H. Wachtel is employee of Boehringer Ingelheim Pharma GmbH & Co. KG, Germany.
Success factors for pediatric inhalation:

- the inhalation device,
- the pharmaceutical formulation
- the patient (adherence..)

Impactor measurements acc. to USP/Ph.Eur. vs. replica
- flow profiles and electronic lung

Comparison with in vivo deposition data

Checking ped. M-T replica using monodisperse particles
- 3 micrometers (and below?) are our target size

Applications to device and formulation development

Summary
Motivation: Success factors for pediatric inhalation...

(1) The inhalation device
Motivation: We are prepared for any challenge...

(2) The pharmaceutical formulation

SALE – Powders for inhalation – SALE – Powders for inhalation – SALE -

Lactose
Glucose
Concrete

toxicologically acceptable force control agents?

IPAC-RS, IVIVC in Pediatric OIPs, H. Wachtel, March 20, 2014
Motivation: We are prepared for any challenge...

(3) The patient

Attention – Customer approaching – Attention – Customer approaching – Attention

Improper use of devices is common

→ Design inhaler / accessory for the use with children
Summary of motivation section:
- what we want to do:

Make better medicines for children (->EuPFI, US-PFI)

How?
• Demonstrate performance in clinical trials
• Establish laboratory tests
  (draft: <1602> Spacers and valved holding chambers)
• mix Lab.- Methods and flow profile measurements

-> Handling Studies
• low risk
• low cost
The aerodynamic diameter is important, but there are additional influencing factors (inhalation, airway dim. …)

ICRP-Modell

shift expected for younger

Source: ICRP66; 1994 International Commission of Radiological Protection + later updates
The pharmacopeial aerodynamic fine particle assessment:
- lots of work but it is far away from the patient

Apparatus A (EP only)
Q = 60 L/min

Apparatus C, 4
Q = 60 L/min (and calcul.)

Apparatus E, 5, 6 (with presep.)
Q = 15 – 100 L/min

Apparatus D, 1, 3 (with presep.)
Q = 28.3 L/min (preferred)

Apparatus 2 (USP only)
Q = 60 L/min (and calcul.)
Air flow profiles for testing: important, they co-define the delivered dose, site, ...

Example HandiHaler with flow resistance 0.16 $\text{sqrt}(\text{mbar})\text{min}/\text{L}$

Compendial testing

Duration $T \text{ (s)} = \frac{4 \text{ L} \times 60 \text{ (s/min)}}{Q \text{ (L/min)}}$

flow rate to achieve pressure drop = 4 kPa

alternative testing

(averaged ?)
flow profile corresponding to flow resistance of device
Performance tests closer to reality:
Finlay’s idealized throat models the patient.

The simplistic USP throat used for release testing is complemented by more realistic throat models for early development.
Realistic models of children’s extrathoracic airways for *in vitro* inhaler testing.

V=0.0398 L  V=0.0245 L  V=0.0148 L  V=0.0112 L

Age 4-5 yrs  Age 3-4 yrs  Age 2-3 yrs  Age 1-2 yrs
The *in vitro* patient:

- **Upper airway model**
- **Inhalation device**
- **Mixing inlet**
- **Electronic lung**
- **To pressurized air**
Minimalistic set-up for realistic inhaler tests using filters and a lung simulator

- Throat model
- Filter
- Breathing pattern
- e.g. Eklira Genuair

Lung simulator
ASL 5000
Success factors for pediatric inhalation:
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- the pharmaceutical formulation
- the patient

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Checking ped. replica using monodisperse particles
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Applications to device and formulation development

Summary
Aerosol deposition studies using our realistic pediatric models are close to published in vivo data (1)!

Link to scintigraphic deposition data of Wildhaber et al. (1999) in six 2 year-old children using the same pressurized Metered Dose Inhaler (albuterol) and valved holding chamber (AeroChamberPlus with facemask).

Aerosol deposition studies using our realistic pediatric models are close to published in vivo data (2)!

Link to scintigraphik deposition data of Erzinger et al. (2007) in children aged 1-3 yrs using a pMDI (albuterol) and a valved holding chamber.

* Erzinger et al. (2007), Journal of Aerosol Medicine, Vol. 20, S1, S78-84
Aerosol deposition studies using realistic pediatric models are close to published in vivo data.

Link to scintigraphic deposition data of Erzinger et al. (2007)* in children aged 1-3 yrs using a pMDI (albuterol) and a valved holding chamber.

*Erzinger et al. (2007), Journal of Aerosol Medicine, Vol. 20, S1, S78-84
Summary of the experimental part (1)

The set up has been shown and compared to:

a) pharmacopeial procedures (dose tubes, impactors)

b) literature -> ( ~ Validation?)
   limitation: ethic considerations in children
   our way forward: refer to existing deposition studies

   clear gap:
   Best practice in adults: see e.g. study by Bo Olsson et al.
   - Validation of a General In Vitro Approach …

Recommendation: Please consider recording inhalation flow profiles
when planning your next pivotal pediatric study.
Success factors for pediatric inhalation:
- the inhalation device,
- the pharmaceutical formulation
- the patient

Impactor measurements acc. to USP/Ph.Eur. vs. replica
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Applications to device and formulation development

Summary
Where do our inhaled particles go?

**Inner coating:**
Brij + glycerol + water

**methylene blue**
Checking pediatric replica using monodisperse particles

SEM image of methylene blue particle

manifold & Aerosizer

Vibrating Orifice Generator

particles
Example: In-vitro performance with methylene blue

Relevant, as children < 18 months will inhale through their nose

n.b.: typical mouth, typical nose, not from the same subject!
Example: In-vitro performance with methylene blue

Partly relevant, older children will inhale through their mouth

n.b.: typical mouth, typical nose, not from the same subject!
Success factors for pediatric inhalation:

- the inhalation device,
- the pharmaceutical formulation
- the patient

Impactor measurements acc. to USP/Ph.Eur. vs. replica

- flow profiles and electronic lung

Comparison with *in vivo* deposition data

Checking ped. replica using monodisperse particles

- 3 micrometers (and below?) are our target size

**Applications to device and formulation development**

**Summary**
Application to dry powder inhalers: Easyhaler - Novolizer & idealized child model (4-5 years)

**Constant Flow**

- Flow: 28, 41, 60 L/min

**Flow Profile**

- PIF: 9 L/min

**Drug Mass (%)**

- **Easyhaler**
  - albuterol sulfate
  - lactose blend

- **Novolizer**
  - albuterol sulfate
  - lactose blend

**Flow Rates**

- DD, throat, DTL

**Graphs**

- Comparison of drug mass (% ND) at different flow rates (28, 41, 60 L/min) and flow profiles (PIF: 9, 24, 42, 51 L/min).

**References**

- IPAC-RS, IVIVC in Pediatric OIPs, H. Wachtel, March 20, 2014
Formulation development:
Test with lactose (34µm or 19µm) blend containing albuterol sulfate

Easyhaler:
- Tube-like
- No influence of carrier size
- No throat effect

Testing @ 4 kPa

Novolizer:
- Cyclone+impact+carrier size
- Throat effect

A. Below, thesis
Univ. Düsseldorf (2013)
Formulation dependence: Soft pellets do not work everywhere

Amount of drug [% DD]

Throat
DTL
<5 µm

Alberta Throat
Const. Flow
4 kPa
4 L

A. Below, thesis Univ. Düsseldorf (2013)
Different types of spacers / valved holding chambers lead to different throat deposition and dose to lung.

Results using throat model and flow profiles
a) single breath Respimat and
b) 5 breaths with spacers of a 5 year-old child.

Can Pediatric Throat Models and Air Flow Profiles Improve Our Dose Finding Strategy?
Herbert Wachtel, Deborah Bickmann, Jorg Breitkreutz, Peter Langguth
Focus on the patient:
Very young children (below 5 years)

The young child’s different „hardware“ requires adaptation!
Handling study investigating children below 5 years: stepwise approach

What is checked?

- Child alone
- With help by caregiver
- Valved holding chamber with help by caregiver
In-vitro results using typical flow profiles of children -- valved holding chamber with face mask --

effect of rel. humidity

<table>
<thead>
<tr>
<th></th>
<th>1-&lt;2 years</th>
<th>2-&lt;3 years</th>
<th>3-&lt;4 years</th>
<th>4-&lt;5 years</th>
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</thead>
<tbody>
<tr>
<td>ACh 50%</td>
<td>1.73</td>
<td>0.905</td>
<td>0.947</td>
<td>0.503</td>
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<tr>
<td>ACh 95%</td>
<td>1.78</td>
<td>1.005</td>
<td>1.13</td>
<td>0.595</td>
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<tr>
<td>DTL 50%</td>
<td>0.133</td>
<td>0.393</td>
<td>0.46</td>
<td>0.957</td>
</tr>
<tr>
<td>DTL 95%</td>
<td>0.1</td>
<td>0.38</td>
<td>0.43</td>
<td>0.84</td>
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<tr>
<td>FPD 50%</td>
<td>0.113</td>
<td>0.377</td>
<td>0.394</td>
<td>0.809</td>
</tr>
<tr>
<td>FPD 95%</td>
<td>0.092</td>
<td>0.358</td>
<td>0.386</td>
<td>0.673</td>
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</table>
Dose prediction knowing the inhalation profile (and the inhaler/spacer+mask combination)

Existing theory can be applied

In-vitro calibration data

Typical patient data:

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>sex</th>
<th>age (yrs)</th>
<th>ht (cm)</th>
<th>weight (kg)</th>
<th>mouth-/throat volume of model (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>m</td>
<td>1.4</td>
<td>77</td>
<td>10</td>
<td>0.011</td>
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<tr>
<td>114</td>
<td>w</td>
<td>2.4</td>
<td>91</td>
<td>13.1</td>
<td>0.015</td>
</tr>
<tr>
<td>119</td>
<td>m</td>
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<td>101</td>
<td>16.5</td>
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<tr>
<td>148</td>
<td>m</td>
<td>4.9</td>
<td>114</td>
<td>22.4</td>
<td>0.040</td>
</tr>
</tbody>
</table>

Resulting dosing prediction:

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Two puffs (µg)</th>
<th>µg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>2 x 0.13</td>
<td>0.026</td>
</tr>
<tr>
<td>13.1</td>
<td>2 x 0.39</td>
<td>0.060</td>
</tr>
<tr>
<td>16.5</td>
<td>2 x 0.46</td>
<td>0.056</td>
</tr>
<tr>
<td>22.4</td>
<td>2 x 0.96</td>
<td>0.086</td>
</tr>
<tr>
<td>70 (adult)</td>
<td>2 x 1.6</td>
<td>0.046</td>
</tr>
</tbody>
</table>

A Mathematical Model of Aerosol Holding Chambers

MAREK ZAK, M.D.,1 JOOP MADSEN, M.D., D.M.Sc.,2 ELNA BERG, M.Sc.,3 JENS BÜLOW, M.D., D.M.Sc.,4 and HANS BISGAARD, M.D., D.M.Sc.1

ABSTRACT

A mathematical model of aerosol delivery from holding chambers (spacers) was developed incorporating tidal volume (V_T), chamber volume (V_ch), apparatus dead space (V_D), effect of valve insufficiency and other leaks, loss of aerosol by immediate impact on the chamber wall, and fallout of aerosol in the chamber with time. Four different spacers were connected via filters to a mechanical lung model, and aerosol delivery during “breathing” was determined from drug recovery from the filters. The formula correctly predicted the delivery of budesonide aerosol from the AeroChamber (Trudell Medical, London, Ontario, Canada), NebuChamber (Astra, Södertälje, Sweden) and Nebuhaler (Astra) adapted for babies. The dose of fluticasone propionate delivered by the Babyhaler (Glaxo Wellcome, Oxbridge, Middlesex, UK) was 80% of that predicted, probably because of incomplete priming of this spacer. Of the above-mentioned factors, initial loss of aerosol by impact on the chamber wall is most important for the efficiency of a spacer. With a V_T of 195 mL, the AeroChamber and Babyhaler were emptied in two breaths, the NebuChamber in four breaths, and the Nebuhaler in six breaths. Insufficiencies of the expiratory valves were demonstrated by comparison of pressure flow curves during “inspiratory” flow with and without occluded expiratory openings. Insufficient inspiratory valves were demonstrated by comparison of “expiratory” pressure flow curves with and without occluded inspiratory openings. With children breathing through the spacers, mask pressure variations were generally on the same order as that seen with the mechanical respirator, supporting the clinical relevance of the in vitro findings.

IPAC-RS, IVIC in Pediatric OIPs, H. Wachtel, March 20, 2014
Deposition studies *in vitro* require:

- **Throat models**
- **Inhalation flow profiles**

and a common level of acceptance / standardization. -> CSA Z264 1-02 (Spacers + …)

There is an urgent need for these tools in order to enable studies representing children of all age groups and even sub-groups immediately when devices / formulations are created.

The in vitro studies contribute to a better understanding of device–patient interaction and help e.g. to extend the range of applications a device might face by simplifying tests with accessories, e.g. spacers.
Many thanks to …

- D. Bickmann, A.-M. Ciciliani A. Jung, M. Metzger, R. Winkler:
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- Professor Dr. Peter Langguth:
  Johannes Guttenberg University, Mainz