Inhalation product development
- a short introduction -

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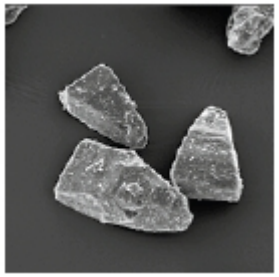
www.inhalationmag.com

This presentation is for teaching purposes only

An Inhalation Product



Formulation
- API
- Excipients
- Others (e.g. propellant)

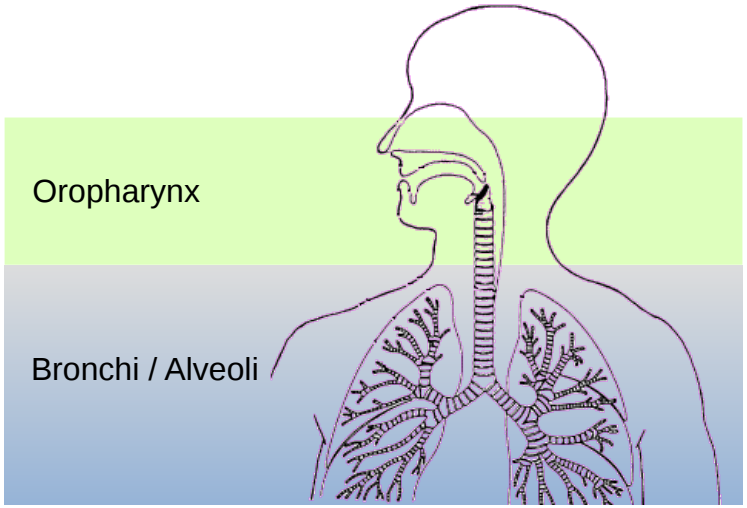
Device
- Containment
- „Mechanics“

Final Product
- Delivered dose
- APSD/FPD

Device and formulation combined are providing an effective and safe inhalation product

Where it works - Aerodynamic performance

During the inhalation maneuver, the effective dose is inhaled into the targeted area of the lung.



Particle properties:

- **Non-Respirable particles (> 5 µm)**

➡ Deposition in oropharynx and upper airways

- **Fine particles (< 5 µm)**

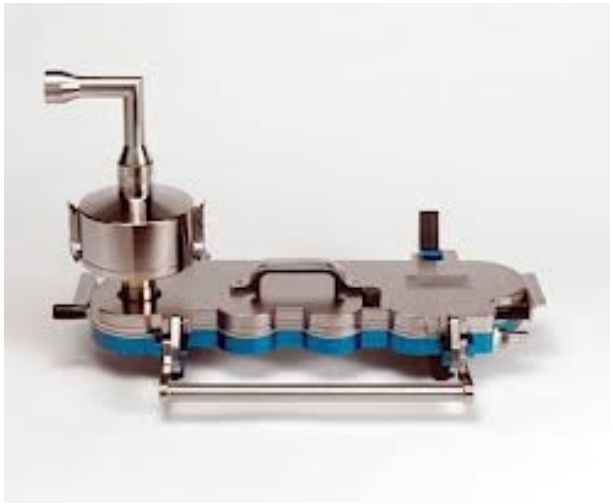
➡ Pulmonary deposition in bronchi

- **Extra fine particles (< 1 µm)**

➡ Alveolar deposition and exhalation of particles

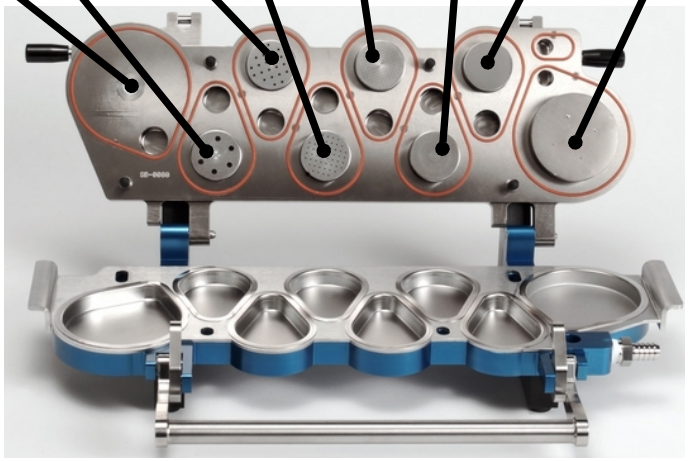
Where it works – Analytics

NGI = Next Generation Impactor



www.copley.com

Cut-off Diameter at a flow rate of 40 l/min [µm]							
10.03	5.51	3.45	2.01	1.17	0.70	0.45	
Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6	Stage 7	MOC



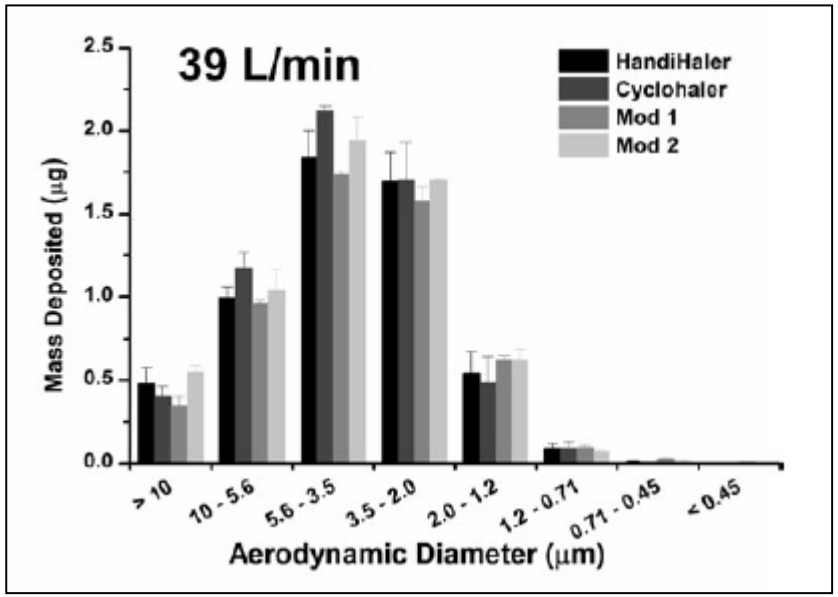
APSD = Aerodynamic particle size distribution

Respirable fraction = fine particle dose (FPD)

Advanced techniques:
- Alberta throat
- Pumps mimicking human air flow ramp

Where it works - Aerodynamic performance

Tiotropium Spiriva® HandiHaler®



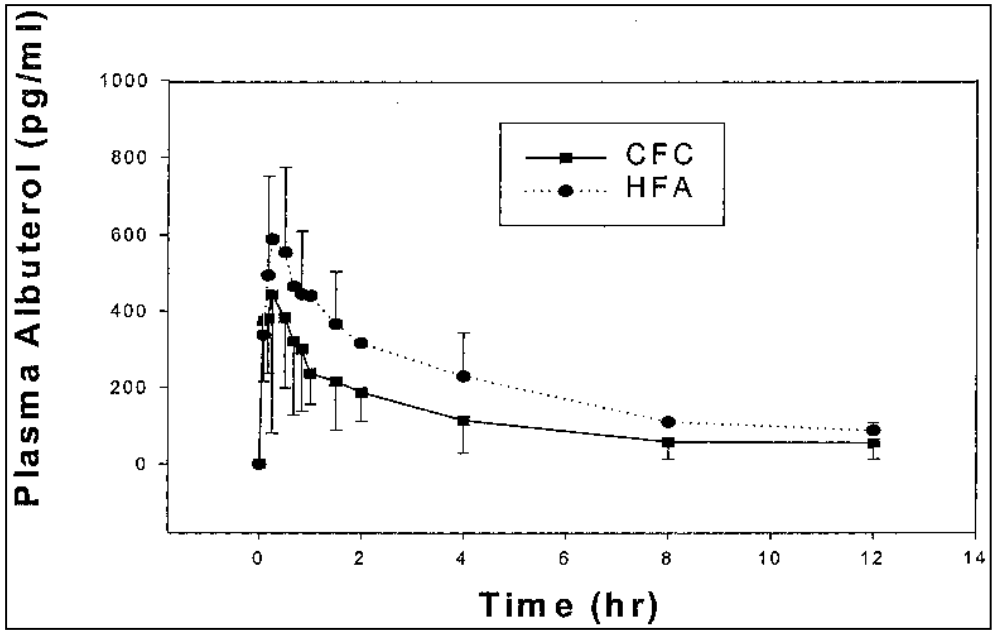
Shur J. et al., AAPS J. 2012, 14(4): 667–676.

The inhalation product is effective at specific areas of the lung.

The *in vitro* measured aerodynamic particle size distribution reflects this desired target region.

Tiotropium leads to a reduction in smooth muscle contraction and mucus secretion and thus produces a bronchodilatory effect.

Reliable Efficacy



Joguparthi V. et al., JAM. 2003, 16(1): 47–53.

Albuterol concentration (mean ± SD) versustime for HFA and CFC formulations of albuterol.

An albuterol/salbutamol pMDI inhaler is a quick-relief or rescue medication used to decrease asthma symptoms.

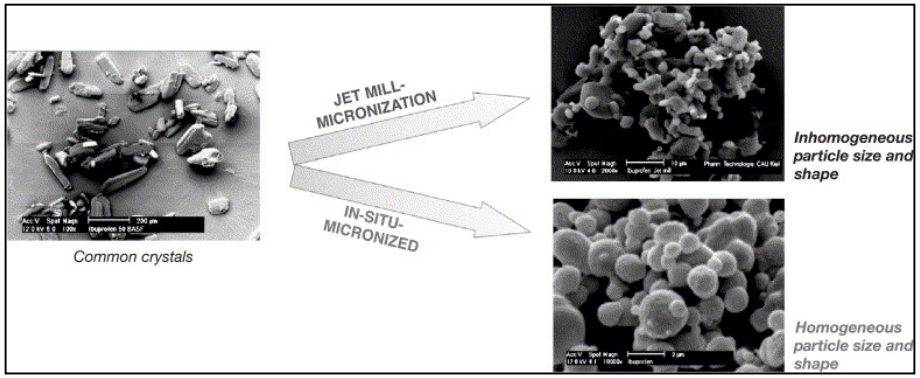
A reliable immediate onset is essential, and need to be demonstrated during clinical studies.

Efficacy and Safety for patient

What could impact efficacy/safety of an inhalation product?

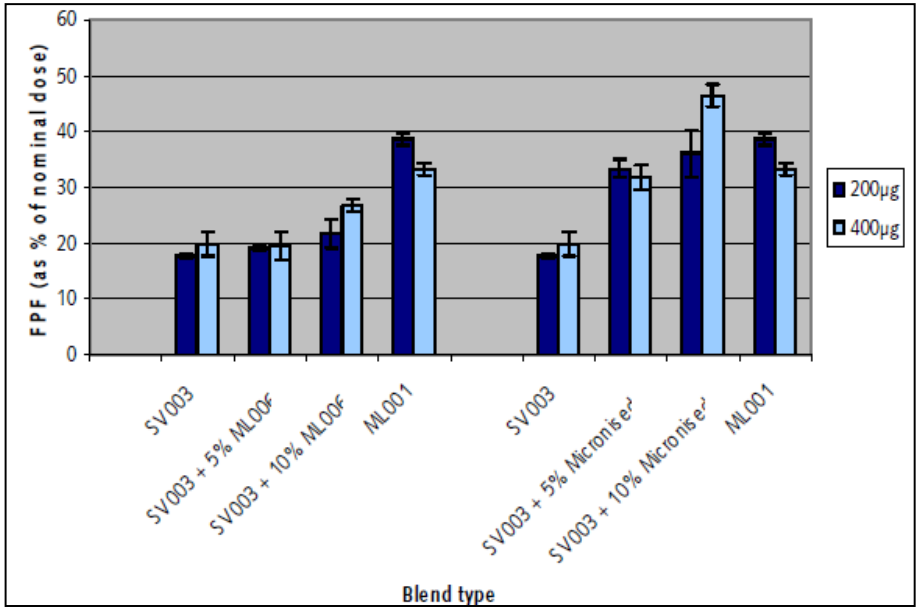
- Properties of API/Excipients
- Properties of device
- Changes during in-use time
- Changes during shelf life

Properties of API/Excipients



Rasenack N. et al., PT 2004,143-44: 291-29

Properties of micron-sized API particles may influence pharmacological behaviour.



www.dfepharma.com

Effect of addition on fine lactose on the fine particle fraction of salbutamol.

Properties of API/Excipients

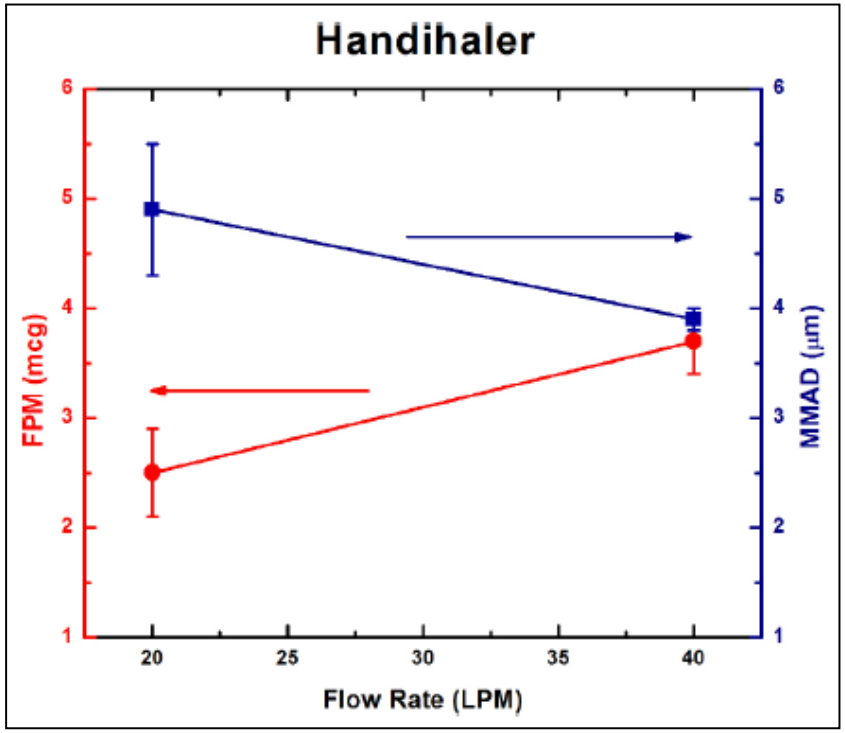
Characteristics of API/Excipient particles may have direct impact on drug product performance.

⇒ **Influence of starting materials need to be well understood.**

How can we analyze properties of starting materials and why are they important?

- Particle size by laser diffraction
- Specific surface/porosity by BET
- Particle morphology by SEM
- Polymorphic composition by XRPD
- Amorphous content by microcalorimetry and DVS

Properties of device



Data from FDA-OGD research studies on DPIs.

Tiotropium FPD at low flow rates need to be sufficient for patients with severe COPD.

Device performance may demonstrate dependence on flow rate achieved by patient.

Clear knowledge required on device performance and required dose for the product to be effective.

Properties of the device

Other device evaluations/and why they are important:

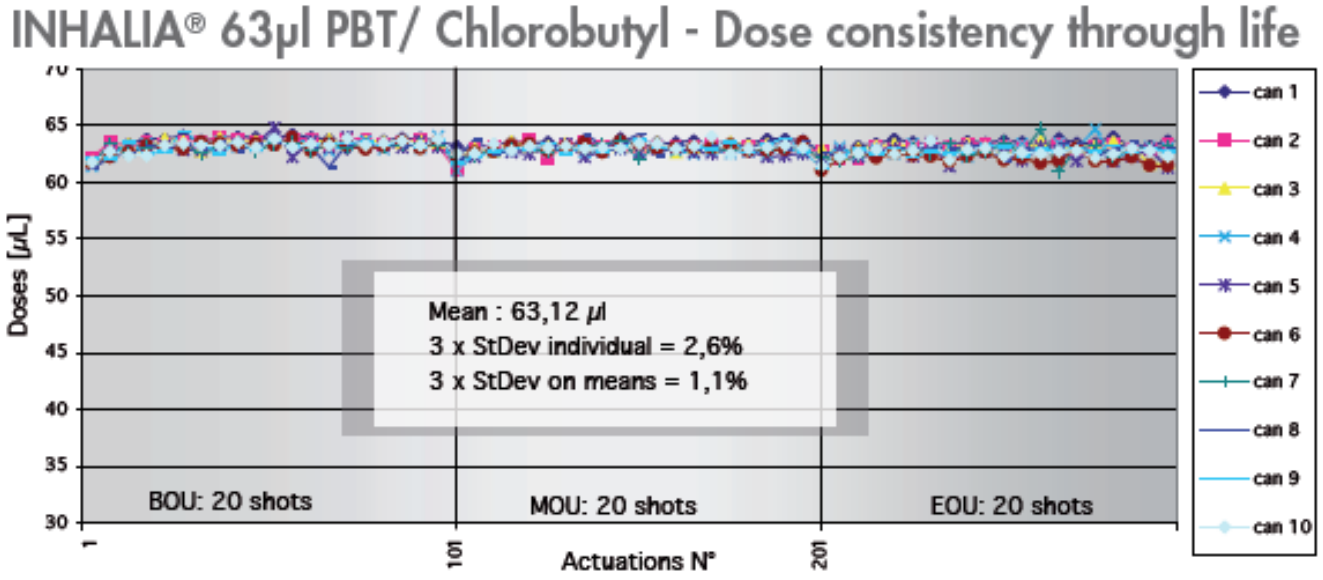
- Device resistance
- Orientation dependence
- Delivered dose/uniformity
- Drop/vibration tests
- Storage condition on device functionality

Efficacy

- Leachables / Extractables
- Foreign particles
- Double dosing
- Functionality of dose counter
- Sealing quality of contaiment

Safety

Changes during in-use time



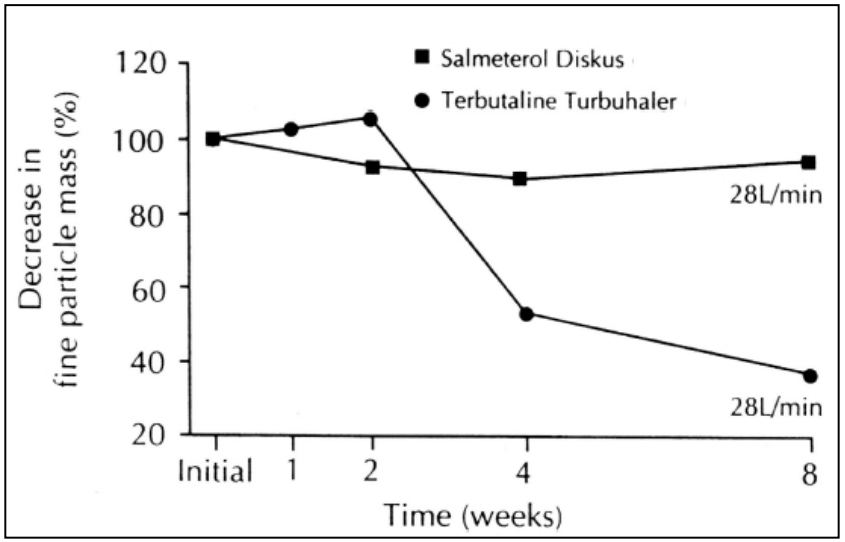
www.rexam.com

Shot weight – HFA Salbutamol suspension

Factors which may influence performance during in-use time

- Leakage
- Environmental moisture
- Storage orientation
- Drug absorption on device components

Changes during shelf life



Fuller R, JAM 1995, 8(Suppl 2): 11–17.

Change in fine particle dose as a percentage of initial value, when stored at 30 °C / 75 RH.

The storage condition of the inhaler may have significant impact on product characteristics, e.g. fine particle dose, formation of related substances.

During development, performance of product at different environmental conditions is monitored to allow appropriate instruction for storage condition. Formulation containment may be optimized or a secondary packaging used.

Summary – how to know the product

Starting Materials

Clinical performance

Device

Changes over time/ In use

APSD

⇒ To be able to manufacture the product in a robust process and to be able to give the patient thorough instructions how to use the product.

Thank you very much for your interest!

Burg Greifenstein in
Bad Blankenburg (Germany),
my former home town