The FDA Critical Path Initiative – In Vitro Techniques and In Vivo Imaging Technology

Anthony J. Hickey
School of Pharmacy, University of North Carolina at Chapel Hill, NC

PQRI Workshop on Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products, Bethesda, MD March 9th, 2009
Objective

This presentation will examine the role that assessment of aerodynamic particle size distribution, aerosol deposition, imaging techniques, and modeling and simulation of product performance/drug delivery could or should play in bioequivalence testing and will review current attempts at establishing possible IVIVCs for locally acting OIPs.
Crowder, Hickey, Louey and Orr, 2003

Bioequivalence

Crowder, Hickey, Louey and Orr, 2003
Broad Bioequivalence Questions

- Relevant in vivo “test”
  - Anatomically
  - Patient Use
  - Statistically Discriminating

- Suitable models
  - Anatomical
  - Imaging
  - Mathematical
Characteristics of Interest

PRODUCT QUALITY

Aerosol Characteristics

Airways Anatomy and Physiology

Receptor Site, Pharmacology and Lung Function

Efficacy
Specific Items Measured

PRODUCT QUALITY

- APSD and Dose
- Lung deposition and Clearance
- Regional Deposition and Disease

EFFICACY
Impaction – Historical perspective

- Invented for sampling chemical warfare aerosols at Porton Experimental station
- Adopted for ambient sampling of environmental aerosols
- Most relevant for inhaled pharmaceuticals
  - Particle size based on mass
  - Whole aerosol is sampled
  - Chemical analysis used to detect particles
  - Aerodynamic diameter relevant to lung deposition
Fig. 3. Schematic representation of the principle of operation of cascade impactors. (A single jet per impactor stage is shown. Impactors with multiple jets in each stage function in the same manner.)
Fig. 4. Apparatus 1: Assembly of induction port and entrance cone mounted on cascade impactor.
Fig. 5. Apparatus 2, 3, 4, or 5: General control equipment. (See *Table 3* for component specifications.)
Fig. 9a. Components of *Apparatus 5*.
Fig. 10. Plot of cumulative percentage of mass less than stated aerodynamic diameter (probability scale) versus aerodynamic diameter (log scale).

\[ GSD = \sqrt[\frac{\text{Size}_X}{\text{Size}_Y}} \]
Graphically $\sigma_g$ may be obtained by dividing the diameter representing the 84th percentile by that of the 50th (median), or alternatively the 50th by the 16th. These values are easily derived from log-probability plots. This value may also be derived as follows:

$$\sigma_g = \frac{D(84)}{D(50)} = \frac{D(50)}{D(16)} = \left[ \frac{D(84)}{D(16)} \right]^{1/2}$$
Operating Manual
Andersen 8 stage impactor, Graseby Andersen, Smyrna GA

But impacts ≠ lungs!
- Flow rate and pressure drop effects are relevant to patient use.

- Can we detect these by inertial impaction?
Issues in aerosol particle size analysis

- Dose delivery from DPIs is highly dependent on inspiratory conditions
  - All approved DPIs are passive, relying on flow through DPI to disperse drug
- Particle size is tested in vitro at a fixed flow rate
- Fixed flow rate fails to account for DPI resistance
- In vitro particle size testing of DPIs may not accurately simulate use by a patient
Pressure drop/flow rate for 6 inhalers

\[ R = \Delta P^{0.5} / Q \]

Clark and Hollingworth, 1993
Peak inspiratory flow for healthy volunteers

Olsson and Asking, 1994
Flow profiles for Spinhaler

Clark and Hollingworth, 1993
Budesonide Turbuhaler Particle Size Distribution

Olsson and Asking, 1994
IVIVC: Quality to Efficacy

**Product Quality**
- In-vitro Performance
- In-silico, In vivo Deposition
- In-vivo Effect

**Efficacy**
Imaging Methods

- Gamma Scintigraphy
- SPECT
- PET

Data Presentation
- Whole Lung
- Central to Peripheral Ratio
- Regions of interest
Planar Gamma- Scintigraphic Images of Healthy Human Lungs

a. A typical lung ventilation image (200k counts) obtained with $^{99m}$Tc-DTPA aerosol;
b. That with $^{81m}$Kr gas (400K counts);
c. $^{99m}$Tc-MAA perfusion image (400k counts)

Ishfaq et al., 1984
Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT)

- **PET**
  - Uses an indirect measure (pairs of gamma rays from a positron emitting radionuclide)
  - Expensive (requires cyclotron to produce short lived radionuclides)
  - Greater contrast to background ratio improving giving higher resolution

- **SPECT**
  - Uses similar principle to gamma scintigraphy but in 3D
  - Less costly than PET
  - Less spatial resolution than PET

Zeissman et al, 2006
Other considerations

- Overall cost
- Accessibility
  - Number of instruments
  - Location
  - Scheduling
Human Subject Deposition Measurements

- **SPECT (Single Photon Emission Computed Tomography)**
  - Gamma Camera
  - Shows the 3D spatial distribution of radiolabeled aerosol deposition
In vivo Deposition Measurements

Healthy

Asthmatic
Correlation between mean whole lung deposition and mean impinger FPF

LD by gamma scintigraphy, FPF<6.8 μm, n=33 inhalers

Newman and Chan, 2008
Correlation between mean whole lung deposition and mean Impactor FPF

LD by gamma scintigraphy, FPF<5.8μm, n=10 inhalers  Newman and Chan, 2008
Correlation between mean whole lung deposition and the mean percentage of dose <3μm

LD by gamma scintigraphy, FPF<3.0μm, n=10 inhalers  Newman and Chan, 2008
Deposition of Particles in the Lung

- **Mechanisms of deposition:**
  - Inertial impaction ($d_a > 1 \mu m$)
  - Sedimentation
  - Diffusion ($d_a < 1 \mu m$)
  - Interception

- **Deposition in the respiratory regions:** $d_a = 1 \text{-} 3 \mu m^*$

- **Aerodynamic diameter $d_a$:**
  
  \[
  V_{TS} = \frac{\rho_p d_e^2 g C_c}{18 \eta \chi} = \frac{\rho_0 d_a^2 g C_c}{18 \eta} \quad (R_e < 1)
  \]

  \[
  \Rightarrow d_a = d_e \cdot \left(\frac{\rho_p}{\chi}\right)^{1/2}
  \]


$V_{TS}$: terminal settling velocity; $d_e$: geometric diameter; $\rho_p$: particle density; $\rho_0$: unit particle density ($1 \ g/cm^3$); $\eta$: viscosity of atmosphere; $\chi$: shape factor; $C_c$: slip correction factor
Regional deposition-fraction curves
US-NCRP (Phalen et al., 1991)

Swift et al., 2007
Computed velocity vector field – Control Case

Musante and Martonen, 2001
Computed velocity vector field at a carinal ridge with model tumor

Musante and Martonen, 2001
In Silico Morphology

Mouth (Oral Cavity)

Larynx

ET

TB

PU

Apiou-Sbirlea et al., 2008
In Silico Morphology: Idealized


Apiou-Sbirlea et al., 2008
In silico Model
(Apiou-Sbirlea et al., 2008)

- Data presented for three regions
  - A Trachea
  - B Tracheobronchial
  - C Pulmonary

- Breathing conditions
  - Tidal volume 1L
  - Frequency 7.5 breaths/min

- Plots
  - x- axis, Aerodynamic diameter (Dae, $\mu$m)
  - y- axis, Deposited fraction ($DF_x$)
**In Silico Model Validation: Particle Deposition in MALES (T)**

![Graph showing measured and simulated DF_T values against Dae (µm).](image)

**Conditions:**
- TV = 1000 ml
- f = 7.5 breaths/min
- Q = 250 ml/s

**In Silico Model Validation: Particle Deposition in MALES (TB)**

Conditions:
- TV=1000ml
- f=7.5 breaths/min
- Q=250ml/s

Heyder et al. (1986), J. Aerosol Sci., 17(5):811-825
In Silico Model Validation: Particle Deposition in MALES (PU)

Heyder et al. (1986), J. Aerosol Sci., 17(5):811-825
Complicating Factors In vivo
Schematic Representation Showing Cascade of Events Following Exposure to Allergen Leading to Early and Late Phase Bronchoconstriction and Pharmacotherapeutic Points of Intervention
Conclusions

- Delivered dose and aerodynamic particle size are the most important measure of in vitro performance of OIDP.
- Flow rate dependence of delivery from DPIs (function of resistance) must be assessed to fully understand performance but cascade impactors cannot be used to simulate *in vivo* performance.
Conclusions

- Imaging techniques exist that are more or less
  - Accurate/Precise
  - Sensitive
  - Costly
  - Physiologically relevant (2D/3D)

- Computer models exist based on
  - Fundamental mathematics of particle behavior
  - Computational fluid dynamics
Potential Complicating Factors

- Clearance mechanisms
- Target Receptors
  - Region of Lungs
  - Region of the Cell
- Disease State
Broad Bioequivalence Questions

- Relevant in vivo “test”
  - Anatomically
  - Patient Use
  - Statistically Discriminating

- Suitable models
  - Anatomical
  - Imaging
  - Mathematical
Specific Questions

- In vivo approaches to Demonstrating Bioequivalence (limit to imaging?)
- What approaches are used (2D, 3D, Data presentation by region)?
- Anatomically correct physical models for use with imaging?
- What's the intended purpose of each test?
- Are the tests discriminating?
- Are the tests representative of patient use?
- What's the biological significance of the tests?
- Statistics - what is the metric and what is the target (goal post)?
- Would in silico tests link usefully into in vivo performance?
- Which "limited" in vivo tests might be useful for the in vivo part of an IVIVC (Is this even possible?)?
References


References


Acknowledgements

- Hak-Kim Chan
- Steve Newman
- Gabriela Apiou-Sbirlea
  - Joy Conway
  - John Fleming
  - Gerhard Scheuch
- Ted Martonen