# Principles of Pulmonary Drug Delivery

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Christine A. Sorkness, Pharm.D.

*Professor of Pharmacy & Medicine (CHS)*

*UW School of Pharmacy*

# Learning Objectives

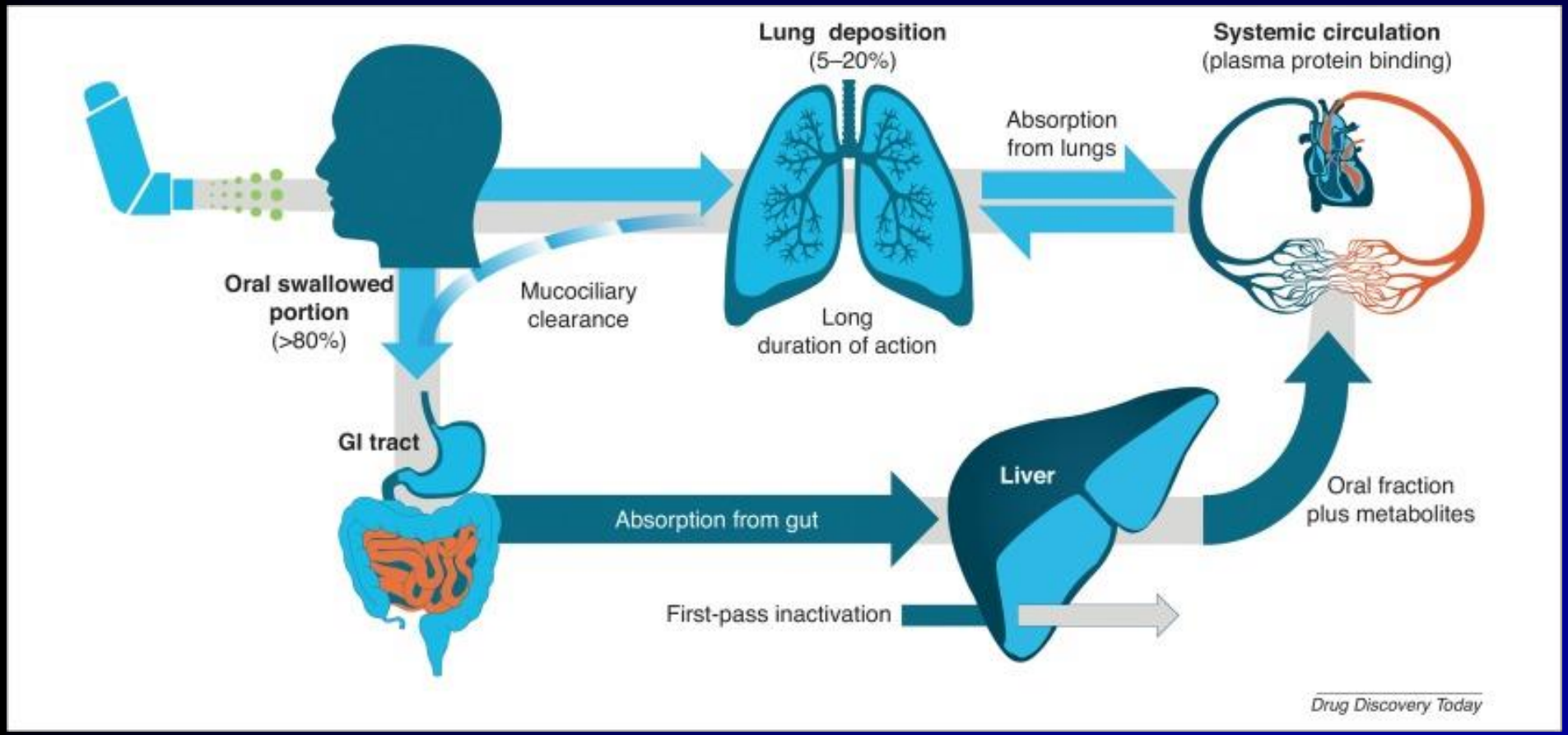
As a result of completing this lecture, the participant should be able to:

1. Discuss device-related and patient-related issues influencing pulmonary drug delivery.
2. Describe the advantages and disadvantages of spacers & valved holding chambers with metered-dose inhalers (MDIs).
3. Outline the major characteristics of marketed drug-powdered inhalers (DPIs).
4. Discuss issues related to nebulizer systems.
5. Outline drug classes administered by nebulizer systems

# General Issues: The Lung as a Target Organ

- Anatomy of the lung/Airway geometry
- Cough reflex
- Mucous production
- Ciliary clearance
- Epithelial lining as a barrier
- Pulmonary blood flow

# Disposition of Inhaled Glucocorticoids



# Patient-Related Issues: Pulmonary Drug Delivery

- Age
- Gender
- Breathing pattern
- Posture
- Extent/severity of pulmonary disease
- Ability to use the selected drug delivery devices
- Concurrent mechanical ventilation

# Influences on Particle Deposition in the Airways

- Particle/droplet properties
- Presence of other substances
  - Diluents (lactose in dry powder devices)
  - Surfactants (oleic acid, lecithin)
  - Propellants (HFA*)
- Breathing conditions
- Respiratory dimensions and geometry
- Drug delivery device (MDI vs DPI vs soft mist)

*HFA = hydrofluoroalkane

# Inhaled Particles are Deposited by 3 Basic Mechanisms, Dependent on Particle Size

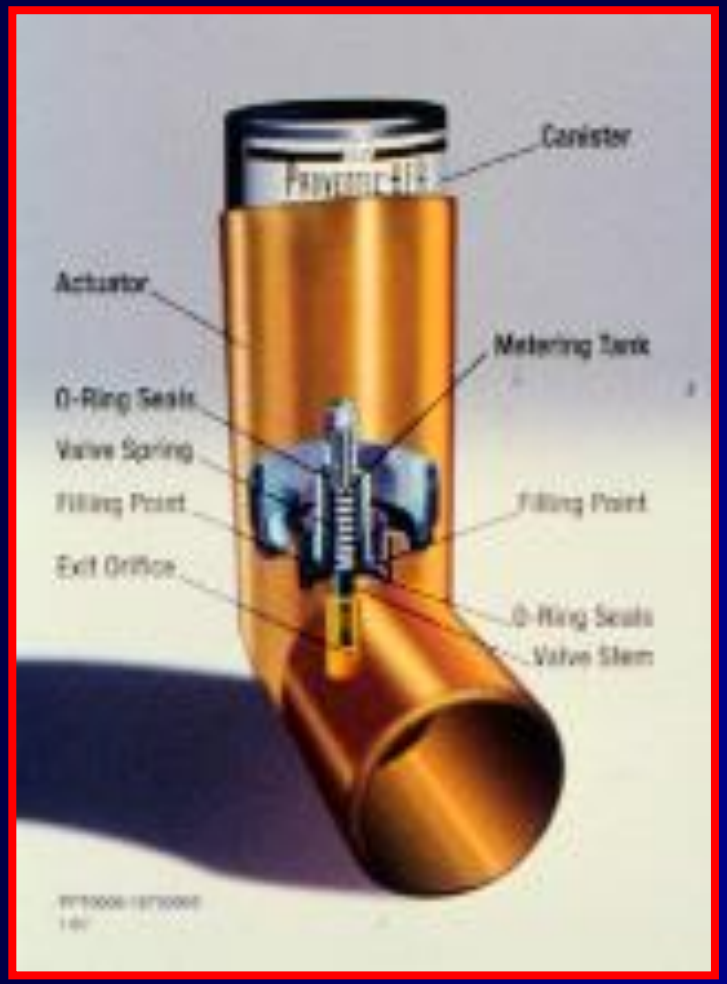
- Inertial impaction is the principal mechanism of large particle deposition and primarily occurs in the posterior pharynx (high airflow area) and upper airway
- Gravity sedimentation for particles 0.1-10 μm
- Brownian movement for particles < 0.1 μm, resulting in deposition in bronchioles and alveoli

Ideal mass median aerodynamic diameter (MMD) = 2.8-4.3 μm

# Characteristics of an Ideal Respiratory Inhalation Delivery System

- Reproducible dose delivery to lungs across wide range of inspiratory flows
- Small particle size (2-5 microns)
- Easy to use
- Small size, easy to carry
- Multidose capability
- Cost-effective
- Built-in dose counter
- Supports rapid onset of drug action

# Valve Illustration
# Proventil® HFA
## (Albuterol Sulfate Inhalation Aerosol)



# Albuterol HFA MDIs

| Brand* | Manufacturer | Inhaler Size | Comments |
|---|---|---|---|
| **Multiple generic manufacturers now available**<br>Check package insert for priming and other information | | | |
| Pro Air HFA | Teva | 200 puffs<br>(90 mcg/puff) | Prime after 2 weeks;<br>built in dose-counter; |
| Proventil HFA | Merck | 200 puffs<br>(90 mcg/puff) | Prime after 2 weeks;<br>Built in dose-counter |
| Ventolin HFA | GSK | 200 puffs<br>(90 mcg/puff) | Prime after 2 weeks;<br>discard 12 months after removing from pouch; built in dose-counter |

# Other Pulmonary Drugs Available as HFA MDIs

- Xopenex HFA® MDI (levalbuterol) - SABA
- Atrovent HFA® MDI (ipratropuim) - SAMA
- Asmanex HFA® MDI (mometasone) - ICS
- Alvesco HFA® MDI (ciclesonide) - ICS
- Flovent HFA® MDI (fluticasone) - ICS
- Advair HFA® MDI (fluticasone/salmeterol) – ICS/LAMA
- Symbicort HFA® MDI (budesonide/formoterol) - ICS/LAMA
- Dulera HFA® MDI (mometasone/formoterol) - ICS/LAMA
- Bevespi Aerosphere® MDI (glycopyrrolate / formoterol)
  – LAMA/LABA
- Breztri Aerosphere ® MDI (budesonide/glycopyrrolate/ formoterol) – ICS/LAMA/LABA

* SABA = short acting beta-agonist, SAMA = short acting muscarinic agent, LABA = long acting beta-agonist, LAMA = long acting muscarinic agent, ICS = inhaled corticosteroid

# 2005 Wisconsin Act 398 (enacted 5/10/2006) – The Inhaler Law

- Allows students with asthma to carry and use their MDIs and DPIs at all times on school property
- Applies to private, parochial, and public schools
- Requires students to provide the school with written permission from their parents and physicians
- Releases the school district, board, and employee from any form of liability due to complying with the law
- The school cannot enforce a policy that contradicts the law

http://www.lungwi.org/wi/publicpolicy/inhaler.asp

# MDI Techniques

Closed-mouth: Hold inhaler in mouth.

*Open-mouth: Hold inhaler 1 to 2 inches away.

Frequent Reinstruction is Necessary

*generally not recommended

*NAEP Report,* NHLBI, 1991: American Academy of Family Physicians

# MDIs with Spacers & Valved Holding Chambers (VHC)

- Addition of a spacer reduces the velocity and size of the aerosol particles
- Obviates need for accurate coordination between actuation and inspiration
- Large particles impact in spacer or sediment due to ↓ velocity
- Propellant enveloping the drug particles evaporates
- Reduces oropharyngeal drug deposition – important with ICS
- Reduces airborne aerosolization
- Many available products on the market

# Factors Influencing Output from a MDI With a Spacer & Valved Holding Chamber (VHC)

- Valve control of the inlet and outlet
- Dead space between the inlet and outlet
- Material of the spacer (plastic, antistatic materials)
- Volume of the spacer
- Presence of a mask with the spacer

# Recommendations on Spacers & VHCs

- Actuate only once into spacer/VHC per inhalation
- Use of a face mask may ↓ lung delivery by 50%
- If face mask is used, it should have a tight fit and allow 3-5 inhalations per actuation
- Rinse plastic VHCs once a month with low concentration of liquid dishwashing detergent (1:5,000 or 1-2 drops per cup of water) and let drip dry
- Static-free VHCs widely available
- Costs vary (↑ with face mask)

# Asthmanefrin® 2.25% Inhalation Solution

- OTC alternative to Primatene® Mist CFC Inhaler (9/12)
- Racepinephrine 11.25mg / 0.5 ml (equivalent to 1% epinephrine)
- Used in a handheld electronic atomizer (EZ Breathe Atomizer)
- Adults and children ≥ 4 years
  - 1-3 inhalations not more than every 3 hours
  - Do not use more than 12 inhalations / 24 hours
  - Use by children should be supervised by an adult
  - Starter kit = 1 atomizer + 10 vials (refills of 30 vials)
- Much less potent than albuterol; may be less effective in treating acute bronchospasm; shorter duration of action
- Pharmacy costs: $26.94/30 vials

www.nephronpharm.com
www.asthmanefrin.com

# Primatene MIST Returns as OTC Asthma Inhaler

- Phased out in 2011 (Montreal Protocol banned CFC products); returned in 2019
- Primatene MIST delivers 0.125 mg epinephrine per spray with HFA propellant; 160 sprays per MDI
- Approved for temporary relief of mild symptoms of intermittent asthma in patients ≥ 12 years of age; max. 8 inhalations/24 hrs.
- Asthma/allergy groups expressed “deep concern” over FDA approval

http://www.Primatene.com/

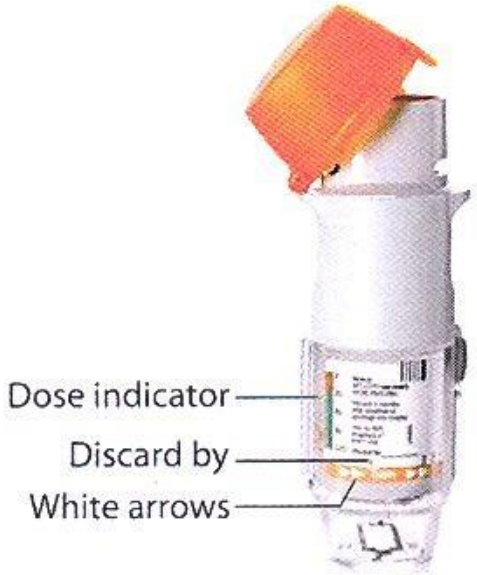
# Respimat Soft Mist Inhaler (SMI)

- Multidose, propellant-free, hand-held, liquid inhaler
- ↑ fraction of fine particles
- Mist exits inhaler more slowly and for a longer duration
- Combivent® (ipratropium/albuterol) – SAMA/SABA
- Spiriva® (tiotropium) - LAMA
- Stiolto® (tiotropium/olodaterol)- LAMA/LABA
- Striverdi® (olodaterol) - LABA

# The Combivent® Respimat® Inhaler

## Front View


## Back View




## Cartridge

# Dry Powder Inhalers (DPIs)

- Breath-actuated; requires minimal hand-lung coordination
- Powder dispersion into respirable particles dependent upon creation of turbulent flow (“flow-dependent”)
- Requires adequate inspiratory flow rate to dispense the powder
- Resistance of the DPI is the limiting factor in determining PIFR that can be drawn through
- Typical PIFRs:  30-120 L/min
- The higher the DPI resistance, the greater the delivery of powder to the lower resp. tract
- Potential effect of humidity on some DPIs

# Dry Powder Inhalers

| Dose Storage | DPI |
| --- | --- |
| Capsule | HandiHaler (Boehringer Ingelheim) |
| | Neohaler (Novartis) |
| | Podhaler (Novartis) |
| | Breezhaler (Novartis) |
| Reservoir | Flexhaler (Astra) |
| | Twisthaler (Schering) |
| | Pressair (Circassia) |
| Multi-Unit Dose Blister/tape | Diskus (Glaxo) |
| | Ellipta (Glaxo) |
| | Inhub (Mylan) |
| | Diskhaler (Glaxo) |

Relenza (zanamivir): influenza

# Breath-Actuated DPI

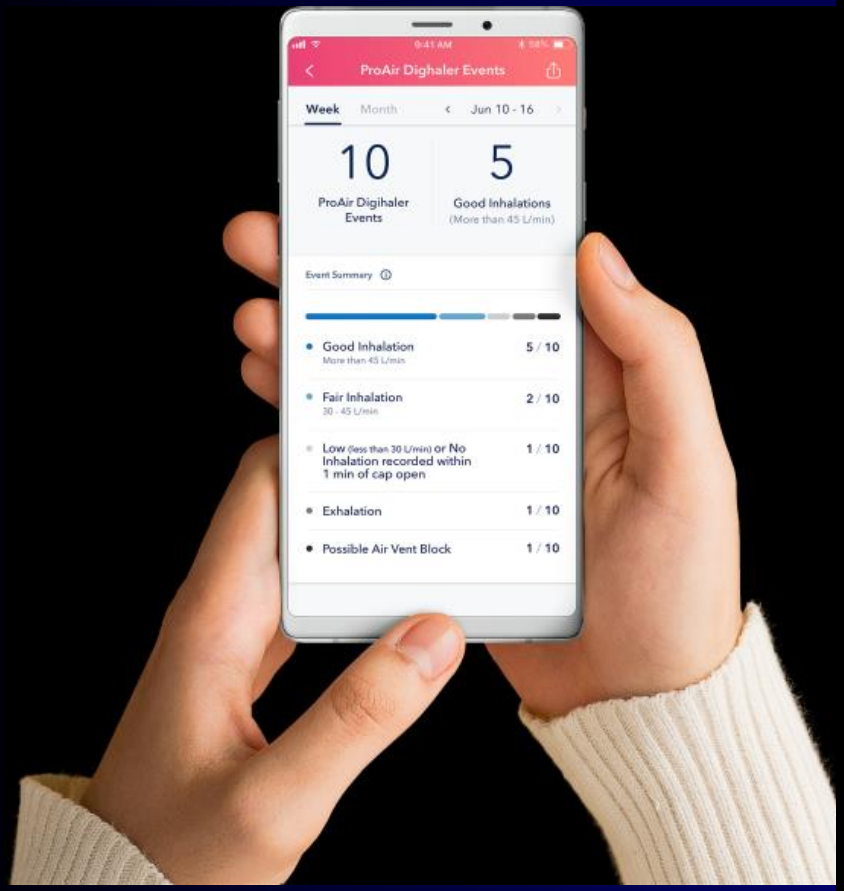
- RespiClick – Teva
  - ProAir (albuterol) – SABA
  - AirDuo (salmeterol/fluticasone) – LABA/ICS
- Redihaler – Teva
  - Qvar (mometasone) – ICS
- Pressair – Circassia
  - Tudorza (aclidinium) – LAMA
  - Duaklir (aclidinium/formoterol) – LAMA/LABA
- Decreased requirement for hand-breath coordination
- Includes dose counter - Discard at “0” or according to other specific instructions
- Does not require priming
- Do not use with a spacer or volume holding chamber

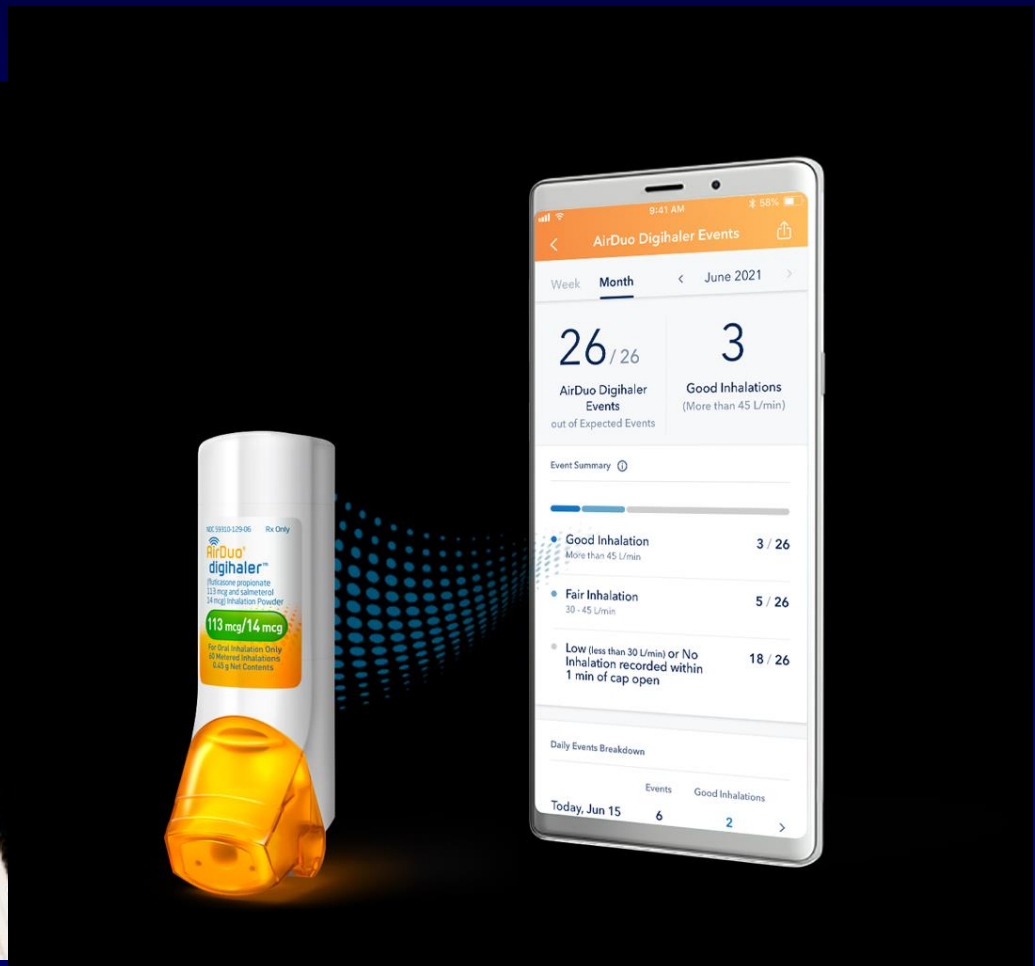
# Digihaler ® - Teva

- ProAir ® (Albuterol - 90mcg base) - SABA
- AirDuo ® (Fluticasone/Salmeterol - 113mcg/14mcg) – ICS/LABA
- ArmonAir ® (Fluticasone proprionate - 113mcg) - ICS
- Built in electronic module which detects, records, & stores inhaler events to mobile App; includes peak inspiratory flow rate (L/min)

http://www.Digihaler.com/#digihaler-technology

# Digihaler ® - Teva




Digihaler.com

# Aerosol Delivery Devices

| Device | Optimal Inhalation Techniques |
| --- | --- |
| MDI | Slow (30 L/min or 3-5 sec) and deep inhalation, then 10 sec breathhold |
| DPI | Rapid (≥ 60 L/min or 1-2 sec) deep inhalation<br>Min. effective inspiratory flow is device dependent |

# Patient Errors in Inhaler Use

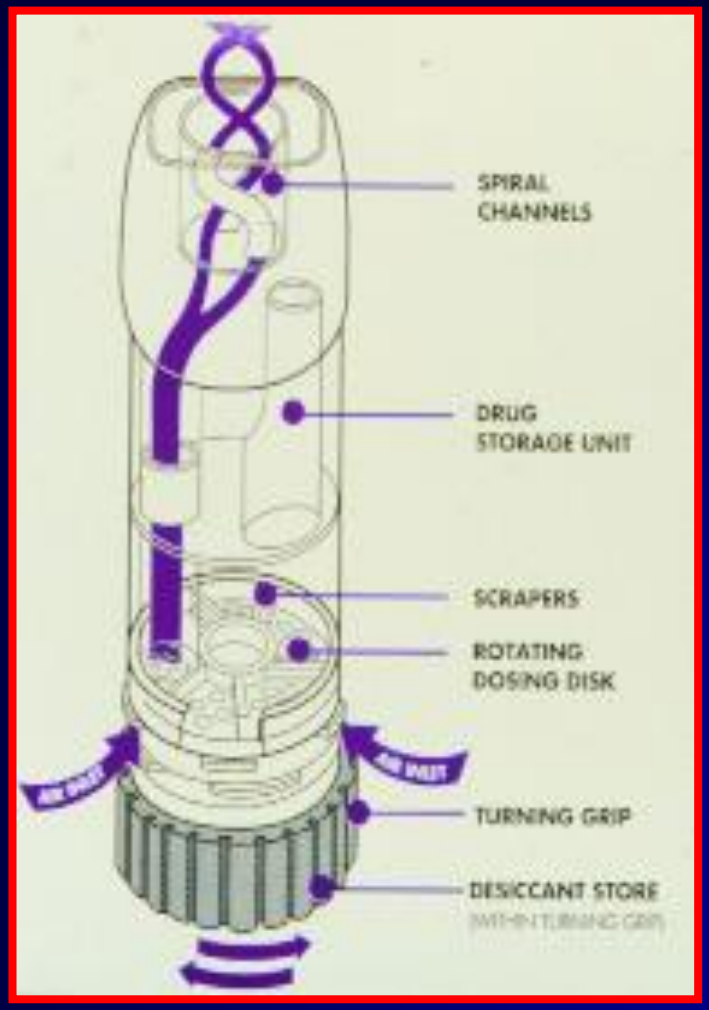
- Most frequent MDI errors:
  - Coordination
  - Speed and/or depth of inspiration
  - No post inhalation breath-hold
- Most frequent DPI errors:
  - Incorrect preparation
  - No full expiration before inhalation
  - No post-inhalation breath-hold

Sanchis J et al. Chest 2016; 150(2): 394-406

# Flexhaler® (Astra)

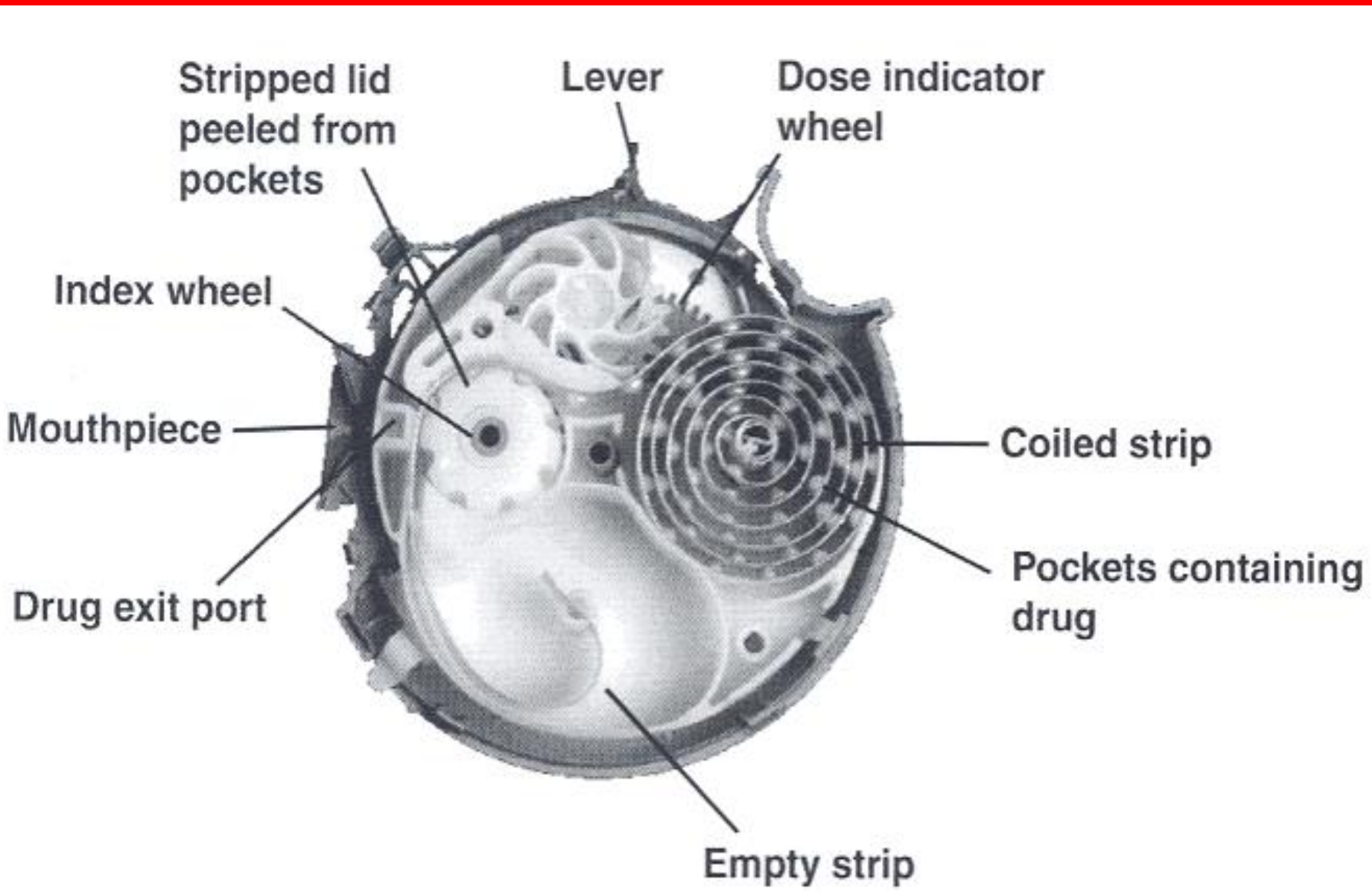
- Dry powder breath-actuated device
- Optimal inspiratory flow rate of 60 L/min (high resistance device)
- Sensitive to ambient conditions, esp. moisture; contains lactose
- Dose indicator starts at 60 or 120 depending on strength and counts down to 0.
- Requires priming prior to initial use.
- Pulmicort (budesonide 90 mcg,180 mcg) - ICS
- Rinse with water after each dose; spit out

# Pulmicort Flexhaler



# Diskus Device (Glaxo)

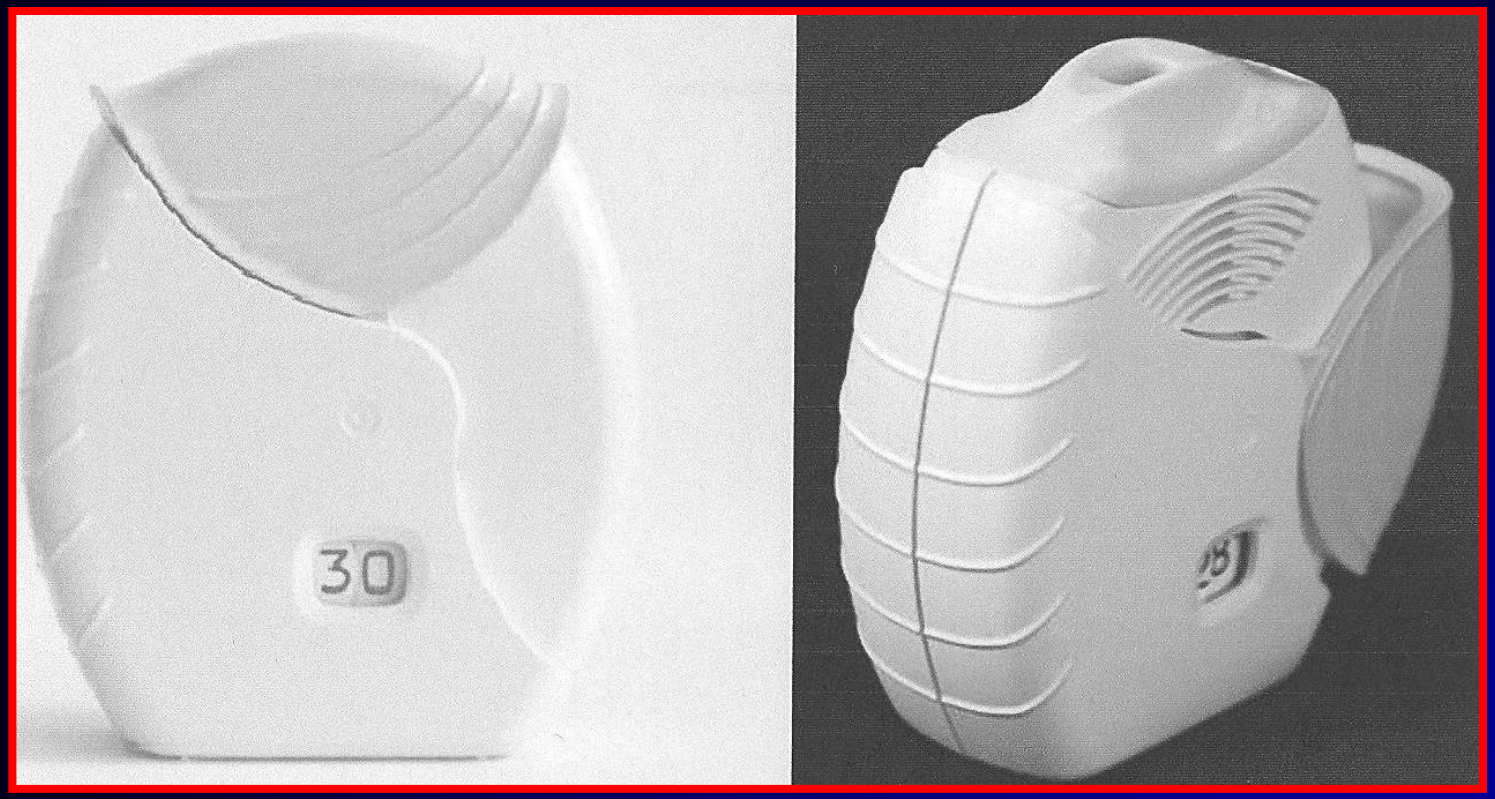
- DPI device of double-foil blister strips (60 doses per Diskus)
- Drug delivery dependent on inspiratory flow (requires 30-60 L/min)
- Indicator tells how many doses are left (numbers turn red when 5 doses left)
- Do not breathe into, nor wash, the device
- Activate and use Diskus® in a level, horizontal position
- Open, Click, Inhale, Close
- Delivers Serevent®, Flovent®, and Advair®


Stripped lid peeled from pockets
Lever
Dose indicator wheel
Index wheel
Mouthpiece
Coiled strip
Drug exit port
Pockets containing drug
Empty strip

# Ellipta Device (Glaxo)

- A multidose breath-activated DPI with moderate airflow resistance
- Contains a number of predispensed double-foil sealed blisters as strips (1 or 2 strips each containing 1 or 2 medications)
- Large dose counter; red flag when 9 doses remain and “0” when no further blisters remain
- Second flag to replace
- Drug delivery dependent on inspiratory flow (tested in asthma and COPD)
- Delivers Breo® (fluticasone/vilanterol), Incruse® (umeclidinium), Anoro® (umeclidinium and vilanterol), Arnuity ® (fluticasone furoate), and Trelegy ® (fluticasone furoate, umeclidinum, and vilanterol)

# Ellipta Device with Mouthpiece Closed and Open



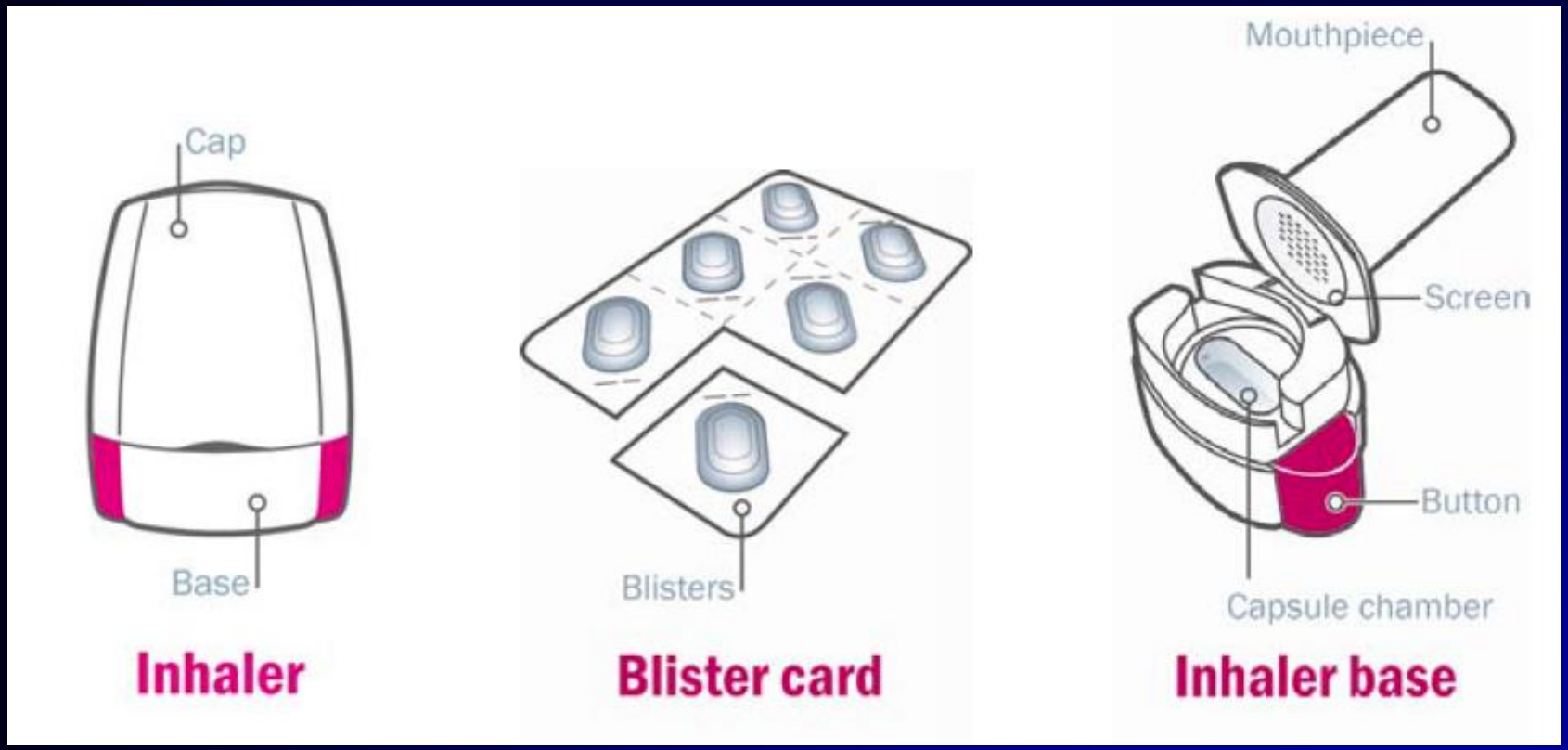
# HandiHaler®
# (Boeringer Ingelheim)

- Dry powder inhalation device for delivery of Spiriva®
- Each Spiriva® capsule contains 18 mcg tiotropium and lactose monohydrate as the carrier; packaged in a blister card
- Avoid contact of powder with the eyes
- Components of the HandiHaler; dust cap, mouthpiece, base, piercing button, center chamber
- "Breathe in slowly and deeply, at a rate **sufficient to hear the capsule vibrate, then hold breath"**
- Repeat steps to get full dose

# Twisthaler® (Schering Corp.)


- Dry powder cap-activated inhalation-driven device for delivery of Asmanax®
- Each inhalation delivers 110 or 220 mcg of mometasone
- Two main steps of administration
- Dose indicator window on the pink base, which “counts down” doses
- When the numbers in the dosing window read “01”, this will be the last dose in the Twisthaler®
- “Take in a fast, deep breath and hold your breath for 10 seconds”
- Rinse mouth with water after use; spit out

# Arcapta Neohaler: Indacaterol Inhalation Powder



# TOBI Podhaler comes in a 28-day multipack that has everything you need for 1 treatment cycle[1,*]

## What's inside a 28-day pack?


### 1 4 WEEKLY PACKS, EACH PACK CONTAINING 7 BLISTER CARDS

*A total of 28 blister cards*

- Each blister card contains 8 capsules
- Take 4 capsules for inhalation in the morning and 4 capsules for inhalation in the evening
- A total of 112 mg per dose

### 2 4 DISPOSABLE PODHALER DEVICES

*plus 1 backup Podhaler device*

- When you start a new weekly (7-day) pack of capsules, use a new inhaler device

### 3 4 INHALER STORAGE CASES

*plus 1 backup*

- When you start a new weekly (7-day) pack of capsules, use a new inhaler storage case

# Types of Nebulizers

**Jet:** Consists of a nebulising chamber in which an aerosol is generated with a flow of gas provided either by an electrical compressor or compressed gas (air or oxygen); standard and breath enhanced systems

**Ultrasonic:** Self-contained electrical devices in which an aerosol is generated by vibrating fluid placed within them

**Vibrating mesh or plate with several apertures:** Faster, more expensive

# Nebulizer Definitions

**Aerosol output:** mass per minute of particles in aerosol form produced by the nebulizer

**Respirable particles:** particles < 5 μm diameter

**Respirable fraction:** mass of respirable particles expressed as % aerosol output

**Respirable output:** mass of respirable particles produced per minute (aerosol output x resp. fraction)

# Technical Factors Influencing Output from a Jet Nebulizer

- Nebulizer design
- Volume fill (usual 4-6 ml)
- Dynamic airflow through the nebulizer
- Environmental temperature
- Humidity
- Inhalation flow through the nebulizer
- Continuous or intermittent nebulization
- Solution or suspension of drug
- Viscosity, density, and surface tension of the drug

# Patient-Related Factors Confounding Nebulizer Drug Delivery

- Interface between child and face mask
- Nasal breathing
- Low tidal volume, flow, and pressure
- Entrainment
- Irregular breathing
- Poor adherence

# Characteristics of an Ideal Nebulizing System

- High output
- Short nebulization time
- High % of respirable droplets
- Reproducible performance
- Adaptable power source
- Easy to assemble and clean
- Quiet and attractive
- Portable/small
- Under control of patient

# Nebulized Medications: Obstructive Pulmonary Diseases

- albuterol – SABA
- cromolyn – non-steroid anti-inflammatory
- ipratropium bromide – SAMA
- albuterol & ipratropium (DuoNeb®) – SABA & SAMA
- glycopyrrolate (Lonhala Magnair®) – LAMA
- revefenacin (Yupelri®) - LAMA
- levalbuterol (Xopenex®) – SABA
- arformoterol (Brovana®) – LABA
- formoterol fumarate (Perforomist®) – LABA
- budesonide (Pulmicort Respules®) - CS

# Nebulized Medications: Cystic Fibrosis

- Aztreonam (Cayston®) – antibiotic
  - Altera Nebulizer System
- Dornase Alfa (Pulmozyme®) – mucolytic
  - Hudson T Updraft II or Marquest Acorn II with Pulmo-Aide Compressor
  - Pari LC Jet or Pari Baby with Pari Proneb Compressor
  - Durable Sidestream with MobilAire or Porta Neb
  - eRapid Nebulizer System
- Tobramycin (Tobi®, Bethkis®, Kitabis Pak®) – antibiotic for pseudomonas aeruginosa lung infections in CF
  - Pari LC Plus with Pulmo-Aide Compressor
- Hypertonic Saline (3%, 6%, or 7%), via jet nebulizer

# Other Nebulized Therapies

- Ribavirin (Virazole®) – antiviral (RSV) via SPAG-2 nebulizer
- Natural bovine surfactant (Alveofact®) –neonatal respiratory distress syndrome
- Pentamadine (Nebupent ®) – antifungal (for PCP related to HIV). Pneumocystis *carinii* pneumonia renamed as *jirovici*
  - Respirgard II nebulizer
- Iloprost (Ventavis®) – pulmonary hypertension
  - I-neb® Adaptive Aerosol Delivery System or Prodose AAD System
  - 2.5 – 5.0 mcg/dose with 6-9 doses per day while awake
- Treprostinil (Tyvaso®) – pulmonary hypertension
  - TD-100 (ultrasonic, pulsed delivery device)
  - TD-300 (user-friendly enhancements)
  - 4 separate, equally-spaced Tx sessions/day (≥ 4 hours apart)
- Levodopa inhalation powder (Inbrija®) - prn “off” episodes in Parkinson’s Disease

# Unlabeled Uses of Nebulized Medications

- Opioids (morphine, fentanyl) – terminally ill patients with dyspnea
- Lidocaine – anesthetic for bronchoscopy; asthma; difficult-to-control chronic cough
- Magnesium sulfate – acute asthma exacerbations
- Liposomal Amphotericin B – antifungal
- Colistin – anti-infective for P. aeruginosa

# Issues With Nebulized Drug Delivery

- Selection of nebulizer delivery system
- Intrapulmonary deposition rates
- Adverse reactions/patient tolerance
- Environmental contamination
- Bacterial contamination
- Administration with face mask or mouthpiece

# COVID-19 Guidelines for Health Care Facilities

- **During COVID-19, asthma treatment with and inhaler & spacer is preferred over nebulizer treatment whenever possible.** MDI's are not considered an aerosol generating treatment.
- **PFM** may elicit/trigger a cough
- If nebulizer treatment is utilized
  - Staff should wear appropriate PPE
    - Face mask, eye protection/face shield, gloves, gown
  - Maintain 6 feet of distance from patient if possible
  - Treatment should be in a designated, "For Aerosol Treatment Only", room and cleaned & disinfected after each treatment/test

CDC.gov

# COVID-19 Guidelines in the Home

- **If therapy cannot be administered via MDI and spacer, then**
- Always administer nebulizer treatments in the same room with closed door
- Maintain 6 feet of distance from patient if possible
- Appropriate PPE should be worn (face mask, eye protection/face shield, gloves)
- No additional family members should be present
- Maintain proper cleaning and disinfection procedures for nebulizer and equipment

CDC.gov

# General Age Requirements for Correct Use of Aerosol Delivery Device Types*

| Aerosol Delivery Method | Minimum Age |
|---|---|
| Small-volume nebulizer | ≤ 2 yr |
| MDI | ≥ 5 yr |
| MDI with spacer or VHC** | < 5 yr |
| MDI with endotracheal tube | Neonate |
| Breath-actuated MDI | ≥ 5 yr |
| DPI | ≥ 4 yr |

**Mouthpiece if ≥4; facemask if 0-3 yrs. Recs inconsistent; cognitive/intellectual abilities should be considered in all ages

*Based on EPR-3 recommendations, NHLBI

# Device Selection and Outcomes of Aerosol Therapy: Conclusions

- Devices used for delivery of bronchodilators and corticosteroids can be equally efficacious
- Selection of an aerosol delivery device for patients with asthma and COPD should be based on:
  - Device/drug availability
  - Clinical setting
  - Patient age and ability to use the device correctly
  - Device use with multiple medications
  - Cost and reimbursement
  - Drug administration time
  - Convenience in both outpatient & inpatient settings
  - Health provider and patient preference

Dolovich MB and Dhand R. Lancet 2011; 377:1032-45