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Goals for Today

• Why should we perform more realistic *in vitro* tests for orally inhaled drug products (OIDPs)?

• Example of a realistic *in vitro* set up for prediction of total lung deposition and APSD characterization

• Review of methods in the literature for capturing inter-subject variability in
  - Population airway geometry
  - Inhalation flow profiles

• Scientific considerations for standardizing more realistic *in vitro* methods
Factors Influencing the Fate of Inhaled Medication

- Inhalation flow profile
- Inhaler design
- Airway geometry
- Local effect
- Systemic effect
Why Should We Perform More Realistic In Vitro Tests for OIDPs?

• *In vivo* methods (Gamma scintigraphy, PK) are expensive

• Current *in vitro* methods (Impactor study of APSD) are designed for quality control purposes and may not be predictive of aerosol deposition in vivo

• Development of more realistic methods have focused on:
  - Realistic inlet airway geometries
  - Realistic inhalation flow conditions

• Realistic *in vitro* methods that could predict *in vivo* drug deposition and variability from inhalers would be an excellent product development tool
Realistic *In Vitro* Method: Concept

In *vivo* deposition predicted by *in vitro* method
Example of *In Vitro* Set Up for *In Vivo* Total Lung Deposition (TLD) Prediction

**Dry Powder Inhaler**

**Plexiglas® Chamber**

**Mouth-Throat (MT)**

**Total Lung Deposition**

**Breath Simulator (ASL 5000®, IngMar inc.)**

**Computer**

**In Vitro – In Vivo TLD Comparison**

Example of a Realistic In Vitro Method for APSD Prediction

Olsson et al., J Aerosol Med Pul Drug Del 26(6), 2013, 355-369
Capturing Population Geometric Variability in Adult Airway Models

APPROACH: Scaling average model to capture size variability

Small (S) (mean-2SD AM)
Medium (M) (mean AM)
Large (L) (mean-2SD AM)

AM – anatomical measure

Capturing Population Geometric Variability in Adult Airway Models

APPROACH: Scaling average model to cover the span of aerosol deposition behavior

Finlay et al., RDD 2010, Vol 1, 185-194
Capturing Population Geometric Variability in Adult Airway Models

APPROACH: Imaging several airway geometries under different inhalation conditions

Olsson Bo et al., J Aerosol Med Pul Drug Del 26(6), 2013, 355-369

Burnell et al., J aerosol Med, 20(3), 2007, 269-281

Adapted from Byron et al., RDD 2013, Vol 1, 85-92
Capturing Inhalation Flow Profile Variability

APPROACH: Representative *in vivo* recorded profiles

Olsson et al., J Aerosol Med Pul Drug Del 26(6), 2013, 355-369
Capturing Inhalation Flow Profile Variability

APPROACH: Statistically derived profiles from *in vivo* recorded profiles

Individual flow profiles (gray; volumetric flow rates entering mouth vs. time) from DPI-trained normal adult volunteers inhaling through an inhalation recorder with an identical airflow resistance to Novolizer. Red profiles are the 10th, 50th (median) and 90th percentile results that illustrate the range of profiles seen across this population. The smoothed profile shown in black is the simulated profile used to program the breath simulator for the *in vitro* comparisons.

Adapted from Byron et al., RDD 2013, Vol 1, 85-92
Capturing Inhalation Flow Profile Variability

APPROACH: Sine wave profiles based on reported average and variability values for inhalation parameters

Based on Results in Delvadia et al, J Aerosol Med Pul Drug Del 25(1), 2012, 32-40

In vivo- medium (range) ; In vitro -mean (range), n=5
Is there a Need for Standardized Models?

FOR DISCUSSION: Standardize idealized models, real geometries, healthy geometry or diseased state, materials for manufacture ??

Adapted from Byron et al., RDD 2013, Vol 1, 85-92
Deposition Prediction May Vary Between the Models

Adapted from Byron et al., RDD 2013, Vol 1, 85-92
Scientific Considerations for Standardizing Realistic \textit{In Vitro} Methods

- \textit{In vitro} models should be selected first based on their \textit{in vivo} predictability and then based on their anatomical representativeness.

- Models should be simplified/idealized, as long as simplification does not compromise the predictability of the model.

- Predictability should be evaluated across the wide range of inhalation products, for example DPIs with different resistances or lung deposition.

- A minimal number of models should be used to represent inter-subject variability.

- Ease of production and precise reproduction of the models should be considered – for example, making the models in metal.

- Standardized inhalation profiles should be developed, corresponding to different airflow resistance, training conditions and disease states.
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