Innovation in Inhaler Devices

울산의대 울산대학교병원
호흡기내과 나승원

What is innovation?

- New idea, creative thoughts, new imaginations
  in form of device or method

- The application of better solutions
  that meet new requirements

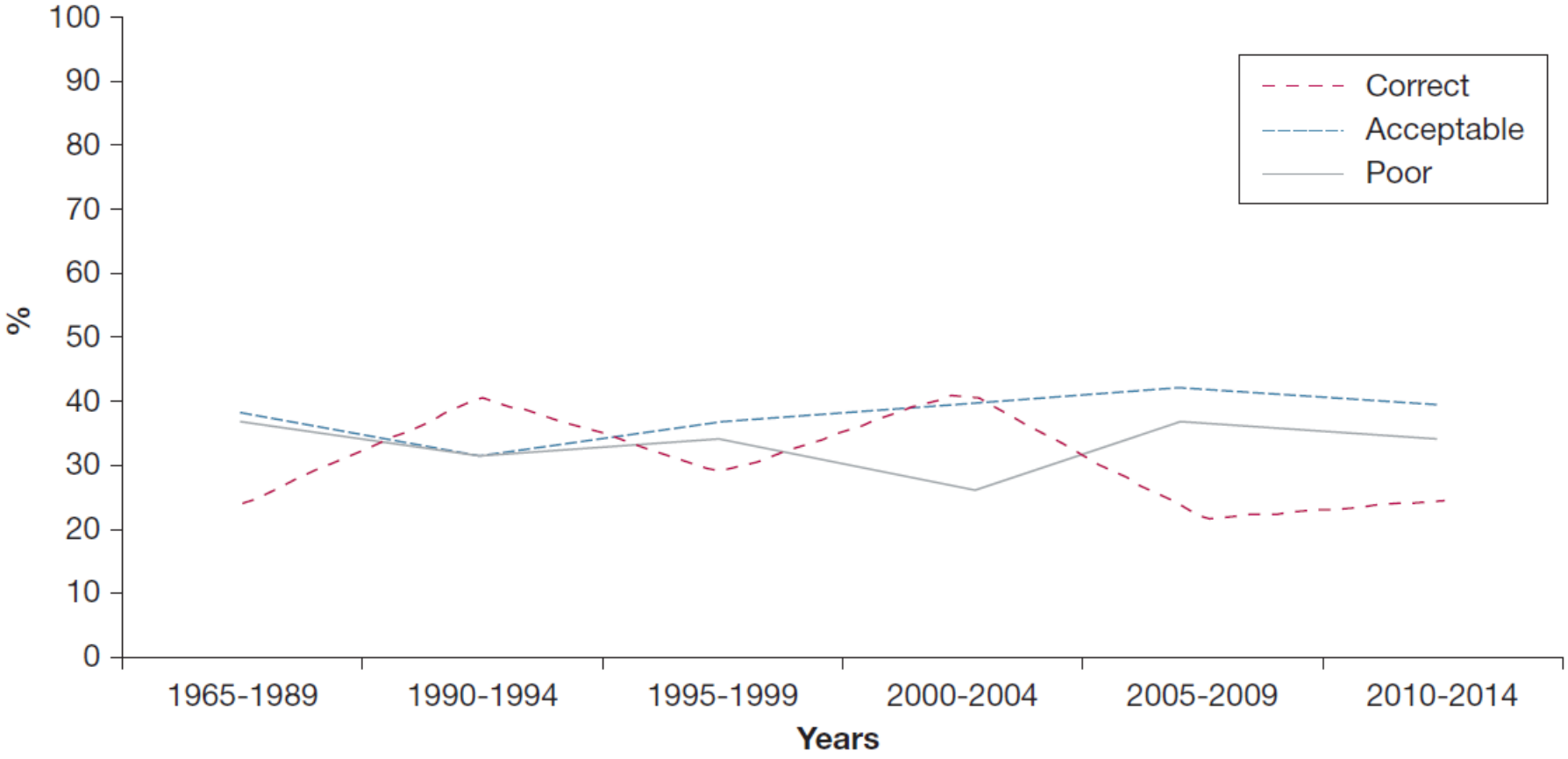
- The practical implementation of an invention
  to make a meaningful impact (not same as invention)

→ How can this definition be applied to inhaled therapy?

Wikipedia.

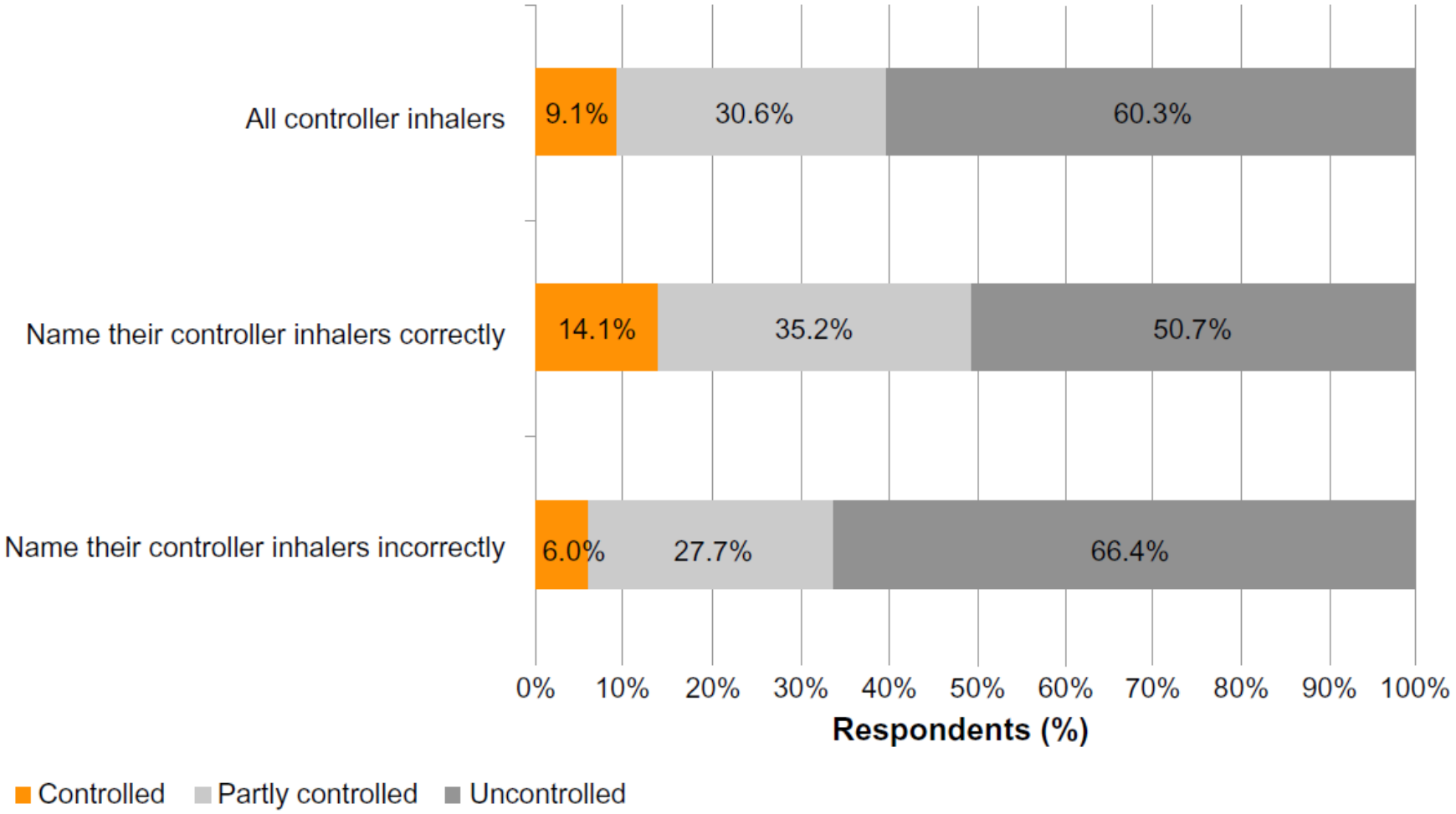
Has Patient Technique Improved Over Time?

Currently, there are over **230** **device & drug combinations** available



CHEST 2016;150(2):394-406

Knowledge of controller inhalers



Journal of Asthma and Allergy 2015:8;93–103

Innovation in inhaled therapy

1. Device engineering and design
2. Chemistry and formulations
3. Digital technology associated with Inhalers

- Healthcare professionals
  - **Want** see innovations that motivate their patients to achieve their goal of improving their health, through better adherence to treatment.
- Patients
  - **Want** devices that are easy to use and to see that their efforts are rewarded by improvements in their condition.

→ How this may translate to new devices?

Breathe 2018; 14: 216–224

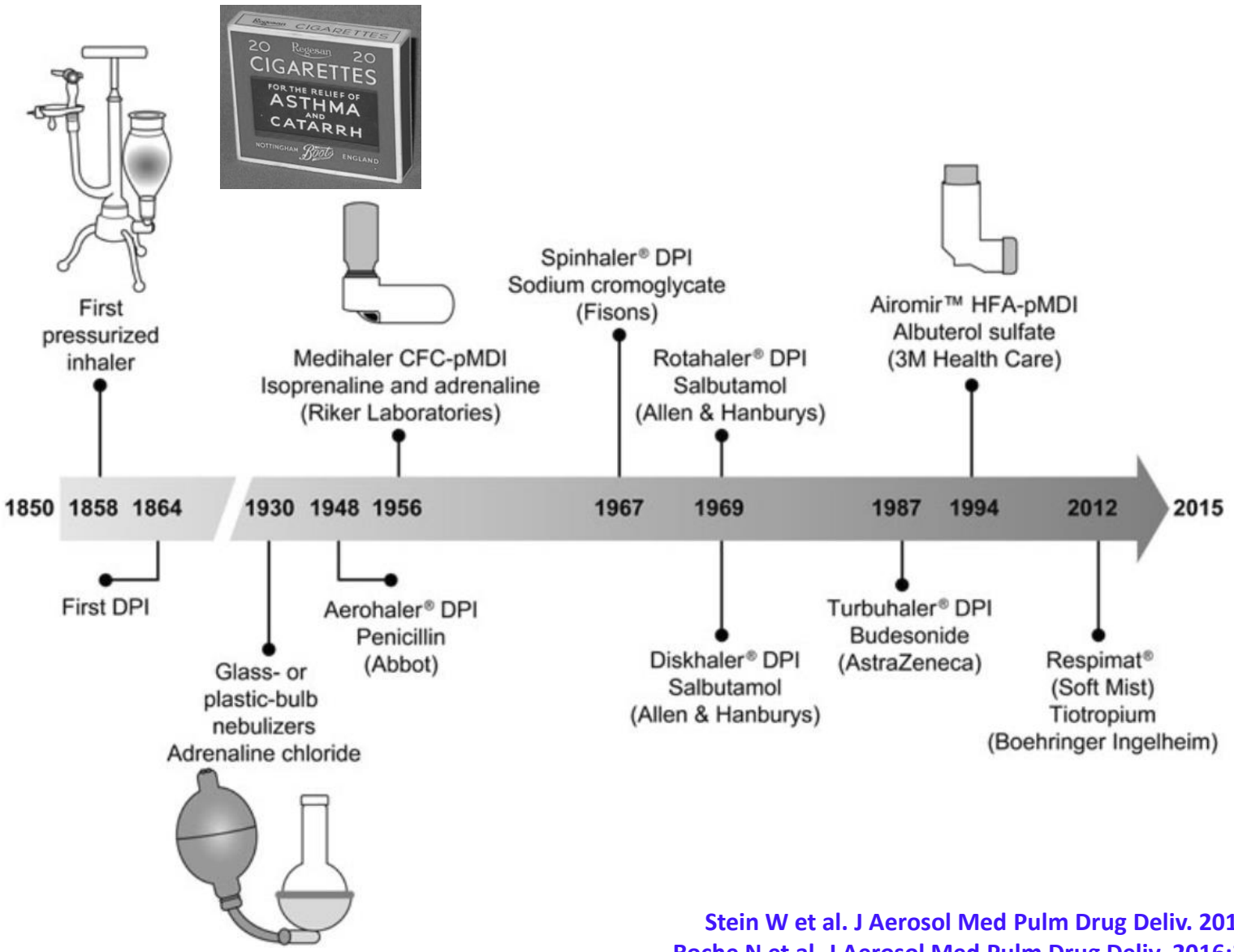
The Delivery of Therapeutic Aerosols in Ancient Times

- **에베르스 파피루스 (Ebers Papyrus)**
  - ✓ B.C. 16세기에 기록된 고대 이집트의 유명한 의학 문서의 하나.

Black Henbane, 사리풀

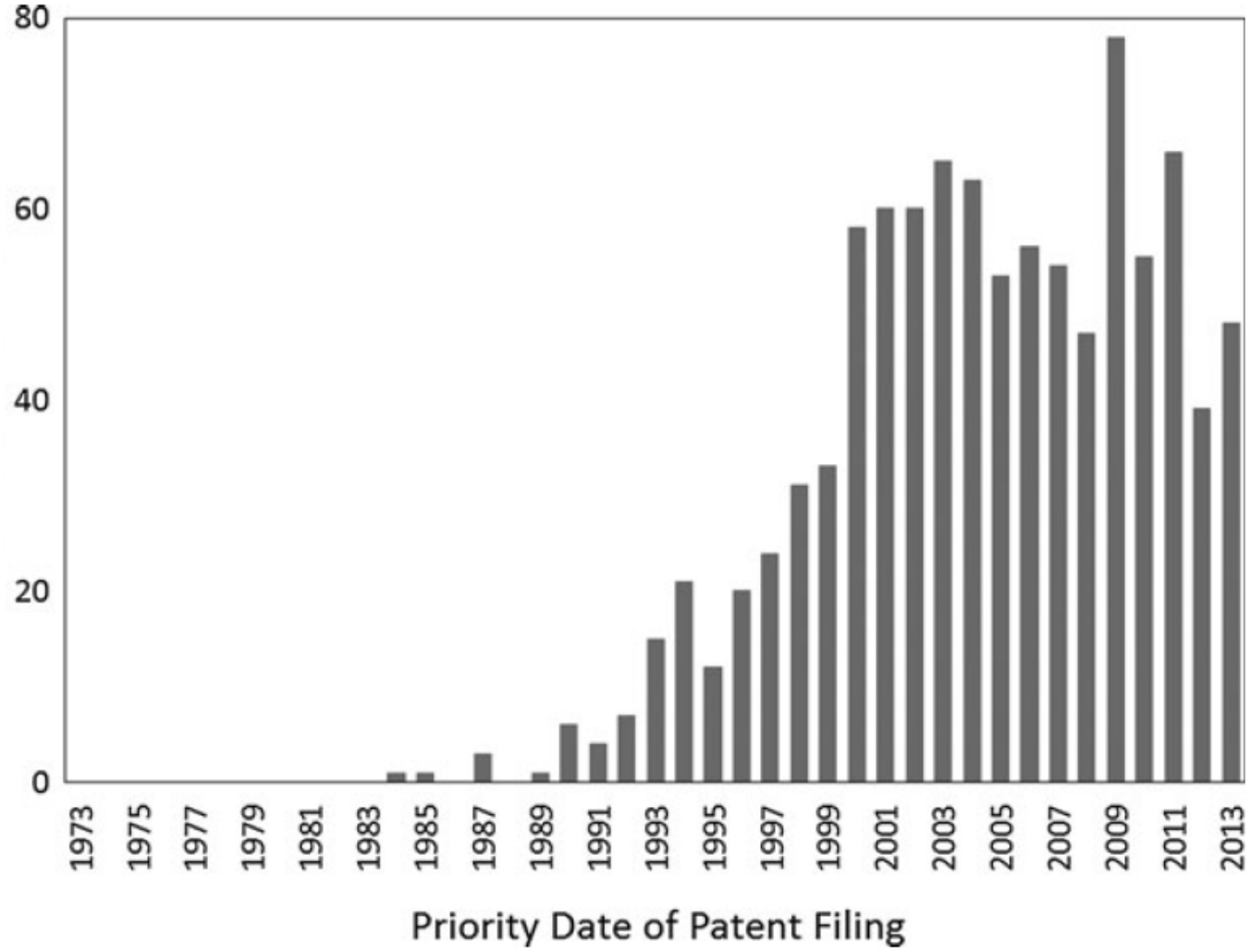
Stein W et al. J Aerosol Med Pulm Drug Deliv. 2017;30(1):20-41

Milestones in the development of inhaler therapy



Stein W et al. J Aerosol Med Pulm Drug Deliv. 2017;30(1):20-41
Roche N et al. J Aerosol Med Pulm Drug Deliv. 2016;29(4):311-327

The No. of U.S. patent for inhaler devices



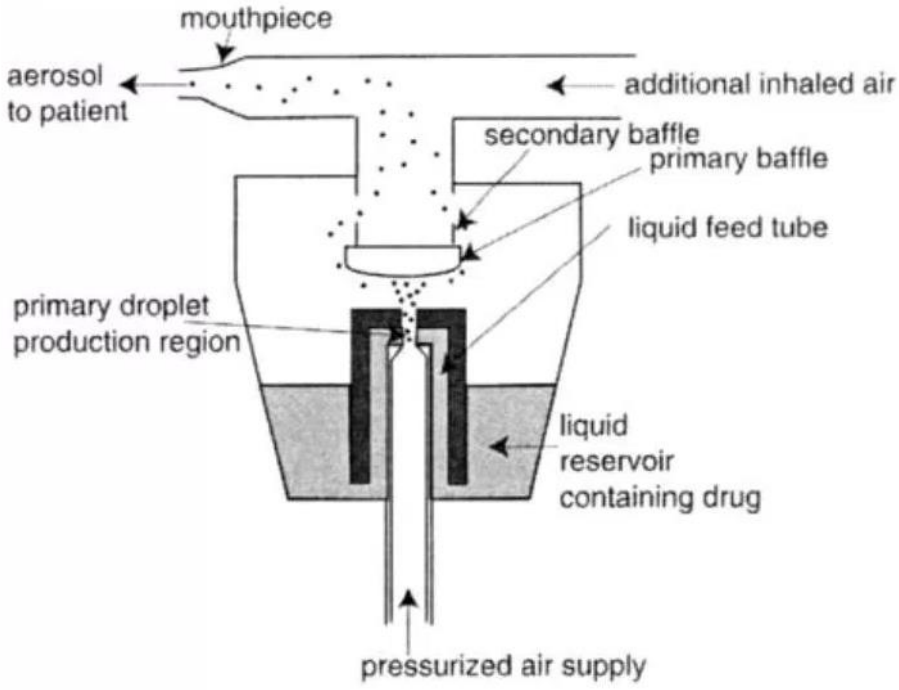
Stein W et al. J Aerosol Med Pulm Drug Deliv. 2017;30(1):20-41

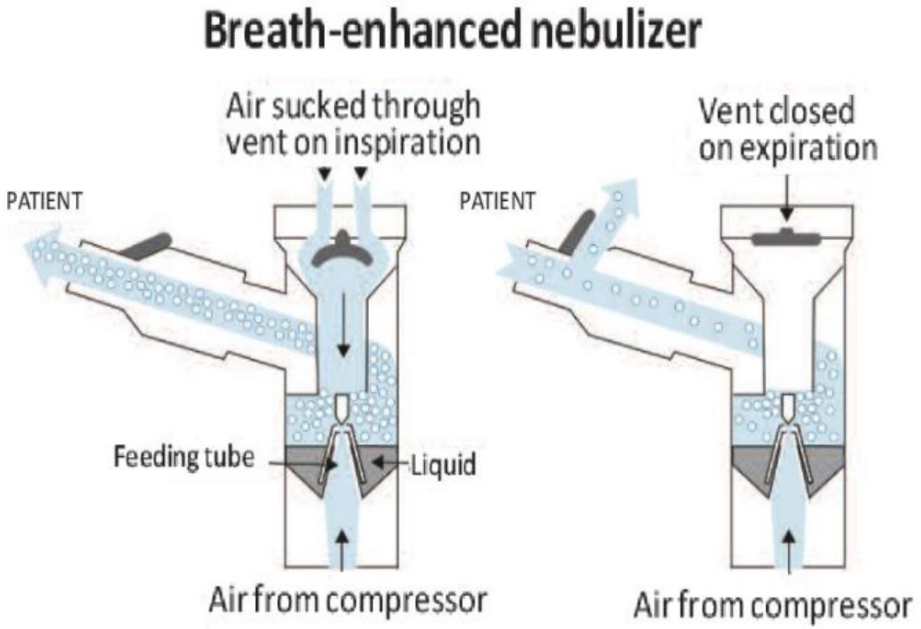
Innovation in inhaled therapy

1. Device engineering and design
2. Chemistry and formulations

Innovation in nebulizer

① Jet nebulizer

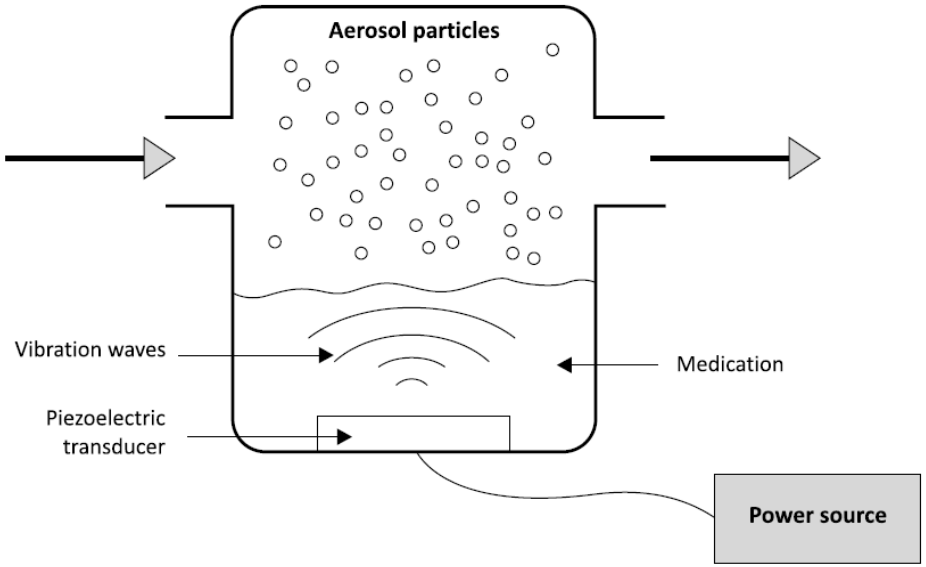




EPJ Web of Conferences 180, 02068 (2018)

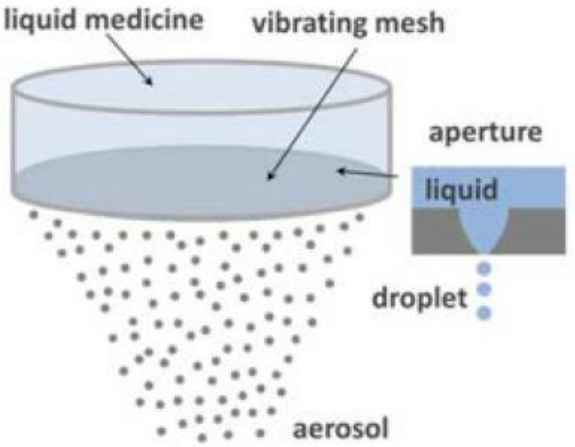
Innovation in nebulizer

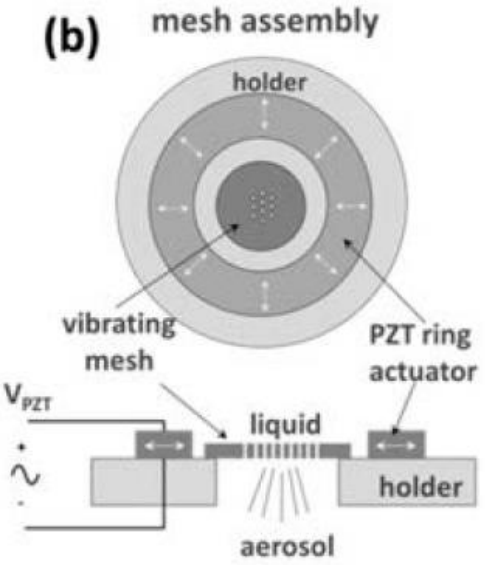
② Ultrasonic nebulizer



J Pediatr (Rio J). 2010;86(5):367-376

③ Vibrating Mesh nebulizer



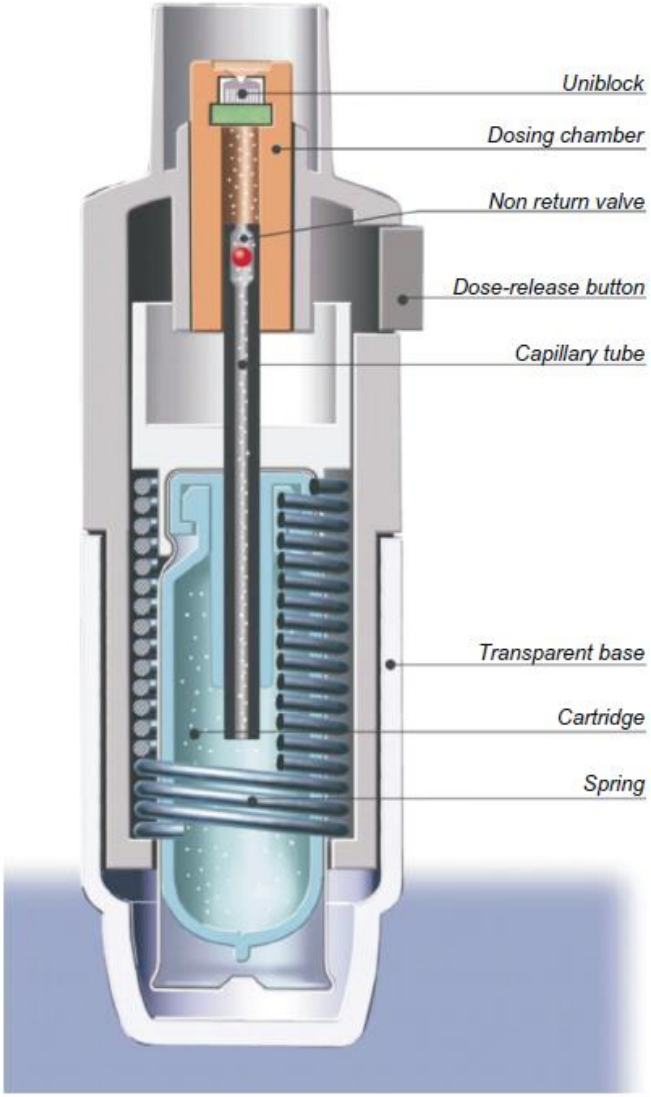


Procedia Engineering 168 (2016) 1521–1524

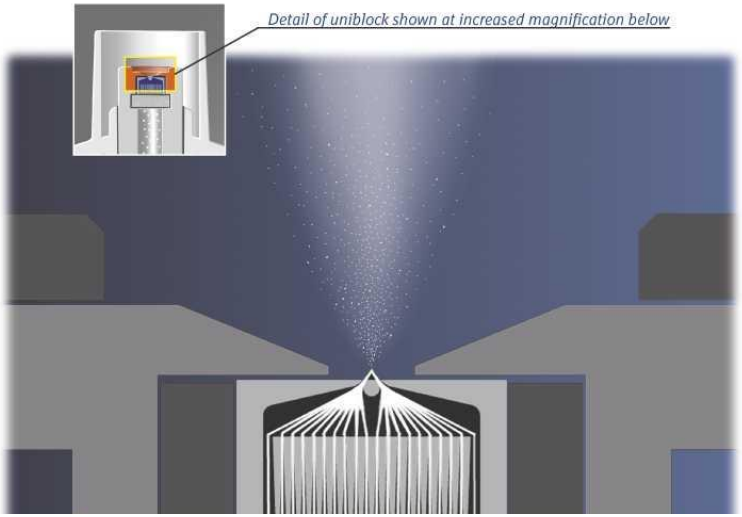
Advantage of Vibrating mesh technology over other technologies

- Vibrating mesh nebulizer does **not destroy** the medication due to heat and high pressure.
- The nebulization process is **fast and quiet**.
- The nebulizers are **small and portable**.

Colliding jet nebulizers: Respimat SMI (soft mist inhaler)



Uniblock structure



Dalby RN, et al. Medical Devices: Evidence and Research 2011;4:145–55.

Innovation in pMDI

- Propellant
  - Montreal Protocol in 1987
  - CFC (chlorofluorocarbons) → HFA (hydrofluoroalkane)

Innovation in pMDI

- K-haler

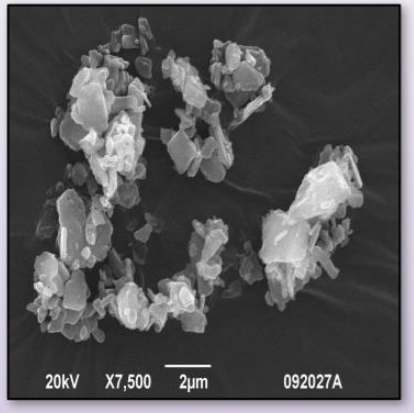
Innovation in pMDI

- Co-suspensions delivery technology

Respiratory Medicine 134 (2018) 16-23

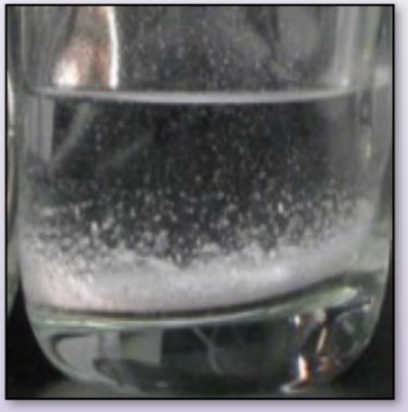
Co-Suspension™ Delivery Technology

Micronized Drug Crystals



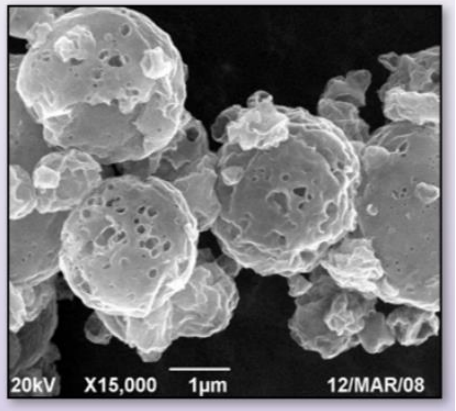
Cohesion, Adhesion, Sedimentation, Drug-drug interaction

Crystal suspension



Co-Suspension™

Phospholipid Porous Particles



Free-flowing buoyant

Vehring et al., Langmuir, 2012

Innovation in DPIs

- Nexthaler

The first Extra-fine DPI

- Ellipta

vs

- Breezhaler

vs

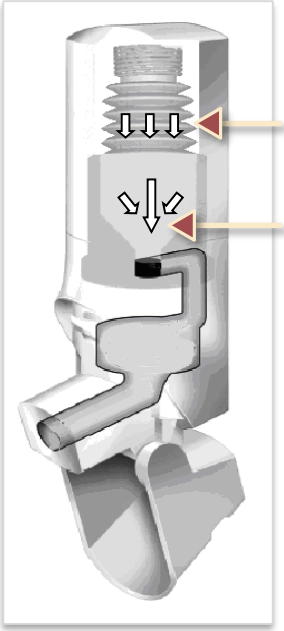
- Spiromax

vs

The X-ACT™ system

Active metering

Ensures that an accurately metered dose is consistently delivered on each actuation of the inhaler

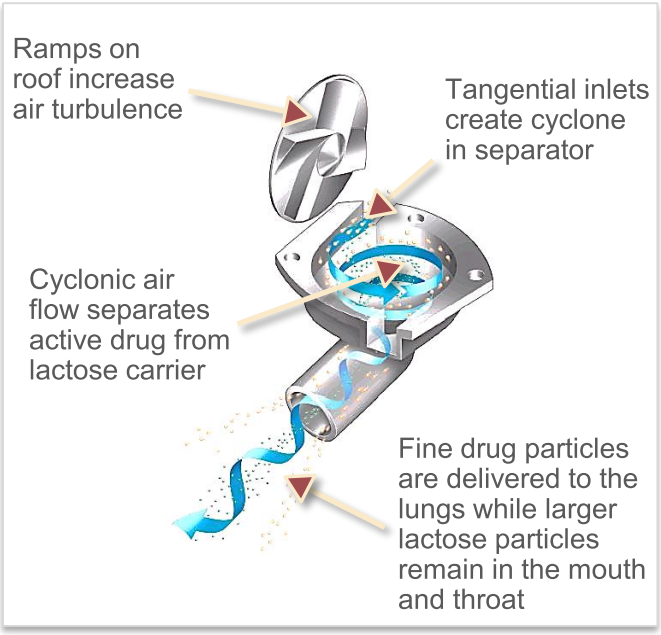


Air from pump applies pressure evenly to powder in drug reservoir

A highly accurate and consistent dose is metered into the dose cup

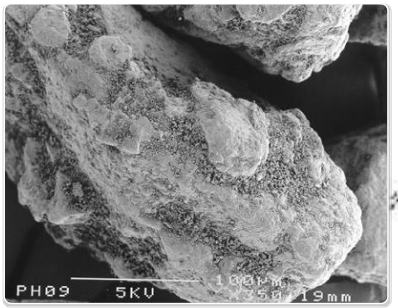
Cyclone-separator technology

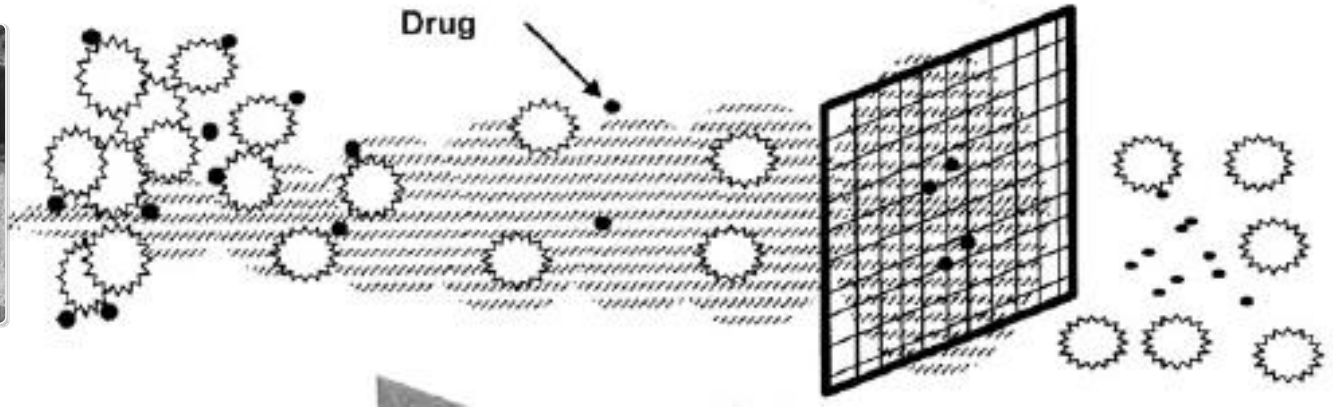
Ensures that a highly effective dose of drug can always be delivered to the site of action in the small airways, even at low inspiratory flow rates

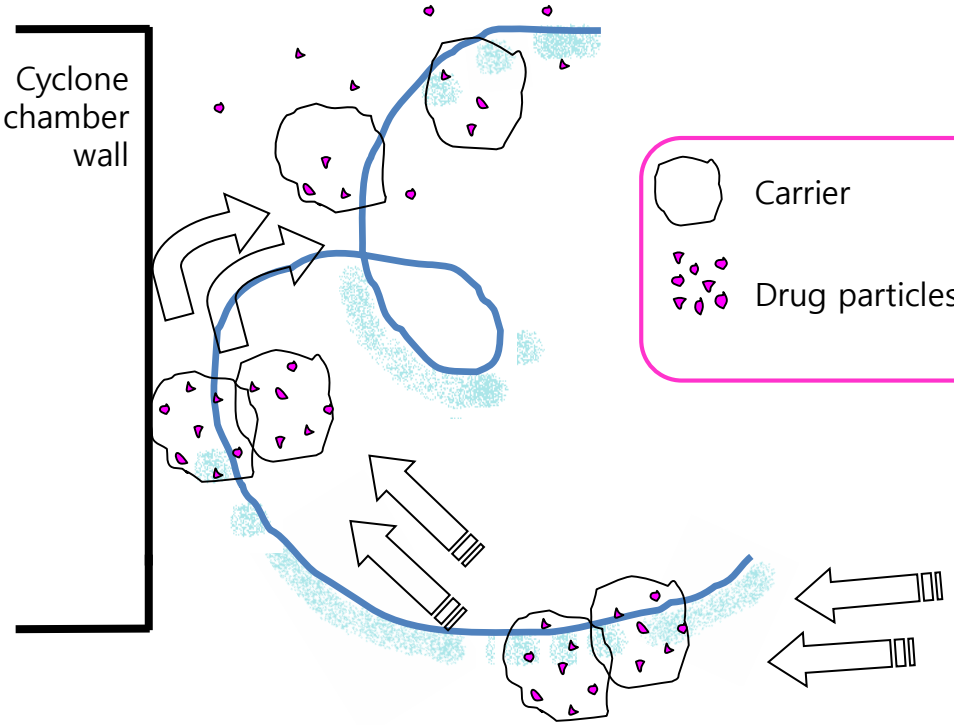


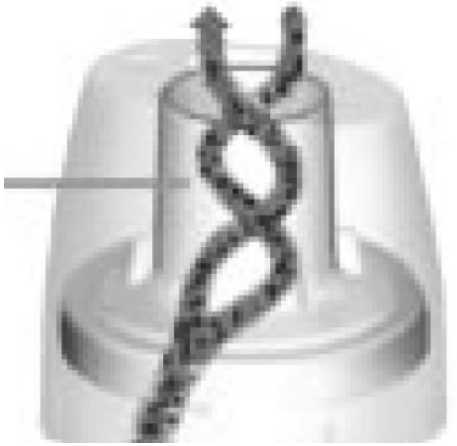
DuoResp® Spiromax®
budesonide/formoterol

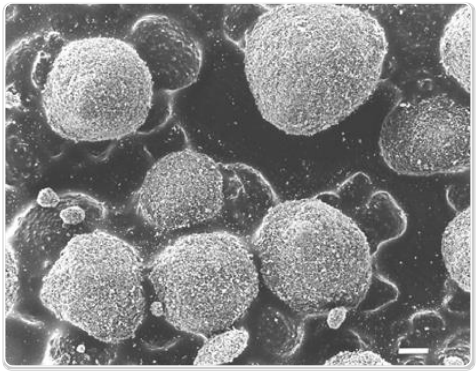
1. DuoResp Spiromax Product Monograph 2014.


PH09 5KV

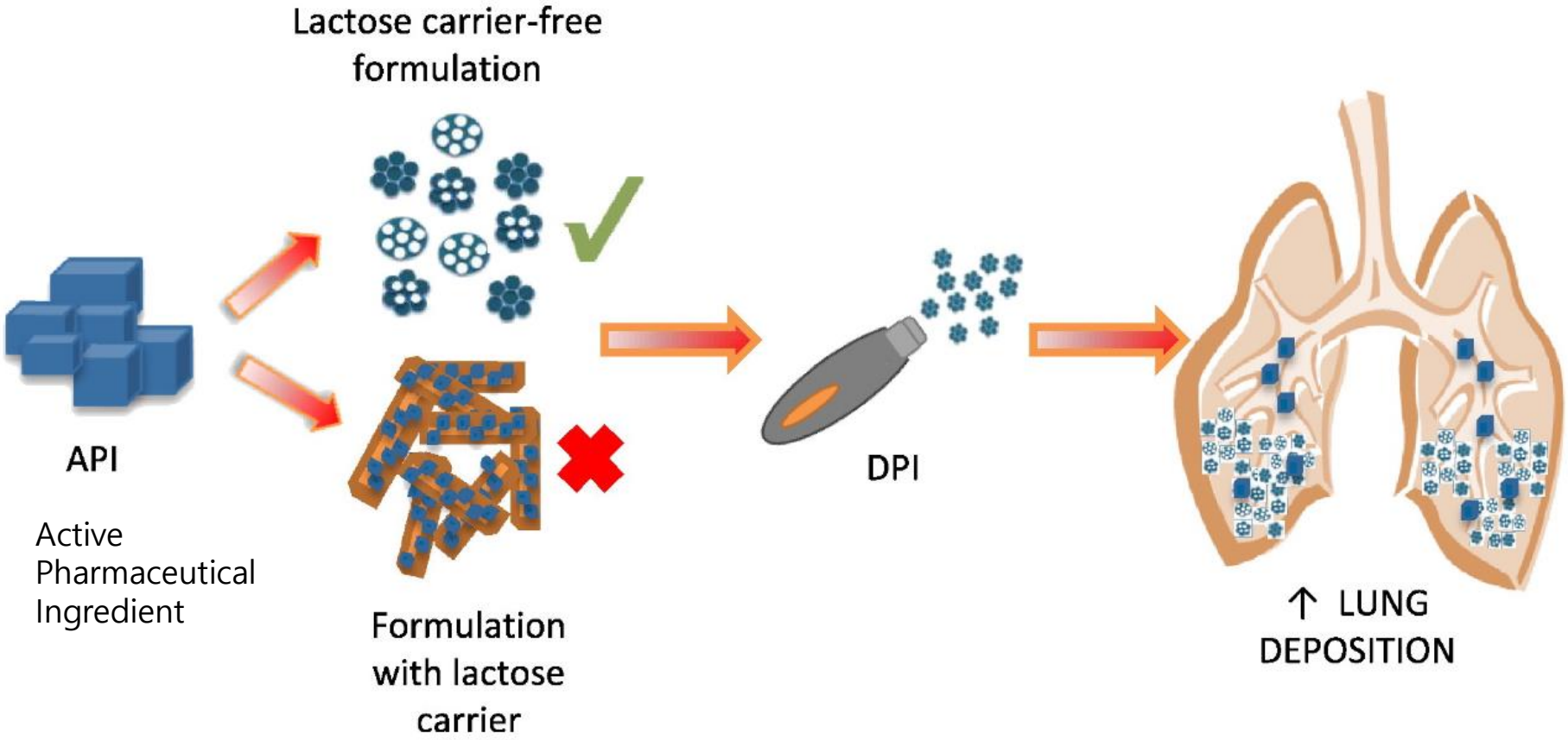

Drug


Cyclone chamber wall
Carrier
Drug particles



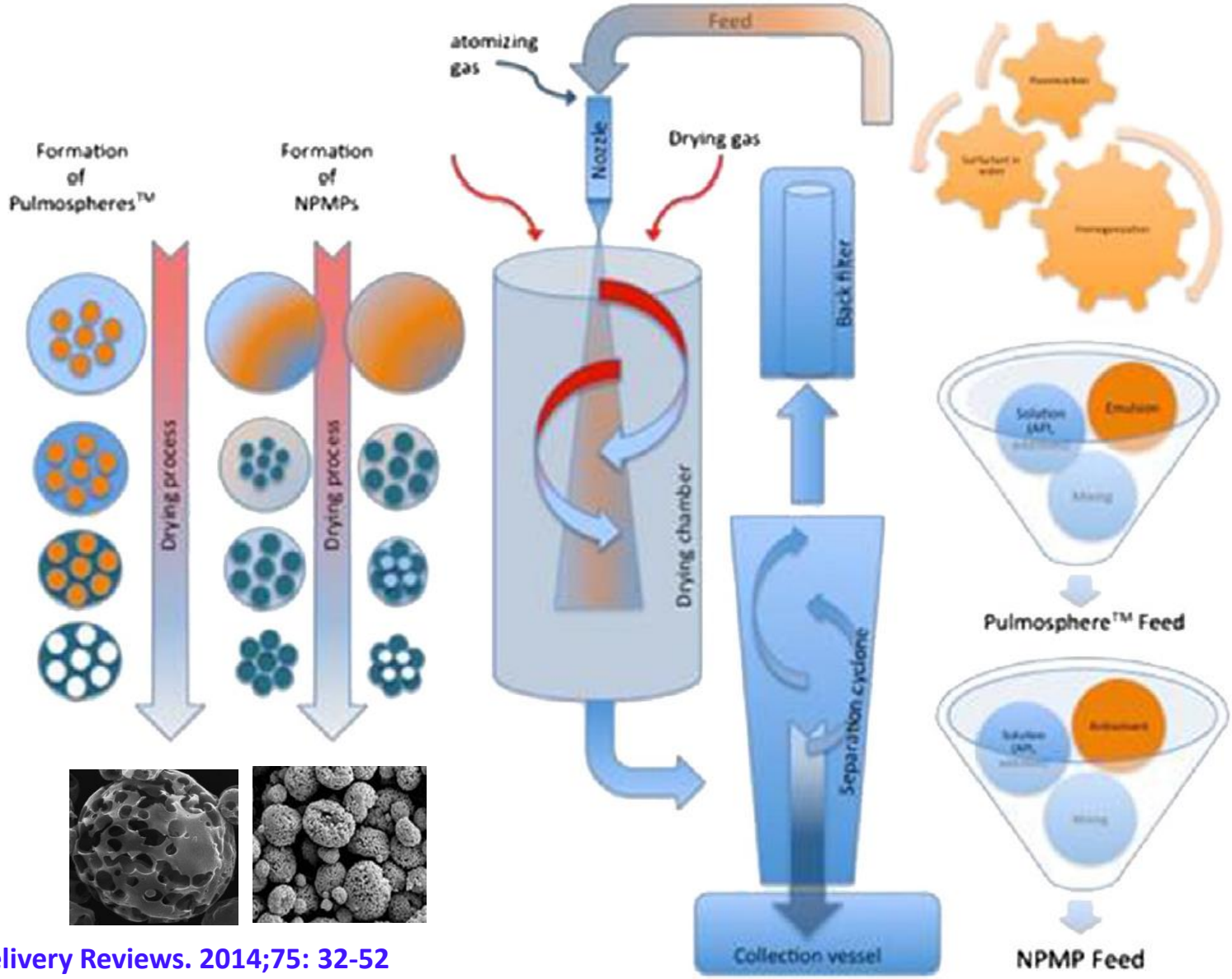


Dry powders for oral inhalation free of lactose carrier particles



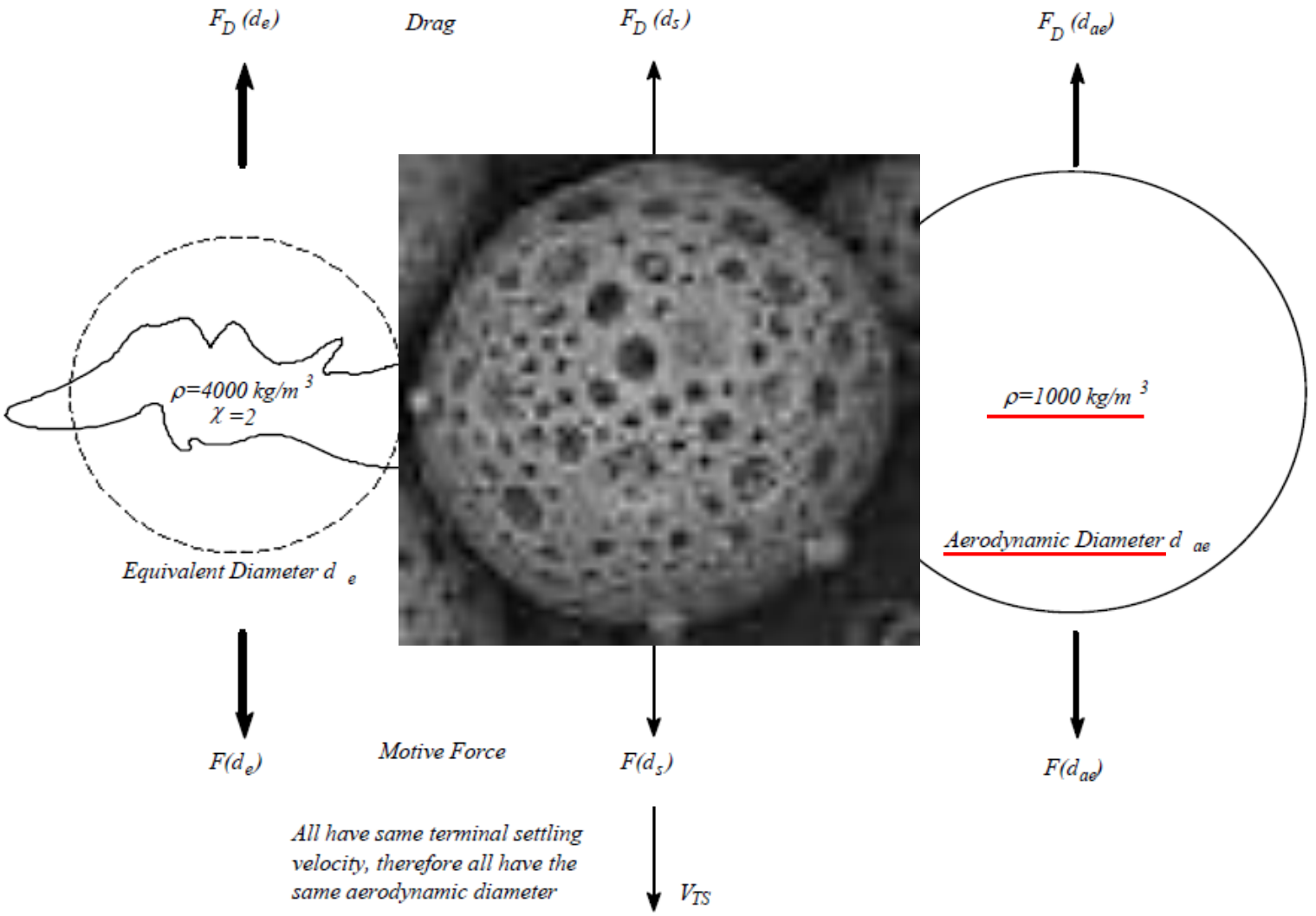
Advanced Drug Delivery Reviews. 2014;75: 32-52

Large porous particle (LPP) technology

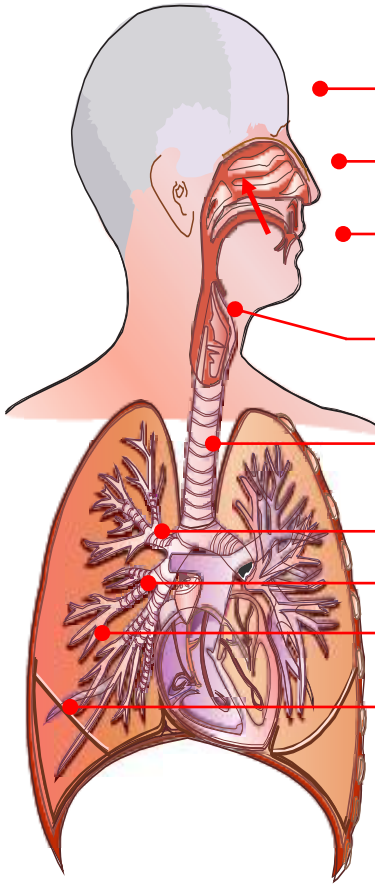


Advanced Drug Delivery Reviews. 2014;75: 32-52

Aerodynamic diameter



Determining the in vitro fine-particle fraction of an aerosol: Andersen Cascade Impactor



Pre-separator: > 10 µm

Stage 0: 9.0–10 µm

Stage 1: 5.8–9.0 µm

Pharynx — Stage 2: 4.7–5.8 µm

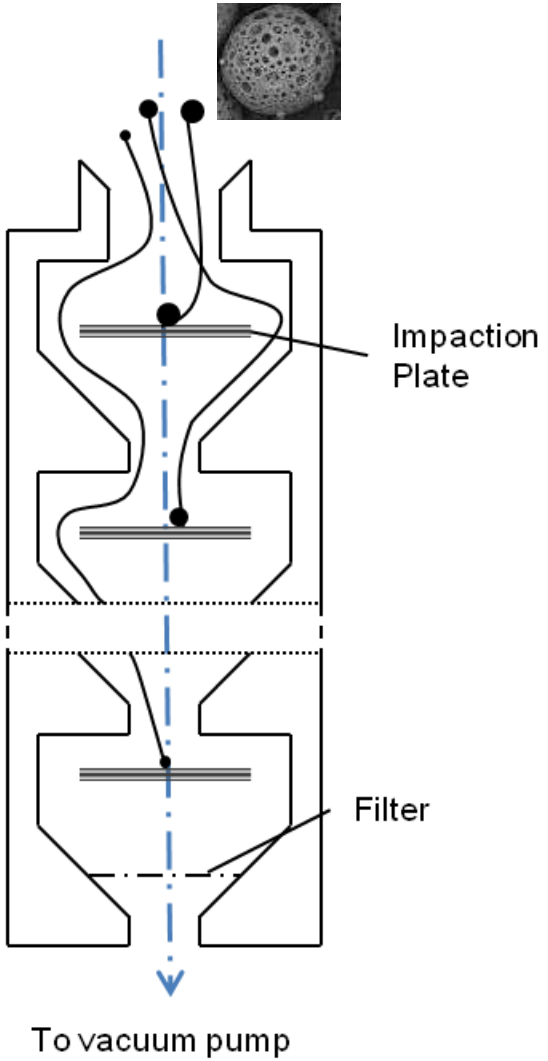
Trachea & bronchi — Stage 3: 3.3–4.7 µm

Segmental bronchi — Stage 4: 2.1–3.3 µm

Terminal bronchi — Stage 5: 1.1–2.1 µm

Alveoli — Stage 6: 0.7–1.1 µm

Alveoli — Stage 7: 0.4–0.7 µm

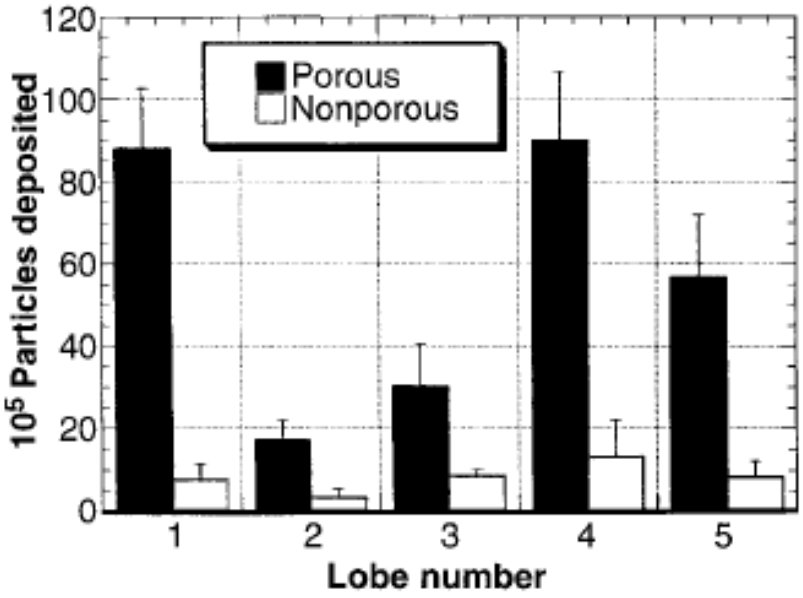


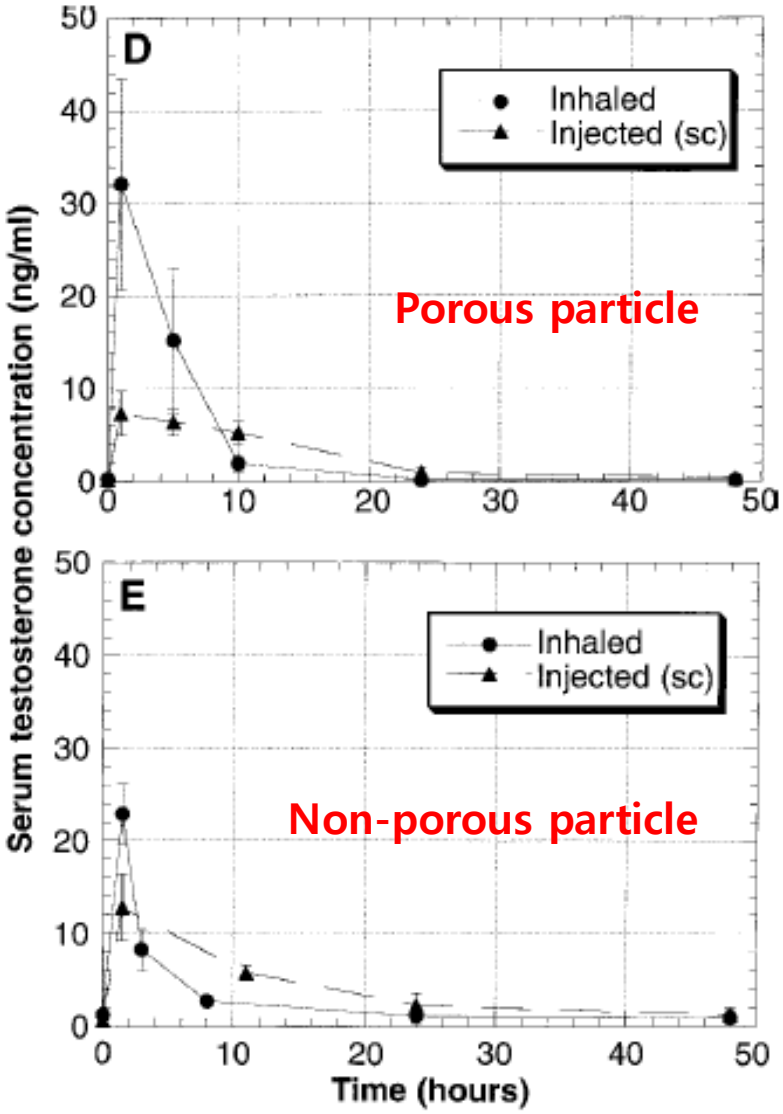
Particle size analysis of aerosols from medicinal inhalers. KONA 2004;22:32–65

Large Porous Particles for Pulmonary Drug Delivery

- Nonporous particles (d = 3.5 μm, ρ = 0.8 g/cm3 exhibited a respirable fraction of 20%, whereas 50% of porous particles (d = 8.5 μm, ρ = 0.1 g/cm3) were respirable.

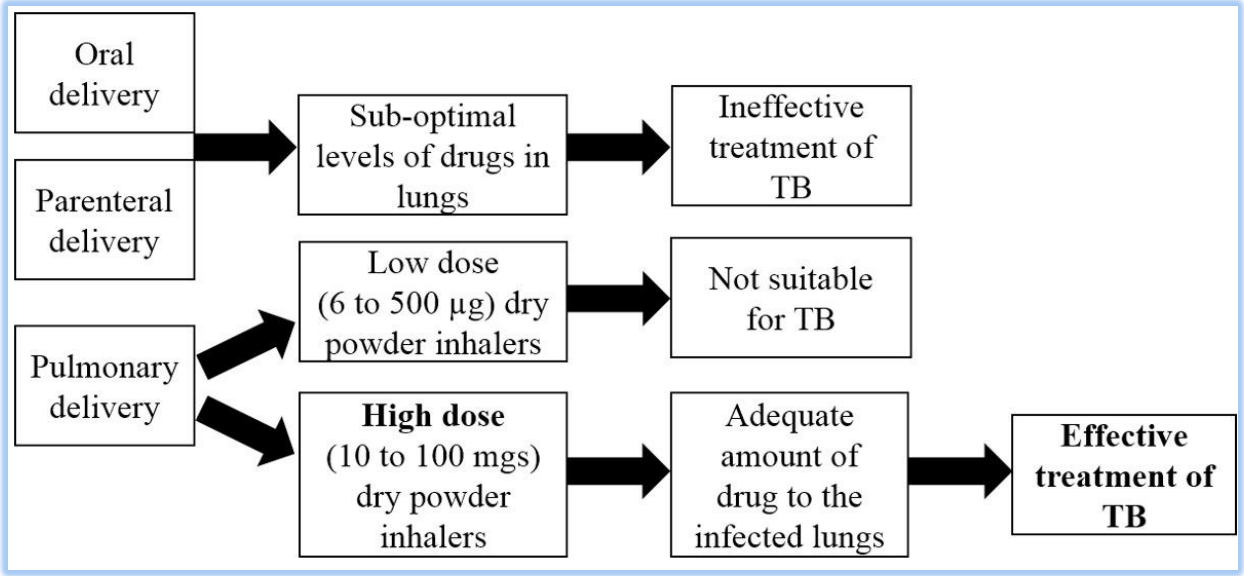
- Very light particles (ρ~0.4 g/cm3) with d > 5 μm can be deposited in the lungs.

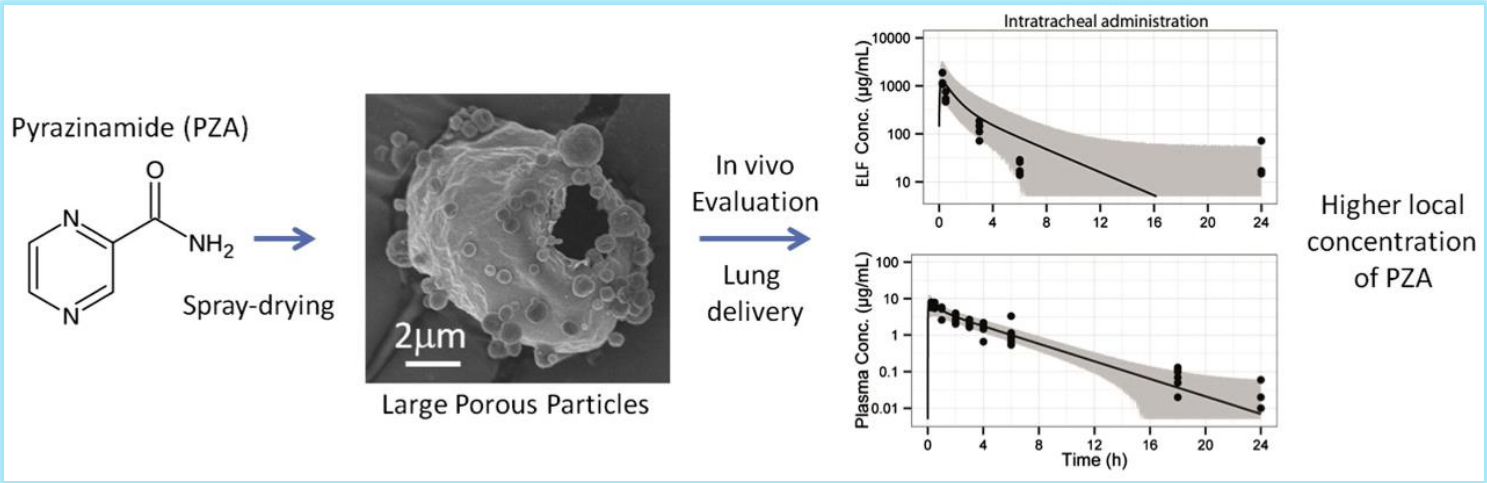




Edwards et al. Science 1997;276:1870

High dose dry powder inhalers to overcome the challenges of TB treatment





International Journal of Pharmaceutics. 2018;550:398-417
European Journal of Pharmaceutics and Biopharmaceutics. 2015;94:241-250

Innovation in inhaled therapy

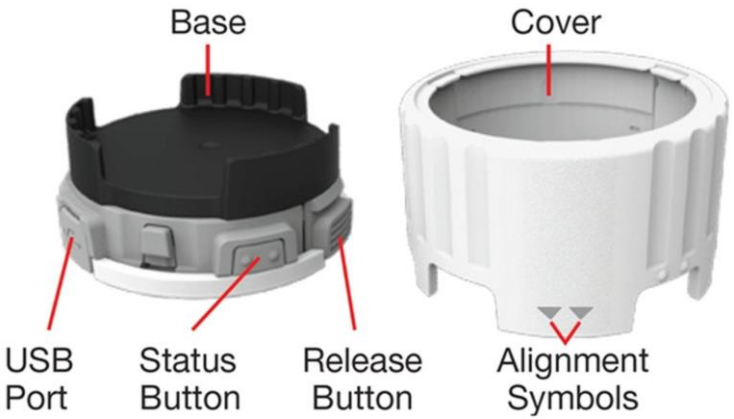
3. Digital technology associated with Inhalers

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma

Eric D. Bateman, M.D., Helen K. Reddel, M.B., B.S., Ph.D., Paul M. O'Byrne, M.B., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Agnieszka Siwek-Posluszna, M.D., and J. Mark FitzGerald, M.D.



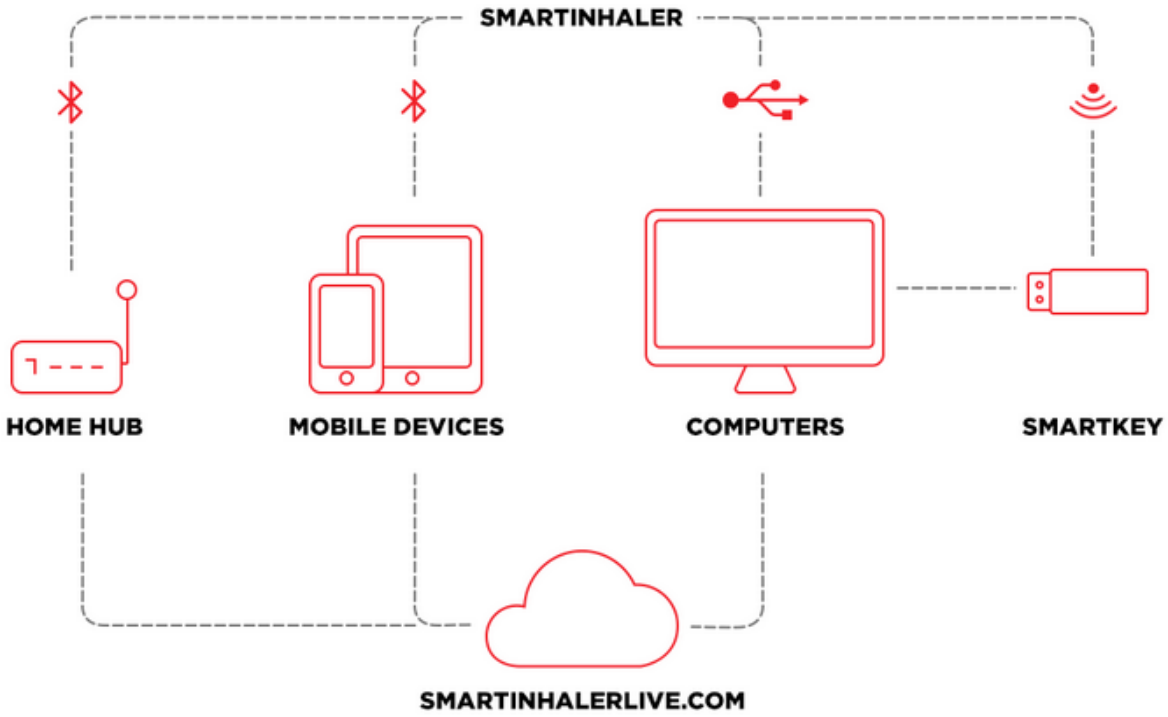
SmartTurbo monitor attached to Symbicort turbuhaler.

SmartTurbo monitor

Janine Pilcher et al. BMJ Open Resp Res 2015;2:e000097

adherium

adherium



Summary: Innovation in inhaled therapy

- Device engineering and design
  - ✓ Vibrating mesh nebulizer
  - ✓ Colliding jet nebulizers: Respimat SMI (Soft Mist Inhaler)
  - ✓ Breath-Actuated Inhaler (BAI): K-haler
  - ✓ A lot of innovative DPI devices
- Chemistry and formulations
  - ✓ Propellant CFC → HFA
  - ✓ Co-suspensions technology
  - ✓ Extra-fine drug particles (Both of pMDI & DPI)
  - ✓ Large Porous Particles: Dry powders free of lactose carrier
- Digital technology associated with Inhalers
  - ✓ Electronic monitoring to enhance adherence