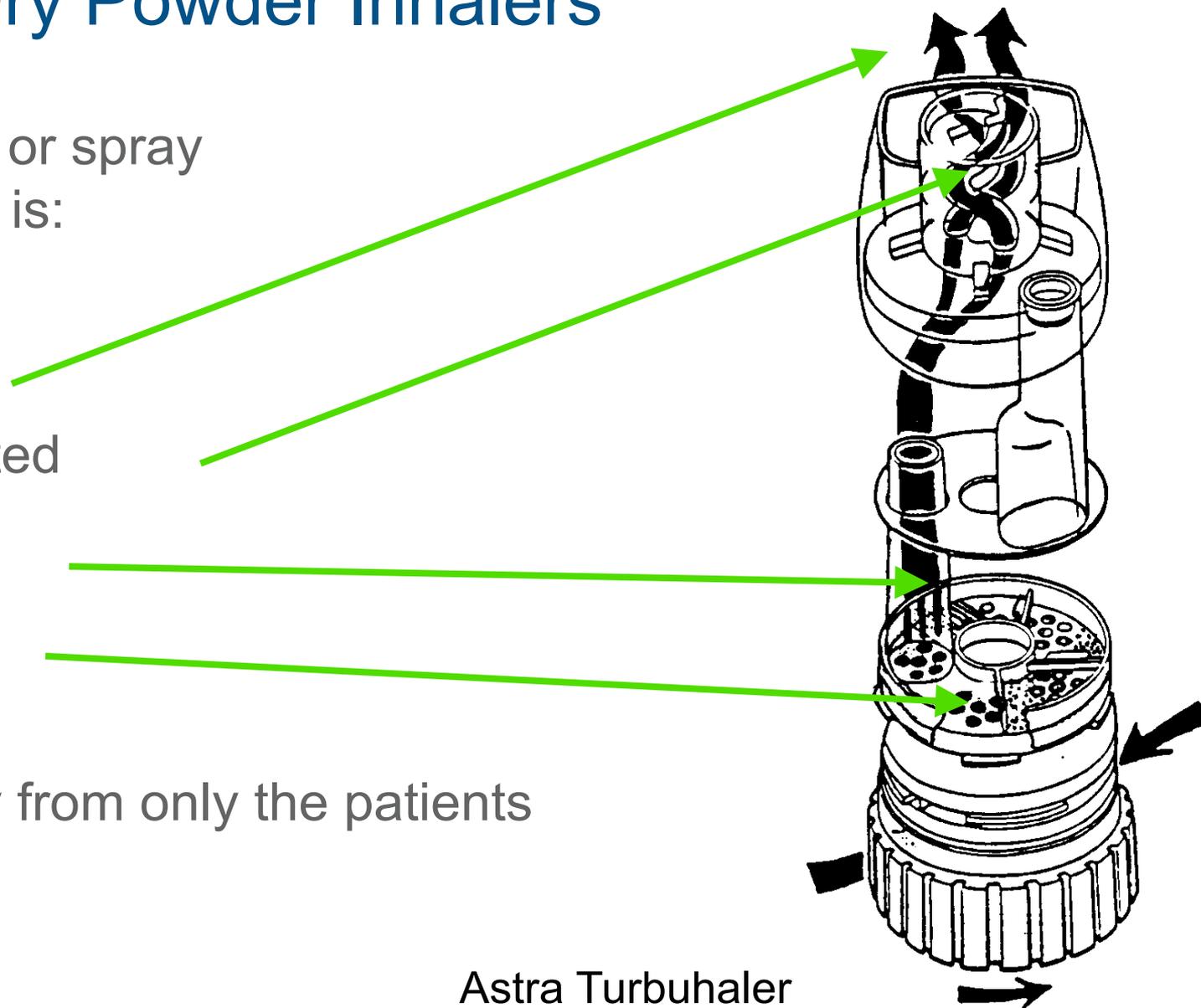
# Dry Powder Inhaler (DPI)



- DPI schematic adapted from Telko and Hickey, 2005
- Drug - Micronized or spray dried
- Carrier - Lactose

# Passive Dry Powder Inhalers

- A micronized or spray dried powder is:
  - Inhaled
  - Deaggregated
  - Entrained
  - Metered
- Using energy from only the patients inhalation



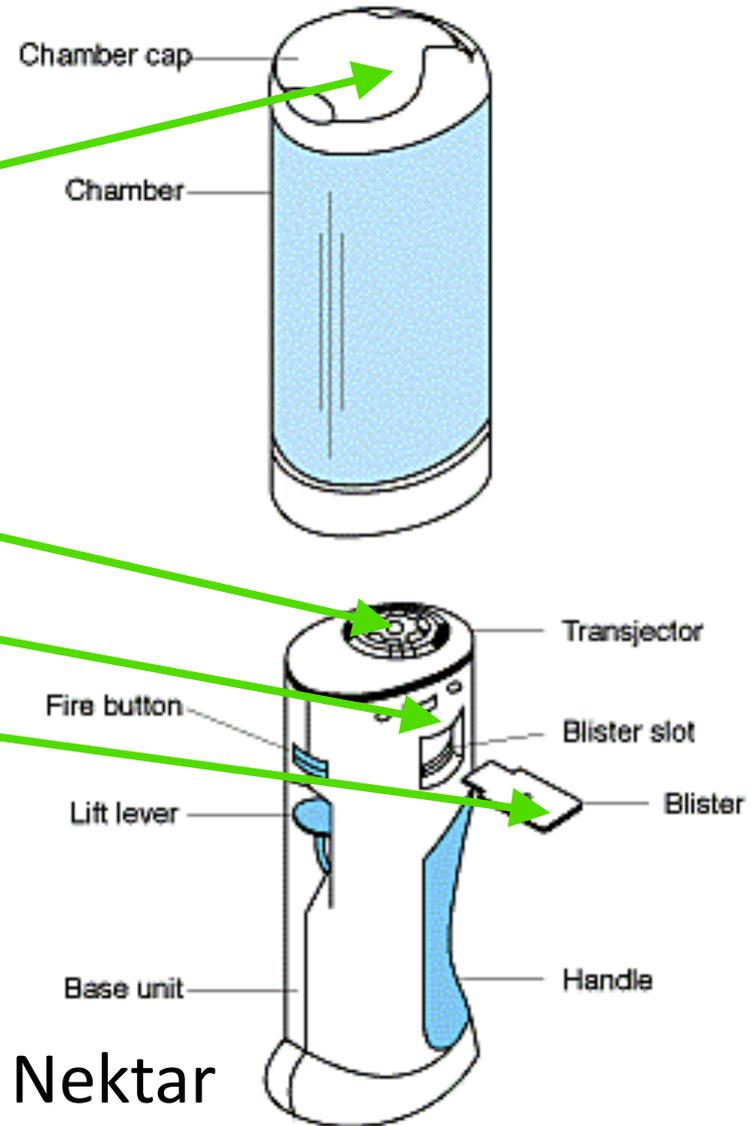
Astra Turbuhaler

# Active Dry Powder Inhalers

- A micronized or spray dried powder is:

- Inhaled
- Deaggregated
- Entrained
- Metered

- Using energy from a patient independent source



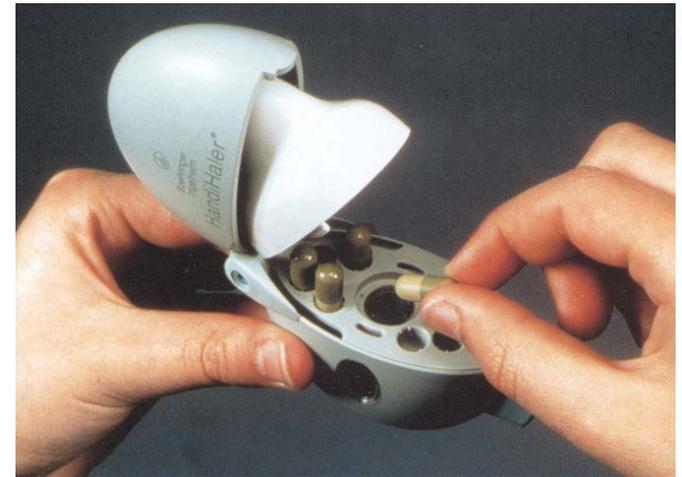
Nektar

# DPI Device Metering

■ ■ Capsule

■ ■ Blister

■ ■ Reservoir



Spiriva



Foradil  
Aerolizer

# Capsule Selection

- Size 3 is a standard capsule format suitable for high speed filling technology
- Size 3 capsule can be easily filled for development & clinical purposes
- HPMC or gelatin
- Filling range between typically between 5-30mg
- Off the shelf solutions available
  - Customization may be required

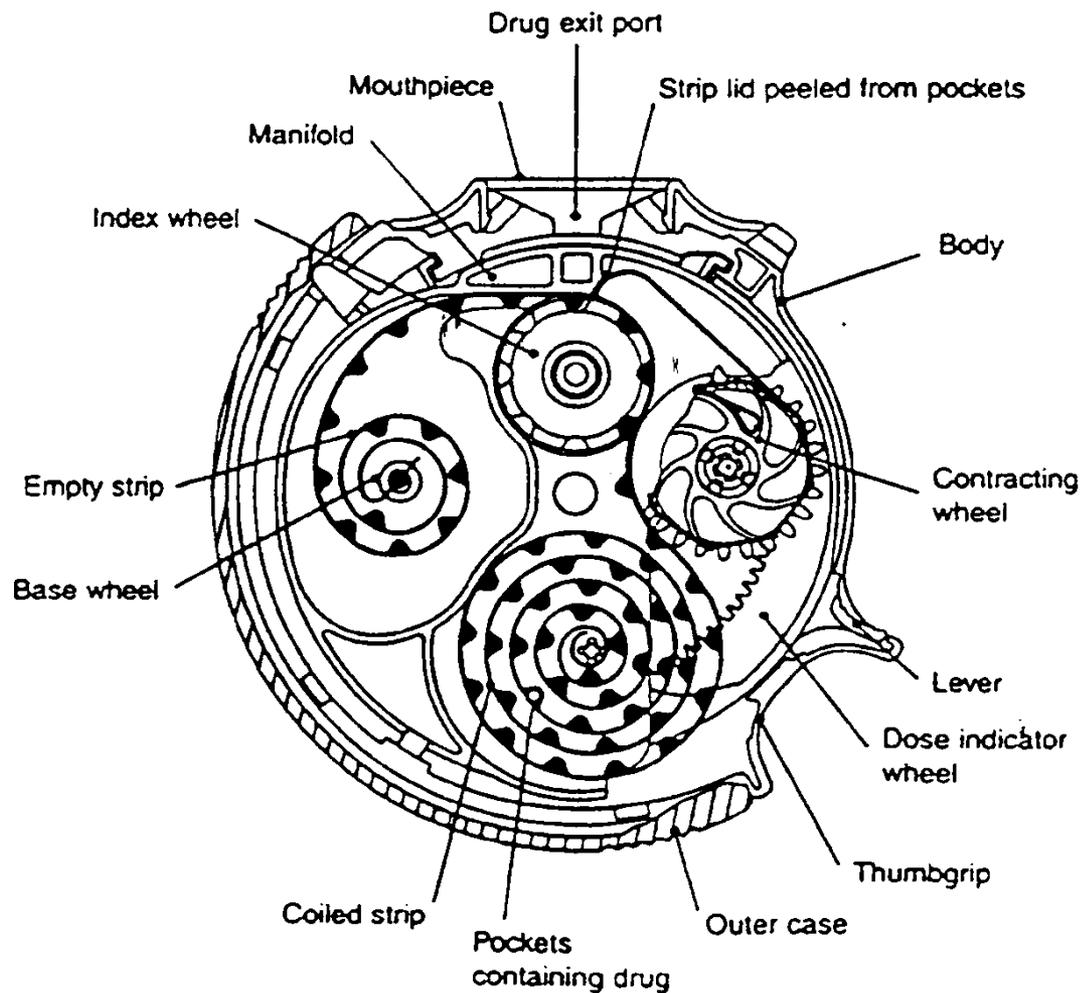


## Capsule Considerations

- Should not fragment if pierced
- Shell should be retained in device during use
- Capsule should be easily inserted and removed
- Capsules from other devices should not be usable
- Capsule should be protected from high and low humidity during storage e.g. capsules in blister packs



# DPI Blisters Systems



Glaxo Wellcome  
Accuhaler / Diskus

# Blister Considerations

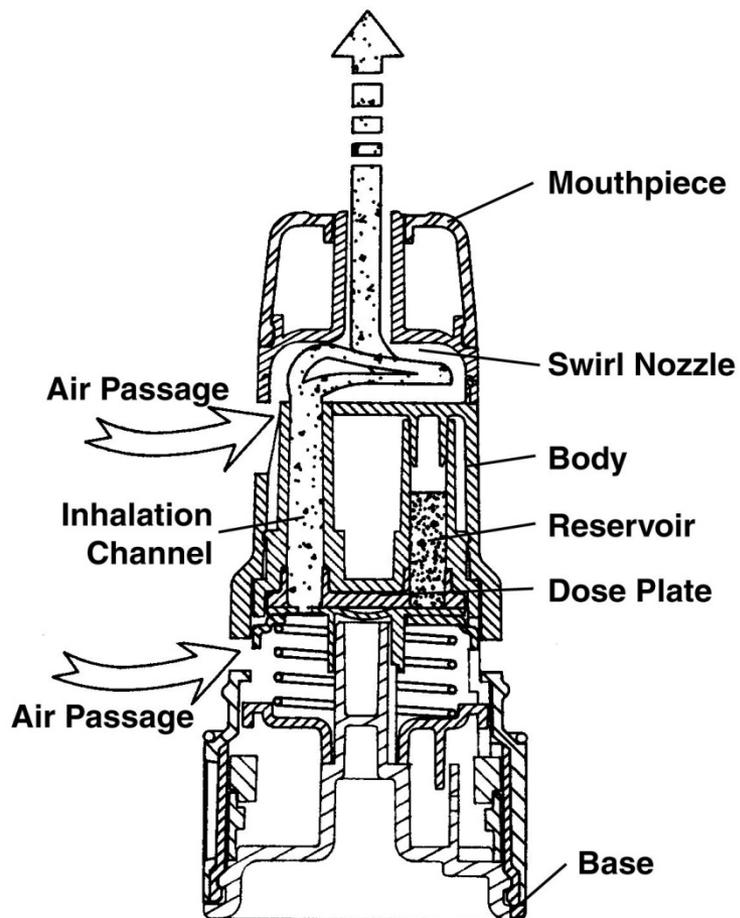
## ▣▣ Advantages

- ▣ Protect powder formulation from humidity
- ▣ Multiple dose pack possible
- ▣ Less chance to inhale fragments from blister

## ▣▣ Disadvantages

- ▣ Non-conventional filling
- ▣ Double dosing potential
- ▣ Difficult for patient to clean

# DPI Reservoir Systems



Asmanex Twisthaler  
Mometasone furoate  
(Merck)

# Reservoir Considerations

- ■ Non-conventional filling and assembly
- ■ Protection of reservoirs against environment and exhalation by patient into reservoir itself
- ■ Dose variance between batches, users, modes of use, and through device lifetime
- ■ Effects of transport

# Device Resistance

Low

High

Aerolizer



Diskus



Novolizer



Turbuhaler



Clickhaler

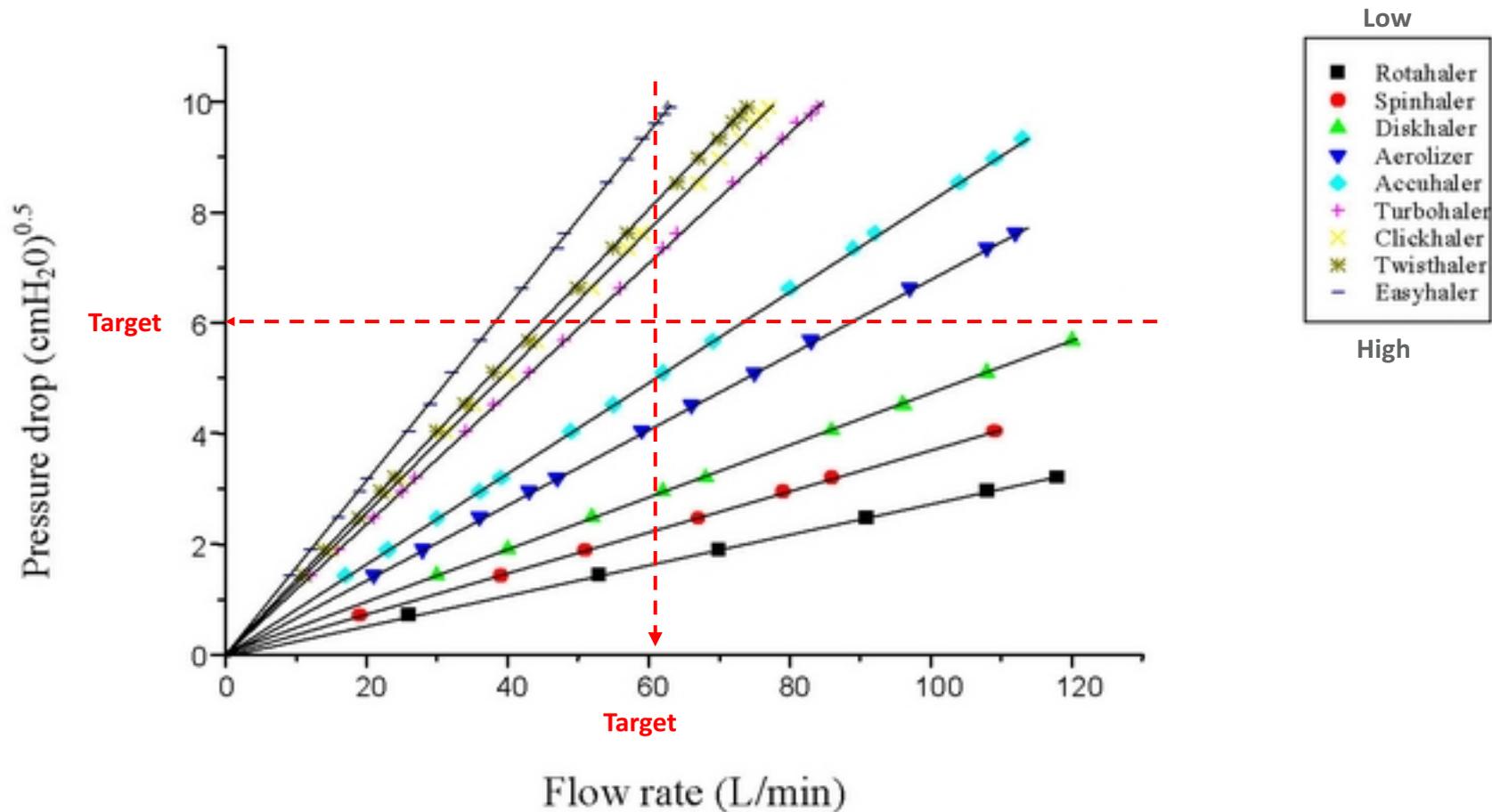


Twisthaler

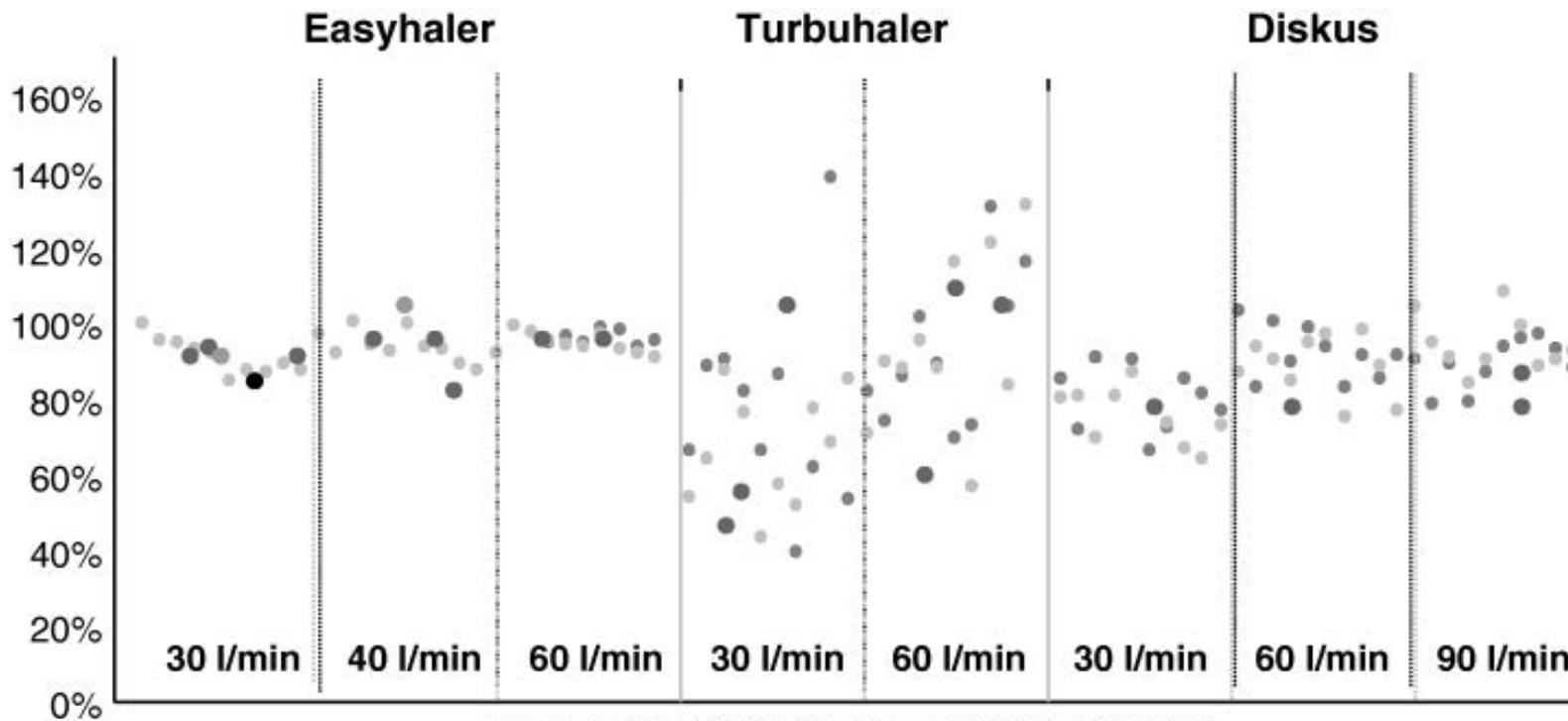


Increasing Resistance

# Device Resistance



# Output Is Dependent On Air Flow Rate?

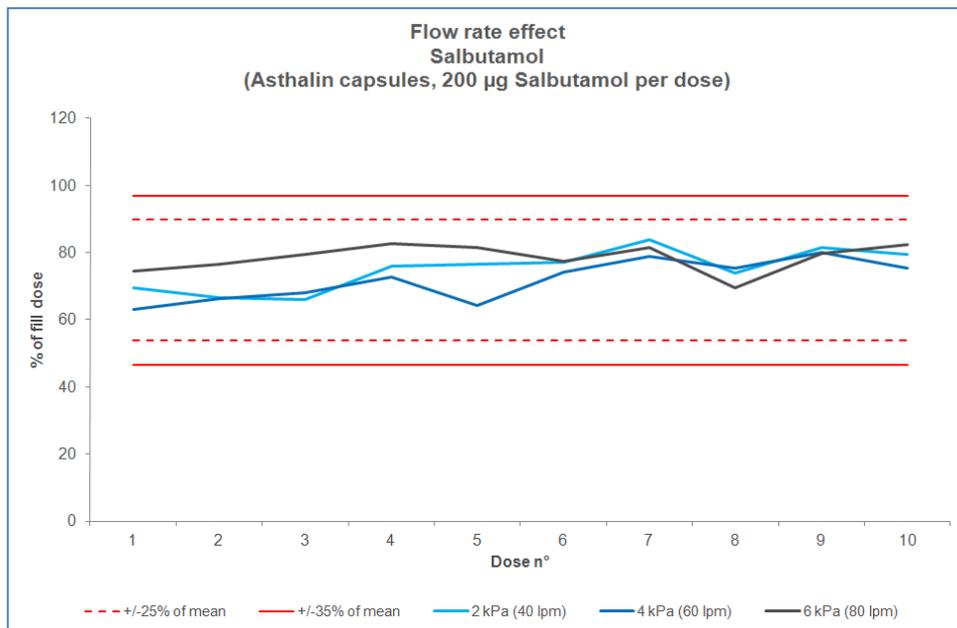


Palander et al Clin Drug Invest 2000;20:25-33

Chrystyn, H. Intl. J. Clin. Pract, June 2007, **61**, 6, 1022-1036.

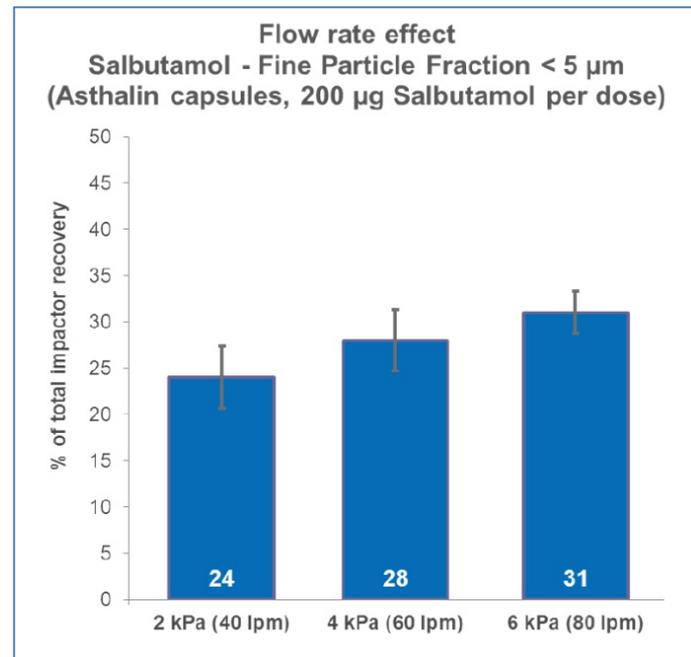
# Effect of Flow Rate

- **Flow rate:** effect on Delivered Dose



Flow Rate has minimal impact on delivered dose values.

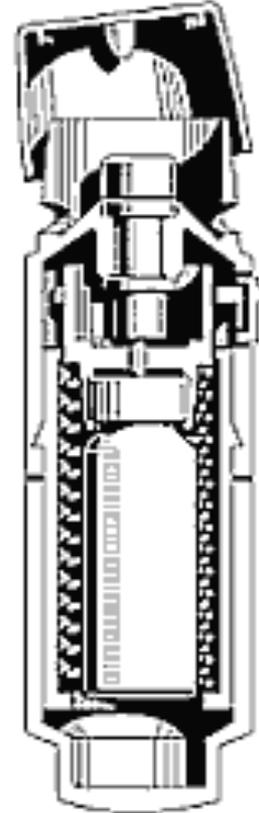
- **Flow rate:** effect on Fine Particle Fraction (FPF)



FPF values increase with increased flow rate.

# Single Breath Atomizers

- “Soft Mist Inhalers”
- Solution based
- Drug delivered in a single inhalation
- Example: Respimat
  - Reservoir holds up to 200 doses in a hand-held unit
  - Drug solution specific to device



Respimat  
(Mechanical break-up)

# Nebulizers

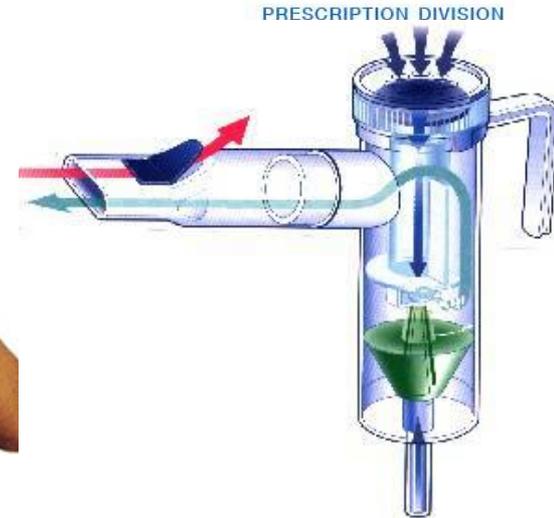
## ■ Inhalation Solutions and Suspensions

- Ampoules or vials marketed independent of device

## ■ Mechanisms

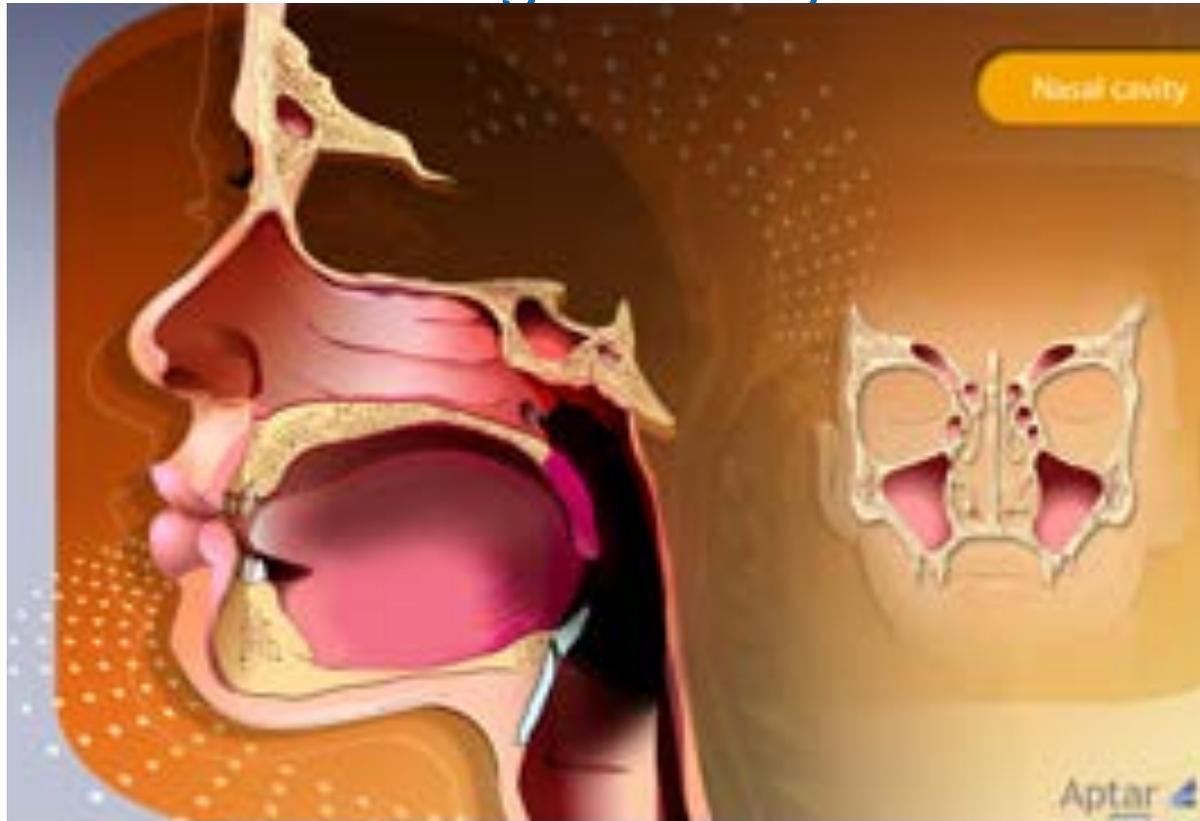
- Compressed air
- Ultrasonic
- Vibrating membrane

## ■ Device typically approved by 510(k) FDA application



MicroAir by  
Omron

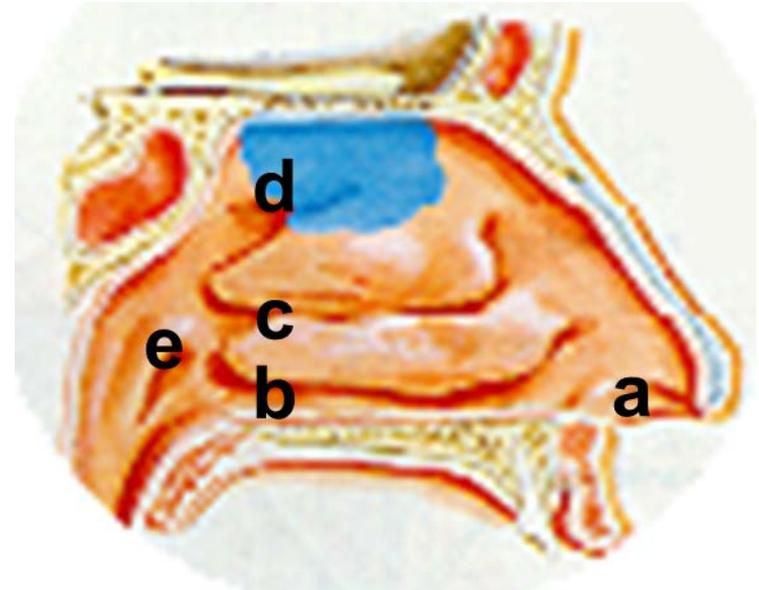
# Rationale for Nasal Drug Delivery



- Large surface area
- Highly vascularized
- High permeability limits effect of high enzymatic activity
- Enables immunization (NALT-nasal associated lymphoid tissue)
- Traps particles as a defense mechanism

## Targeting the Nose

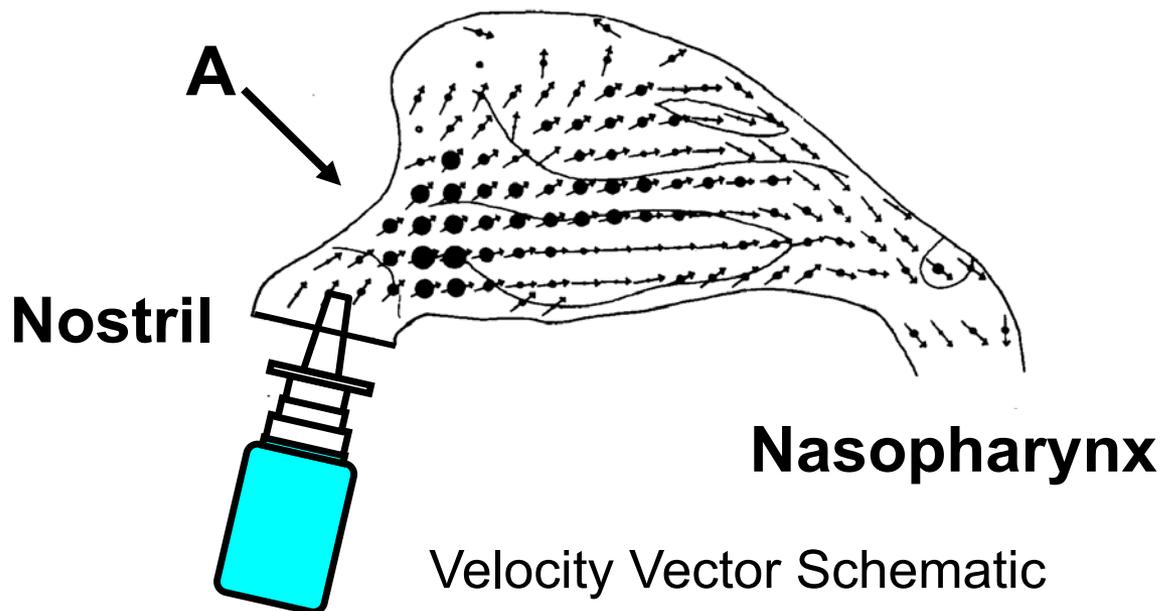
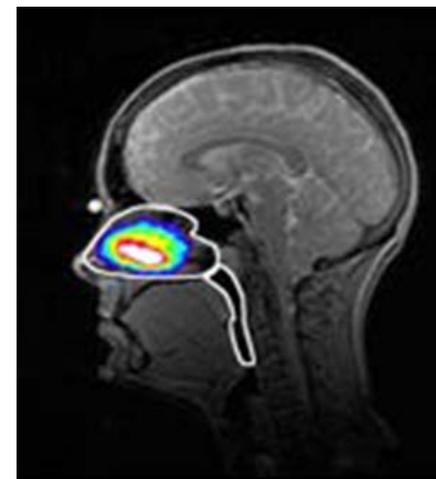
- Local Indications
  - Allergic rhinitis
  - Sinusitis
  - Polyps
- Systemic Indications
  - Pain
  - Migraine
  - Osteoporosis
- Immunization
  - FluMist
  - H1N1



Side View of Nasal Cavity:  
Nostril (a), Turbinates (b-d),  
Olfactory region (blue area),  
Nasopharynx (e)

## Deposition Mechanisms

- Impaction (primary factor)
  - Sedimentation
  - Diffusion (related to olfaction)
- 
- Droplet size and velocity of droplets key factors



# Intranasal Formulations

## ■ ■ Solutions

- Buffered
- Isotonic

## ■ ■ Suspensions

- Polymers

## ■ ■ Gels

## ■ ■ Powders

## ■ ■ HFA Nasal Aerosols

<b>Product</b>	<b>Reported pH</b>
Beconase	4.5 - 7.0
Flonase	5.0 - 7.0
Nasacort	4.5 - 6.0
Nicotrol NS	7.0
Desmopressin	3.5 – 6.0

Product	Viscosity Increasing Agents				
	CMC	MCC	HPMC	GYL	MC
Beconase AQ, Nasacort AQ, Rhinocort Aqua, Flonase	X	X			
Astelin Nasal Spray			X		
Nasonex	X	X		X	
Nascobal Nasal Gel				X	X
Zicam Nasal Gel				X	

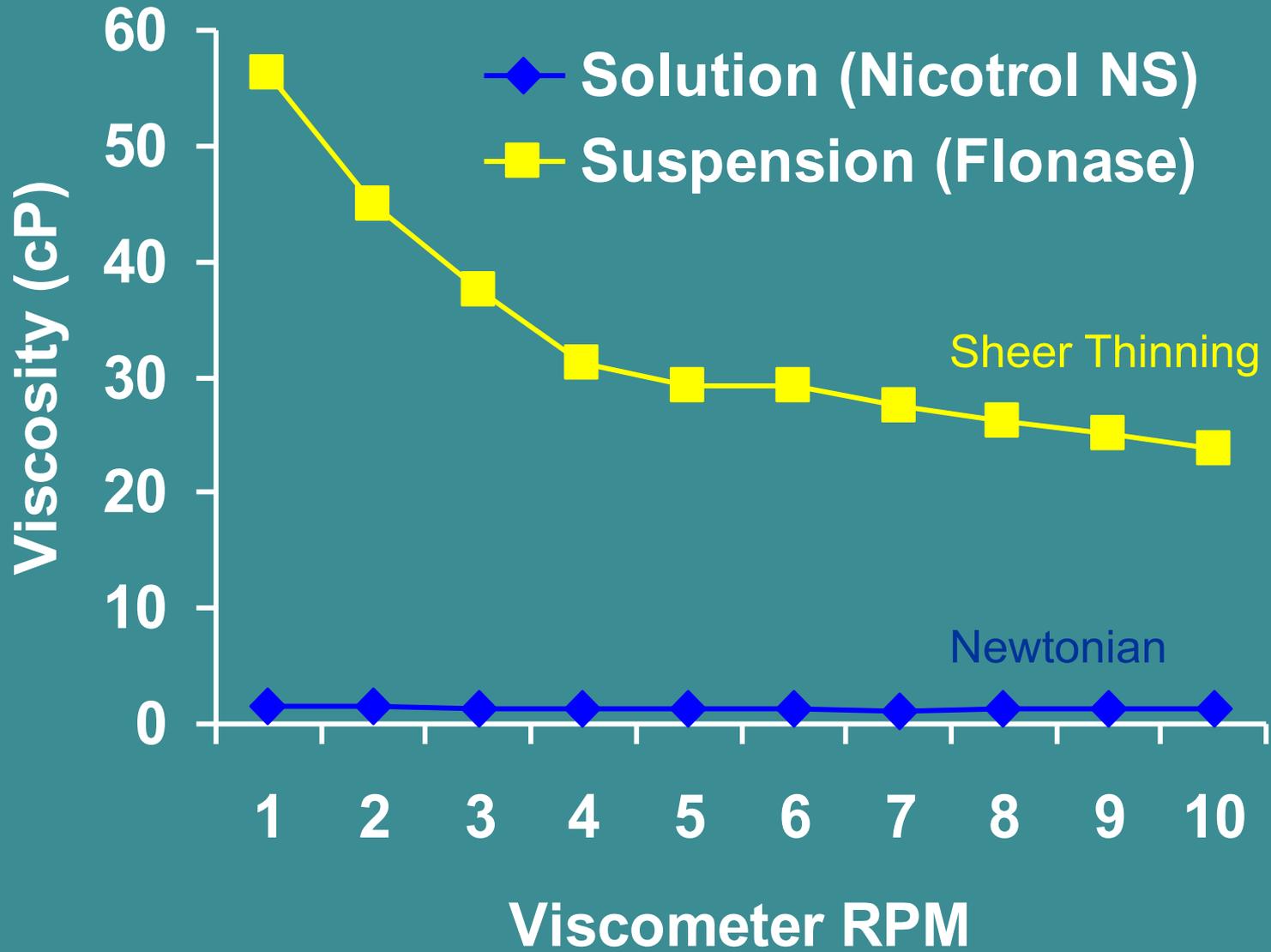
CMC = Carboxymethyl cellulose

MCC = Microcrystalline cellulose

HPMC = Hydroxypropylmethyl cellulose

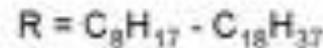
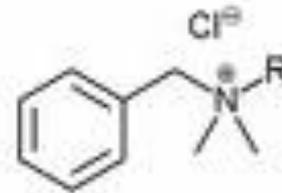
Gly = Glycerin

MC = Methyl cellulose



## Preservatives

- Benzalkonium Chloride (BKC), EDTA, phenylethylalcohol, potassium sorbate, benzyl alcohol



### ■ BKC

- Possible changes to ciliary beat frequency, ciliary morphology, mucociliary clearance, epithelial thinning and/or destruction
- Marple, et. al. conclude safe and well tolerated for both long- and short-term clinical use
- FDA still approving nasal spray products with BKC
- People still ask if BKC is safe → popularity of preservative free systems

# Formulation Effects

## ▣▣ Viscosity

- ▣ Direct correlation to droplet size
- ▣ Inverse correlation to plume geometry

## ▣▣ Surface tension

- ▣ Affects droplet size

## ▣▣ Thixotropic suspensions

- ▣ Extent of shaking affects viscosity

## ▣▣ What does this mean for Bioequivalence (Reference = Generic)?



# Nasal Delivery Platforms

- Multi-dose Metered Spray
- Unit Dose Spray
- Bi-Dose Spray
- Pressurized Aerosol
- Gels

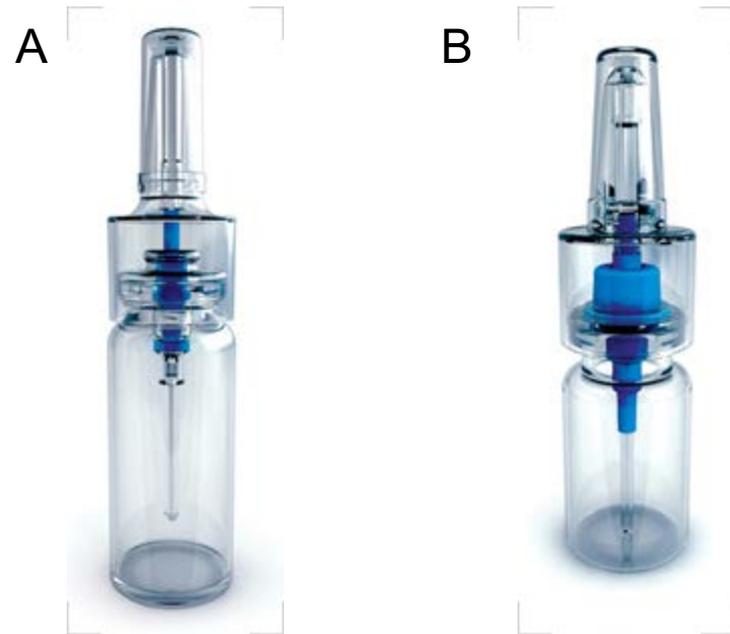
(US Market)



## Mechanical Nasal Sprays

### Multi-dose

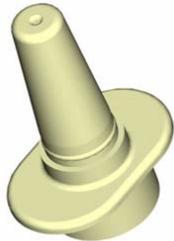
- Up to 240 doses
- Mechanical metering by volume
- 50 to 100 ul per actuation
- Glass or plastic containers
- Require priming / Assembly
- Solutions or suspensions
- Preservative free formulations popular for OTC applications and some countries



Multi-dose Systems for A) Preserved & B) Preservative Free Nasal Sprays. Device images courtesy of Aptar Pharma.

# Multidose Pumps & Actuators

## ■ Actuator:

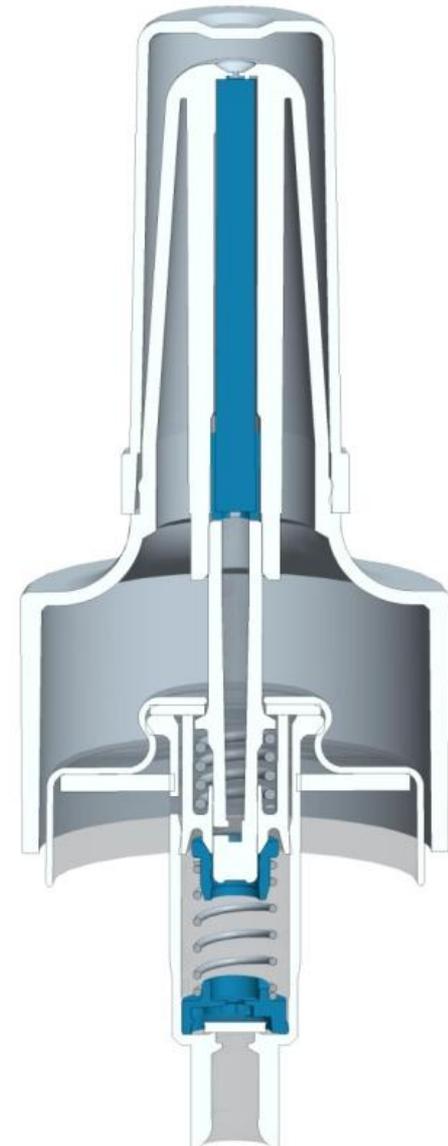


- Direct the spray into the nasal cavity
- Spray/atomize the liquid
- Essential to ensure the Droplet size Distribution (DSD) & Spray Pattern (SP)

## ■ Pump function:



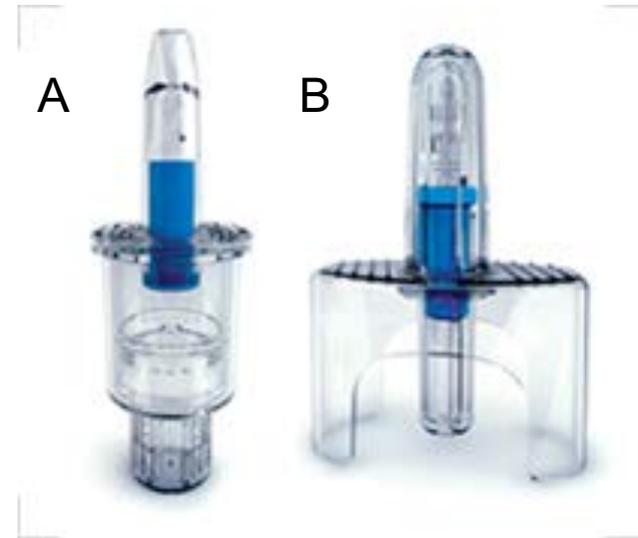
- Meter the dose to be delivered in the nasal cavity of the patient
- Seal the container



## Mechanical Nasal Sprays

### Unit Dose

- Single spray (on market, examples Imitrex or FluMist)
- Bi-dose (two doses)
- Mechanical metering by volume
- No priming or repriming
- Not for suspensions

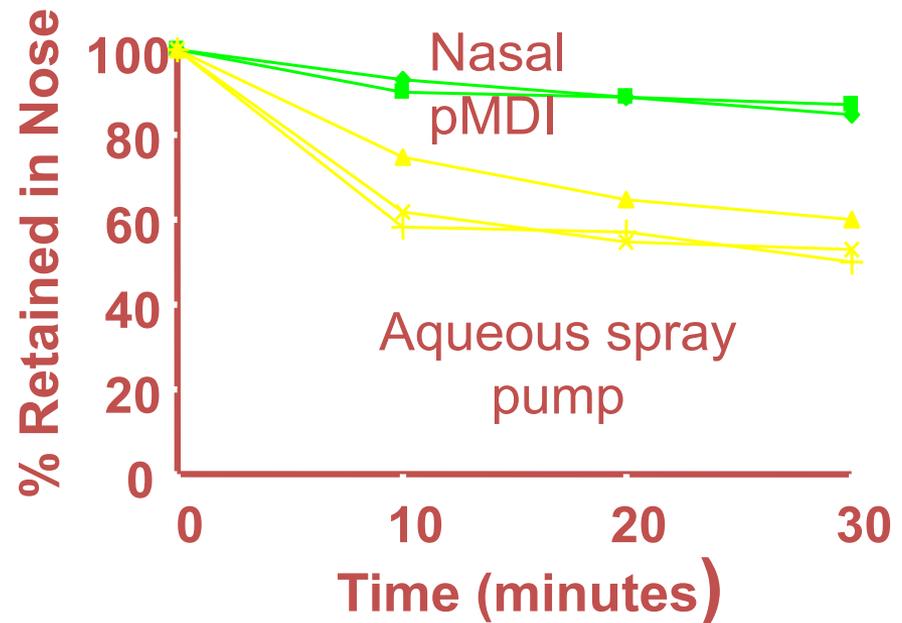


Unit Dose Systems for A) Powders & B) Aqueous Sprays



## Pressurized Nasal Sprays

- Utilize HFA-134a propellants
- Use in patients with runny nose
- Slower clearance
- Deposition primarily in anterior regions of nose (front of nose)



Redrawn from Newman, S.P. et al., *J. Laryngol. Otol.*, 1987

## Nasal Powders-In Development

### ▣▣ Applications

- ▣ Capable of delivering large doses
- ▣ Good for drugs with limited solubility or aqueous instability
- ▣ Platform for vaccines

### ▣▣ Example

- ▣ Sumatriptan powder
  - Phase III clinical trials
- ▣ Locemia



Opt-Powder Device by  
Optinose