Use of Math Modelling to Understand Delivery of Biopharmaceutical Molecules to the Lung

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9th November 2016

Delivery to the Lung is an Important Route of Delivery for Biopharmacueticals
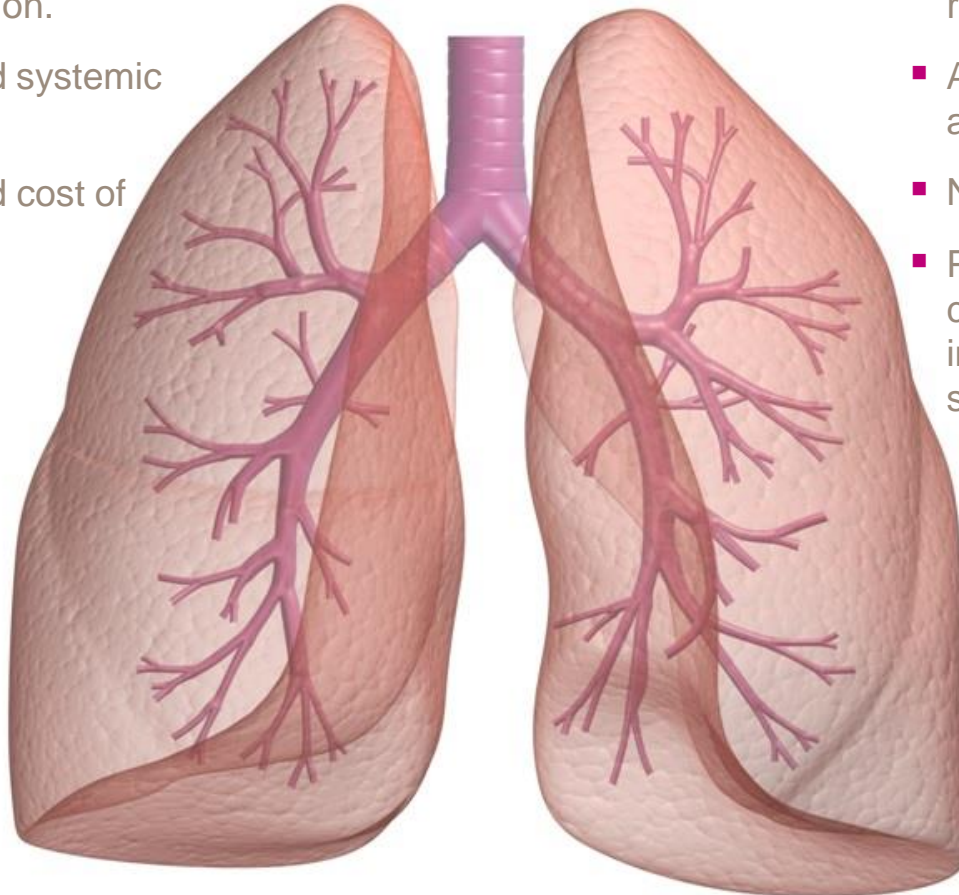
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Treatment of Local Lung Disease

- Reduced dose through local delivery

- Quicker onset of action.

- Potential for reduced systemic side effects

- Potential for reduced cost of goods

E.g. DNase for Cystic Fibrosis

Gene therapy for Cystic Fibrosis / alpha-1-antitrypsin deficiency

Route for Systemic Delivery

- Large surface area and thin cell layer in alveoli result in rapid absorption.

- Absence of extremes of pH and metabolising enzymes

- No first pass liver metabolism

- Potential to provide greater convenience compared to injections. (e.g. cold-chain storage avoidance)

E.g. Insulin

Human Growth Hormone

Delivering Drug to the Lung

Typical Means for Delivery to Lung

- Formation of fine particles containing API together with some excipients, e.g. via spray drying, which are then dosed from a dry powder inhaler by the patient inhalation airflow.

- Delivery of fine droplets containing theAPI in solution or suspension using a nebuliser.

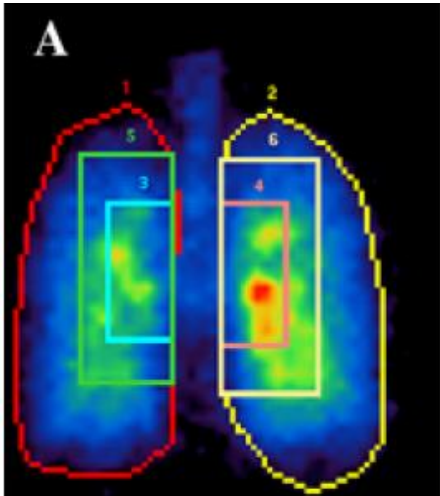Dry Powder Inhalers

Nebuliser
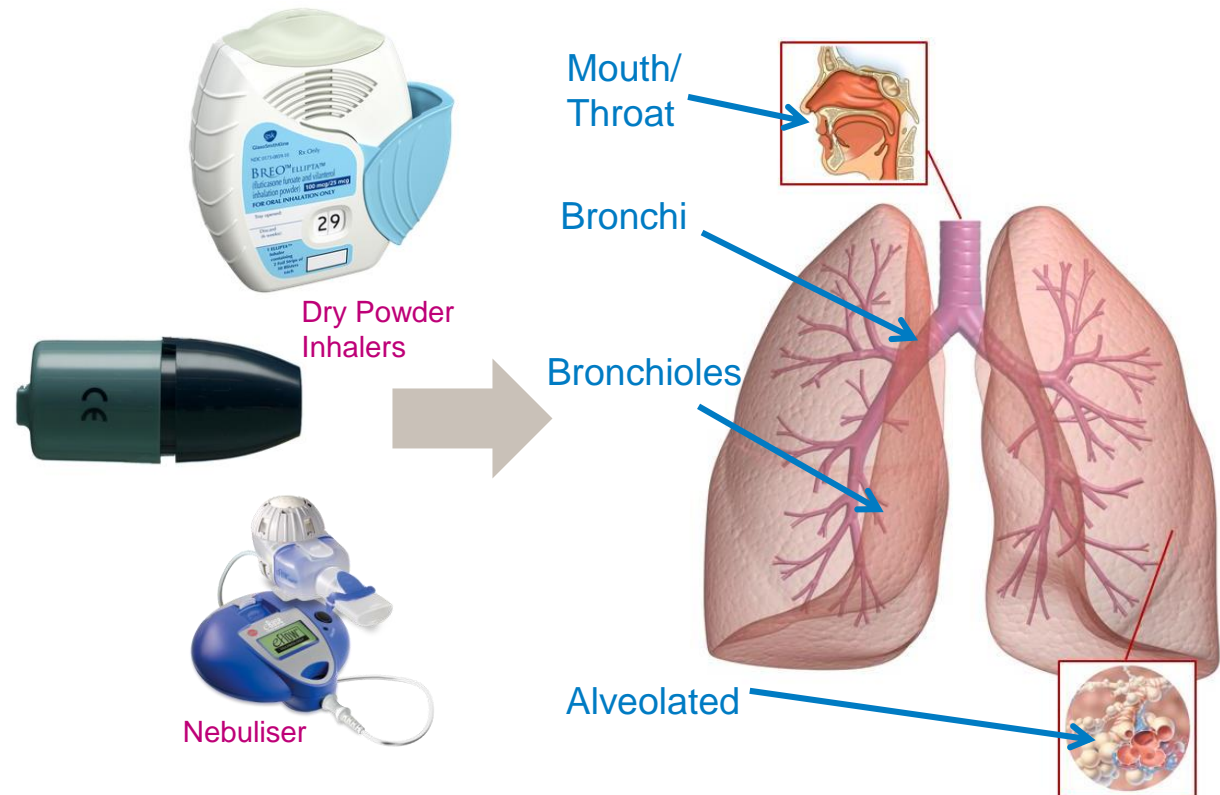
How can we understand where in the lung our drug goes?

Mouth/Throat

Bronchi

Bronchioles

Alveolated

Measuring Lung Deposition
Typical Surrogate Measurement Techniques

Radio-Imaging

Lung Clearance Rates

Bronchi(oles) ciliated and fast clearing

Alveoli – nonciliated and slow clearing
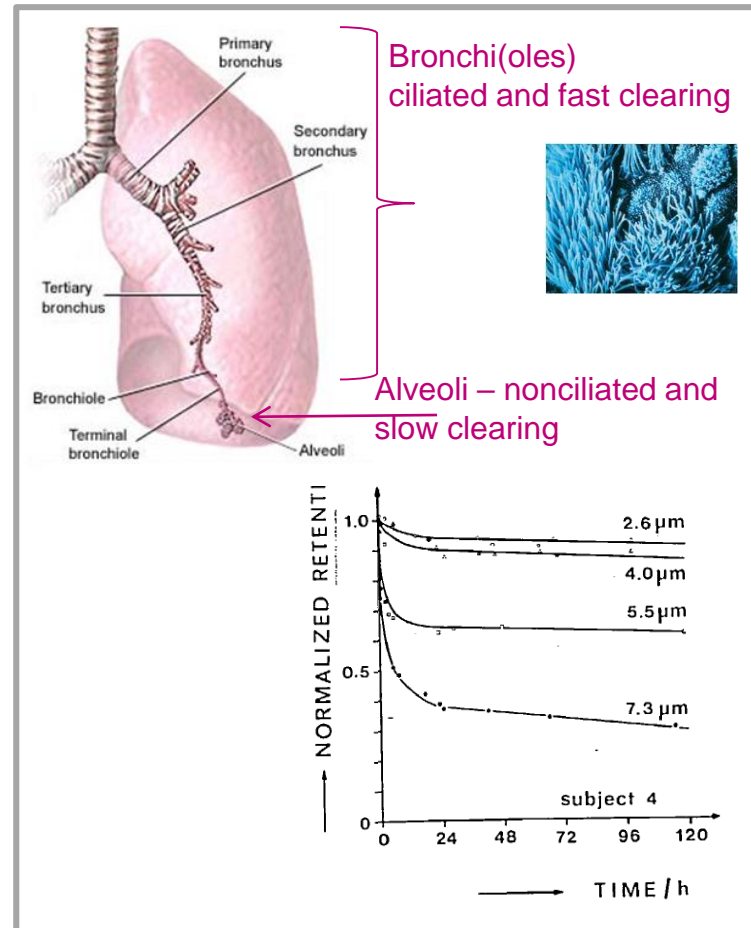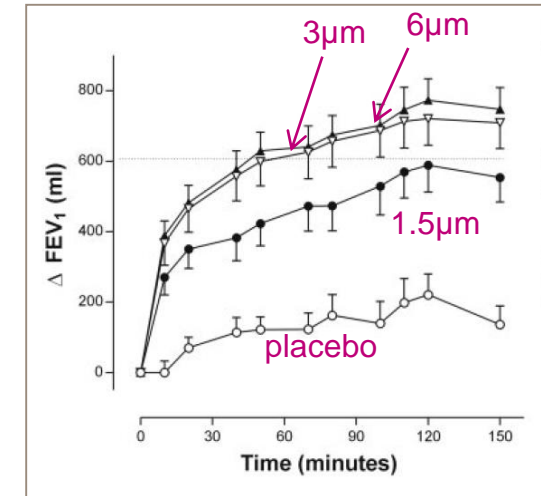
Drug Efficacy

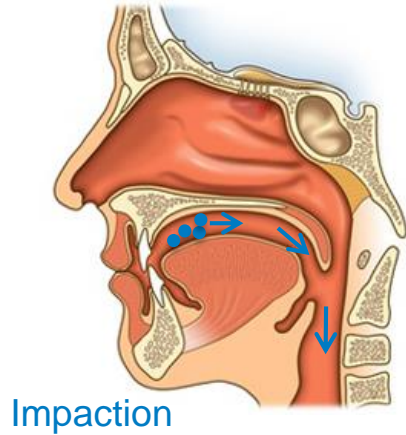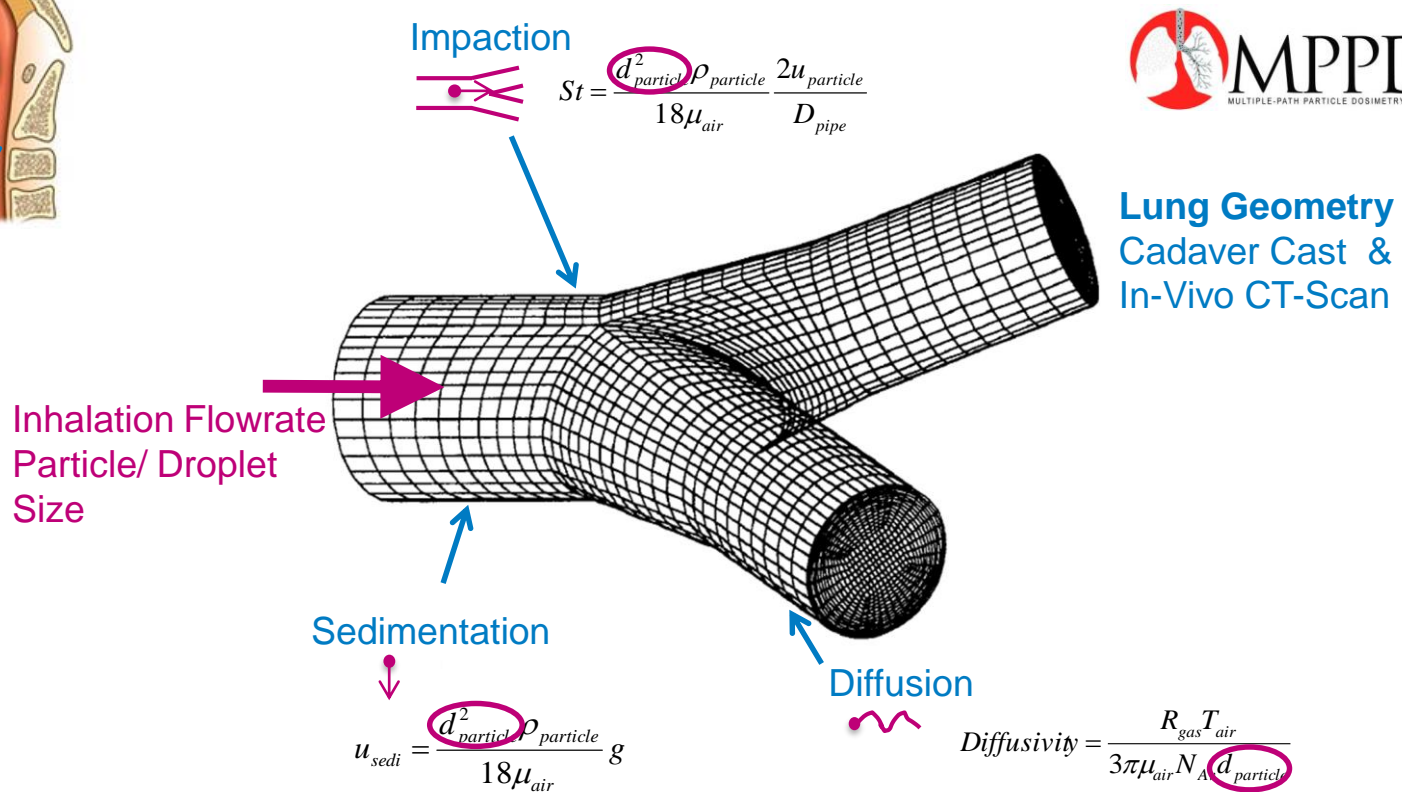**Since measurement is difficult, math models provide a valuable insight into lung deposition trends...**
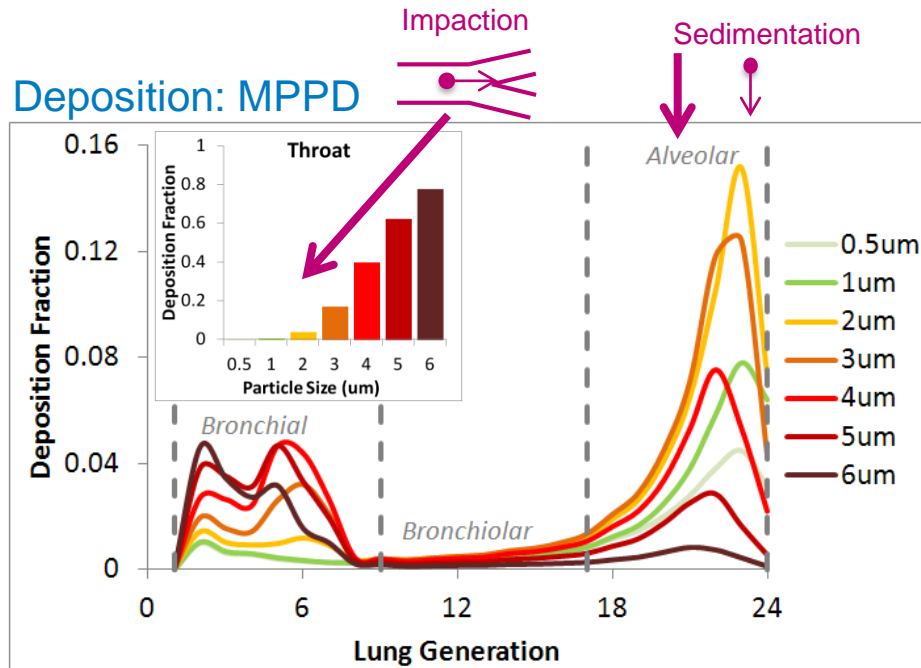
Usmani et al Am J Respir Cric Care Med 172:1497 (2005), Stahlhofen et al American Industrial Hygiene Association Journal 41:385 (1980), Usmani et al J Appl Physiol 95:2106 (2003)

MPPD Lung Deposition Math Model

Mouth / Throat

Impaction

Lung: Bifurcating Airways

Impaction

$$St = \frac{d_{particle}^2 \rho_{particle}}{18\mu_{air}} \frac{2u_{particle}}{D_{pipe}}$$

Lung Geometry
Cadaver Cast &
In-Vivo CT-Scan

Inhalation Flowrate
Particle/ Droplet
Size

Sedimentation

$$u_{sedi} = \frac{d_{particle}^2 \rho_{particle}}{18\mu_{air}} g$$

Diffusion

$$Diffusivity = \frac{R_{gas}T_{air}}{3\pi\mu_{air}N_A d_{particle}}$$

Lung Deposition Physics
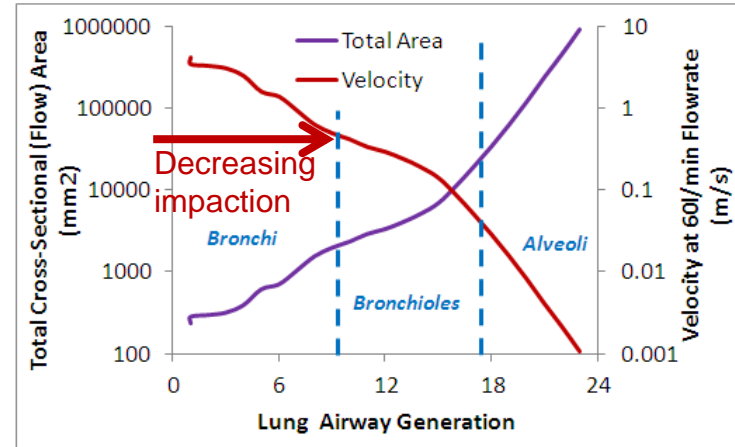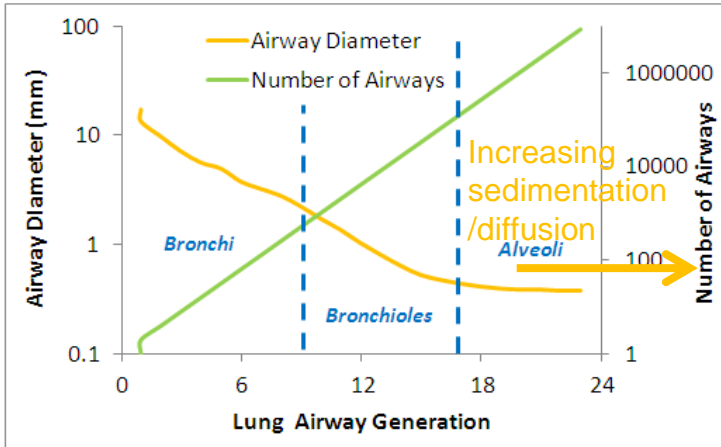
Model Validation against In-Vivo Data
The ICRP66 Lung Deposition Measurements

Throat

Fast-Cleared Lung Deposition

Slow-Cleared Lung Deposition

MPPD – 3 Patient Lungs
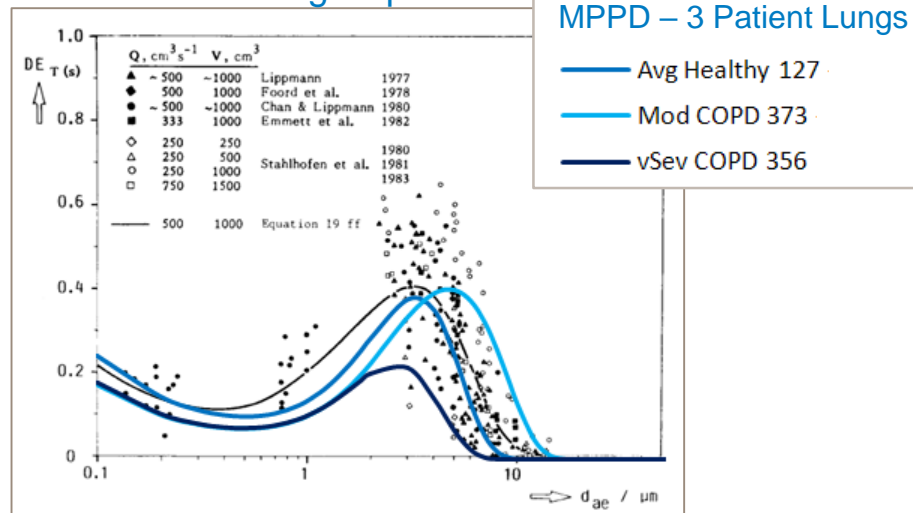- Avg Healthy 127
- Mod COPD 373
- vSev COPD 356

- In-vivo inhalation of monodisperse insoluble radioactive tracer particles

- Lung Regions categorisation/assumption (not wholly correct, but useful guide):-
  – Fast-Cleared (mainly Bronchi/Bronchioles)
  – Slow-Cleared (mainly Alveolated airways)

- Data for 15-45l/min inhalation flowrate. Semi-empirical, semi-theoretical curve based on 30l/min.

- Meta-analysis of multiple studies used in ICRP66 lung model.

Stahlhofen et al Journal of Aerosol Medicine (1989) 2(3): 285-308

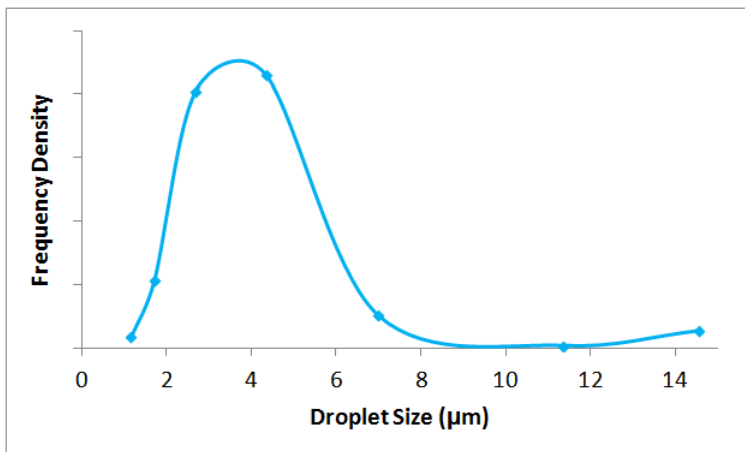# Example 1: A Protein for Treatment of Local Lung Disease

Product Form

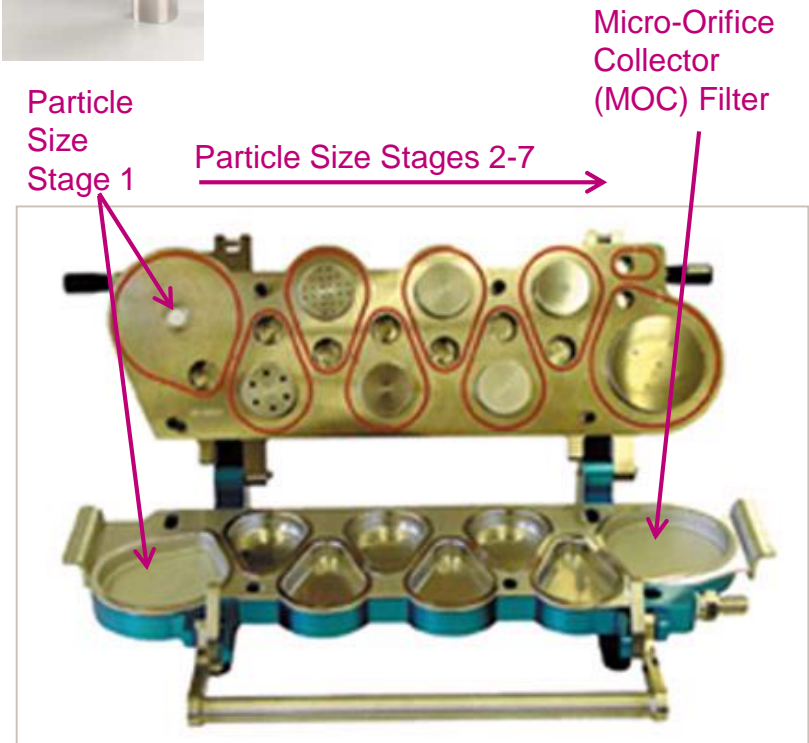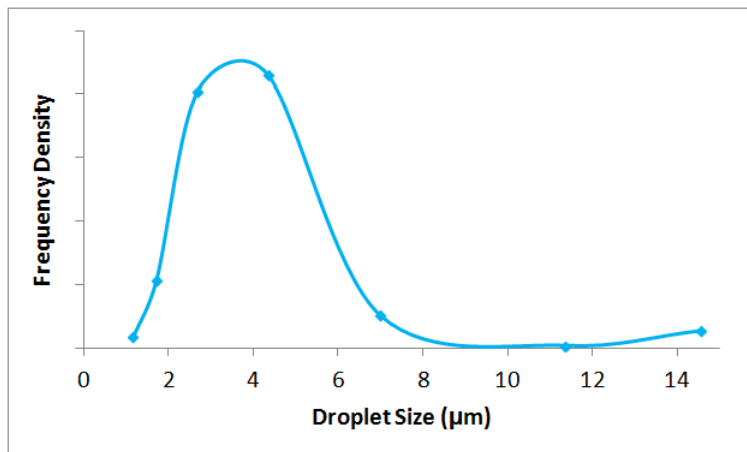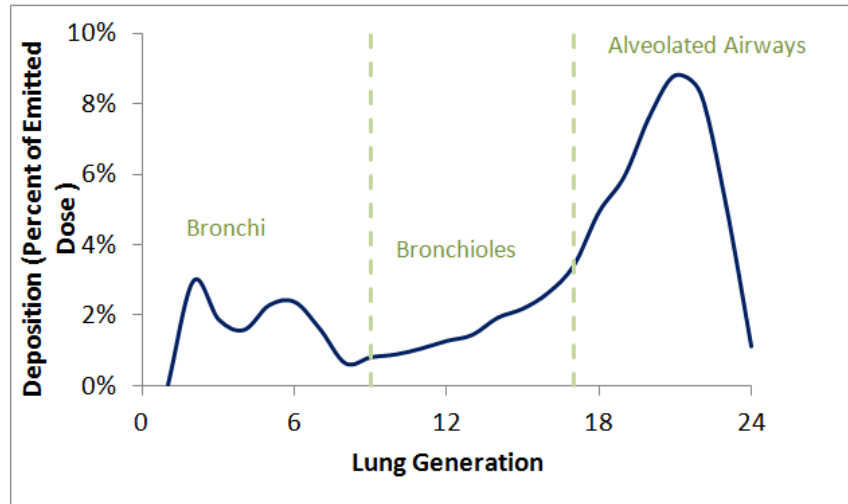- API solution delivered from a nebuliser

Model Inputs

- Aerodynamic particle (droplet) size measurements using an Next Generation Impactor (NGI).

- Gentle 'resting' breathing rates (slow 15l/min and shallow 626ml).
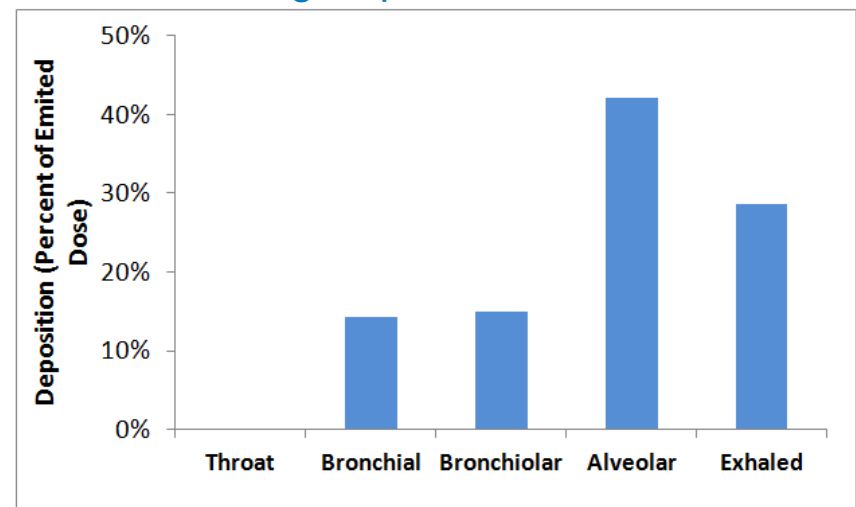
- Healthy average lung model

Droplet Size Distribution

Impactor "Throat"

Micro-Orifice Collector (MOC) Filter

Particle Size Stage 1

Particle Size Stages 2-7

Next Generation Impactor (NGI)

Example 1: A Protein for Treatment of Local Lung Disease

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Lung Deposition Detailed View

Droplet Size Distribution

Predicted Lung Deposition

Example 2: A Peptide for Delivery to Systemic Circulation Via The Lung

Product Form

- Lung delivery preferred over injection since product is targeted at developing markets where cold-storage facilities may be inconsistent / absent.

- API spray dried with Excipient A (hydrophobic shell-forming excipient) then blended with a Excipient B (carrier excipient)

- Final blend delivered from a Dry Powder Inhaler
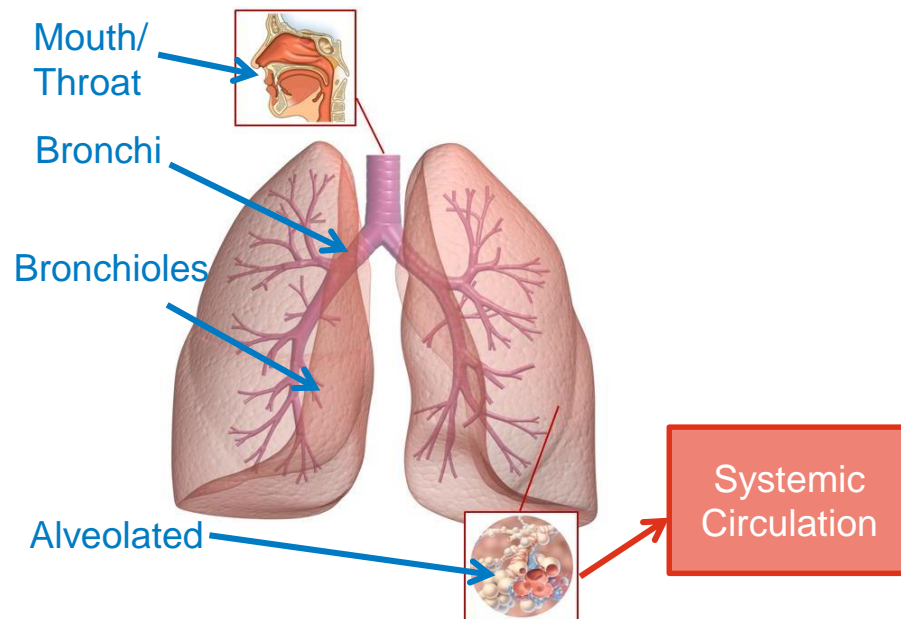
How Does Formulation Affect Lung Delivery?

Does that Performance Change on Stability for 1 month?

Mouth/Throat
Bronchi
Bronchioles
Alveolated
Systemic Circulation

Model Inputs

- Aerodynamic particle size measurements using an Next Generation Impactor (NGI).

- Deep (2679ml) and fast (53.58l/min inhalation with breath hold (3s).

- Healthy average lung model

Factors Affecting Delivery from a Dry Powder Inhaler

How can Formulation & Stability Storage Affect Lung Delivery?

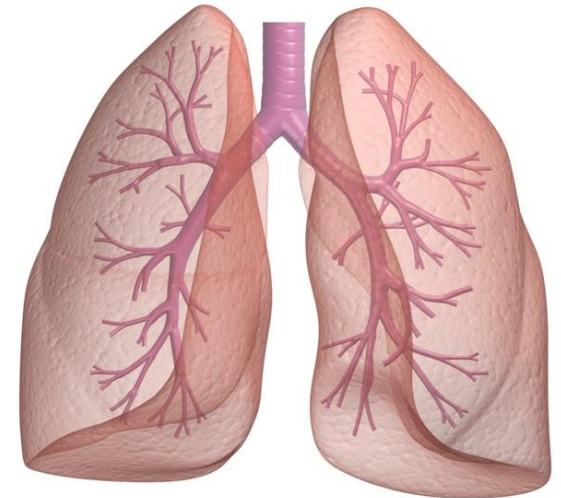**Aerosolisation / Deaggregation of Powder by Patient Inhalation**

Initial Packing

Surface Roughness

Van der Waals

Airflow

Electrostatic Charge

Particle Size

Moisture
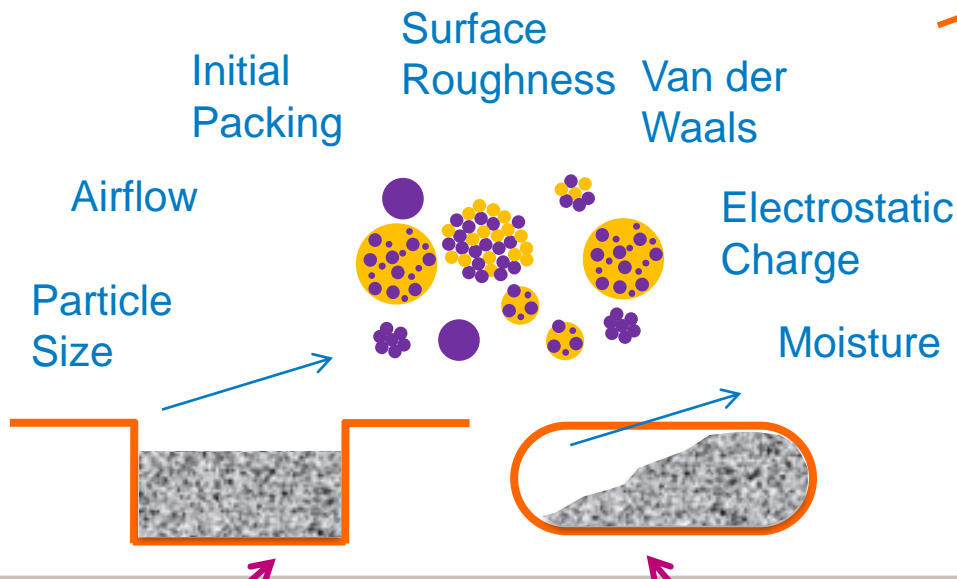
Formulation
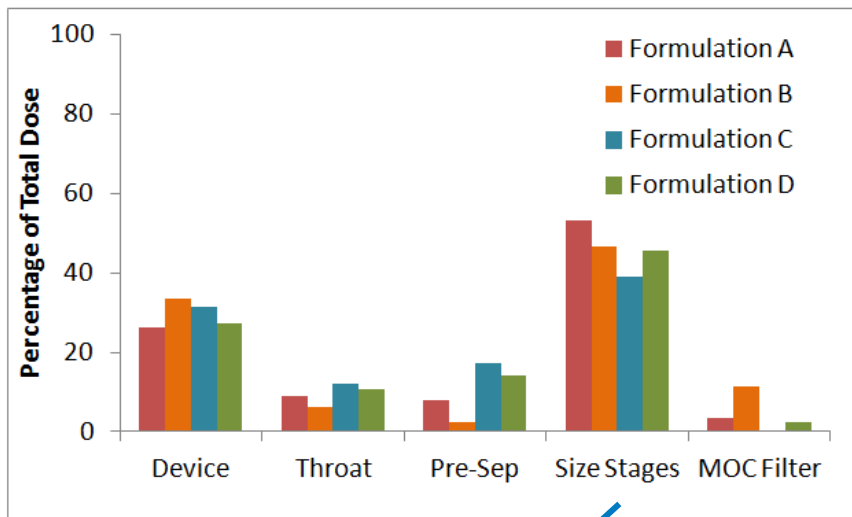
Stability Storage

Emitted Particle Size

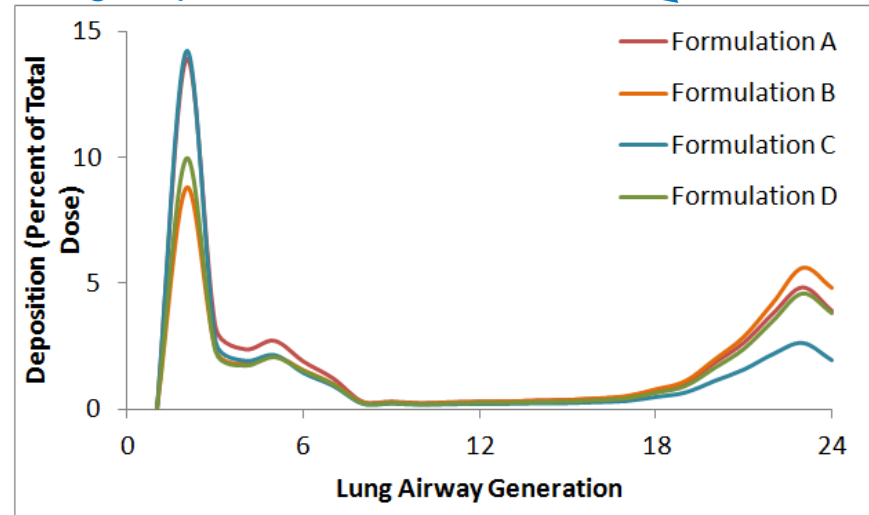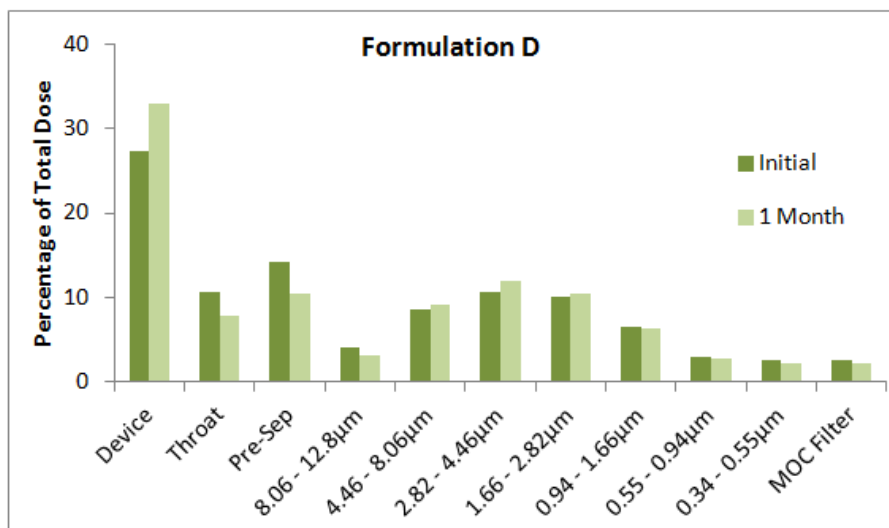**Lung Delivery**

Comparison of Lung Delivery for 4 Formulations
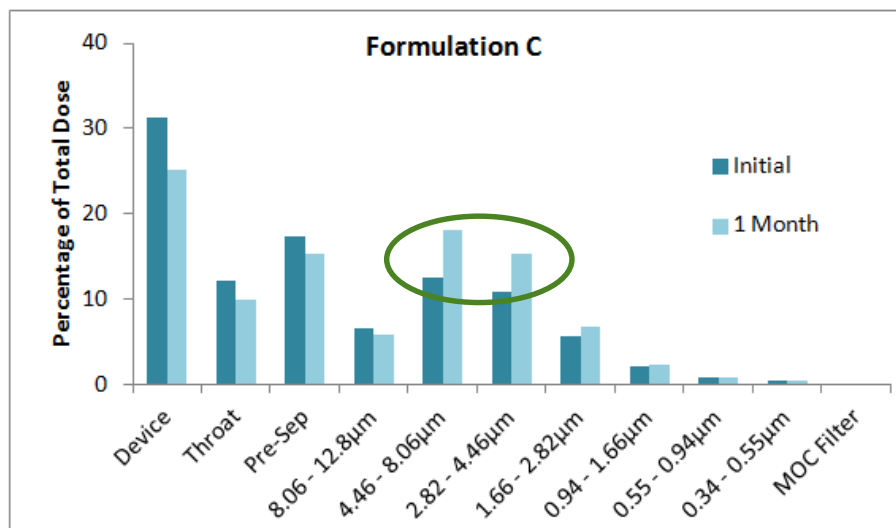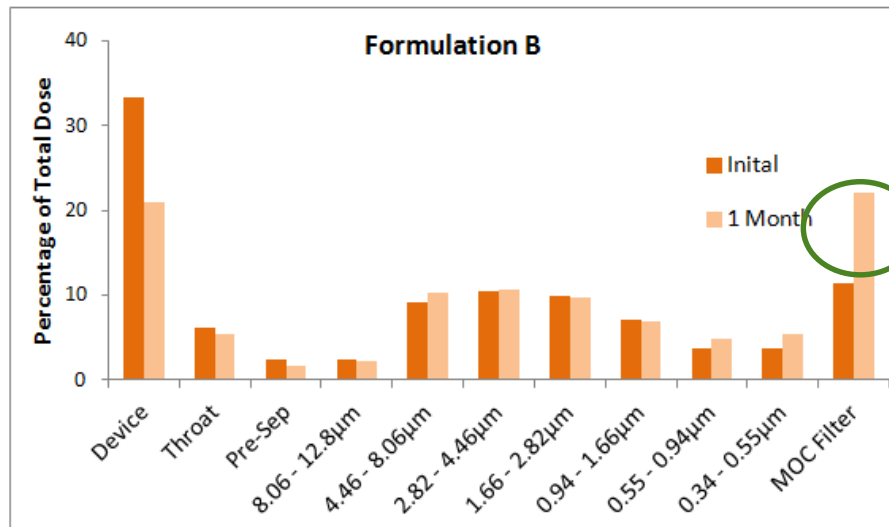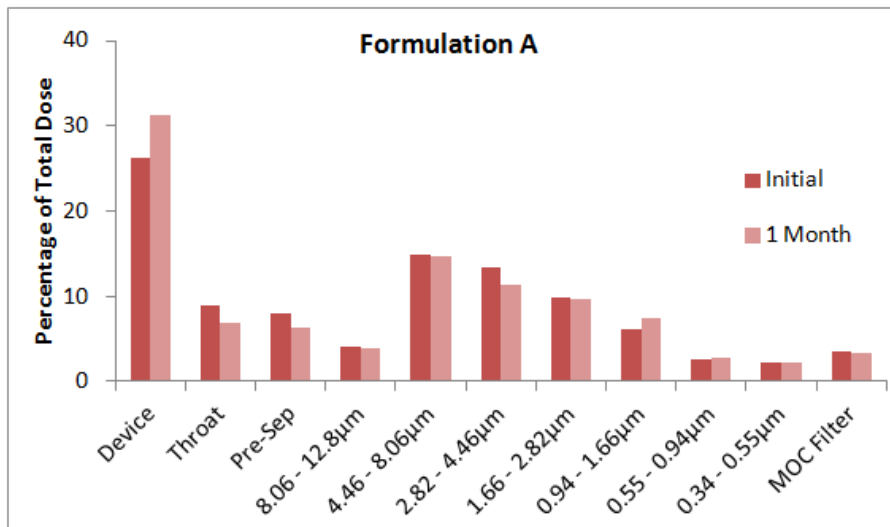

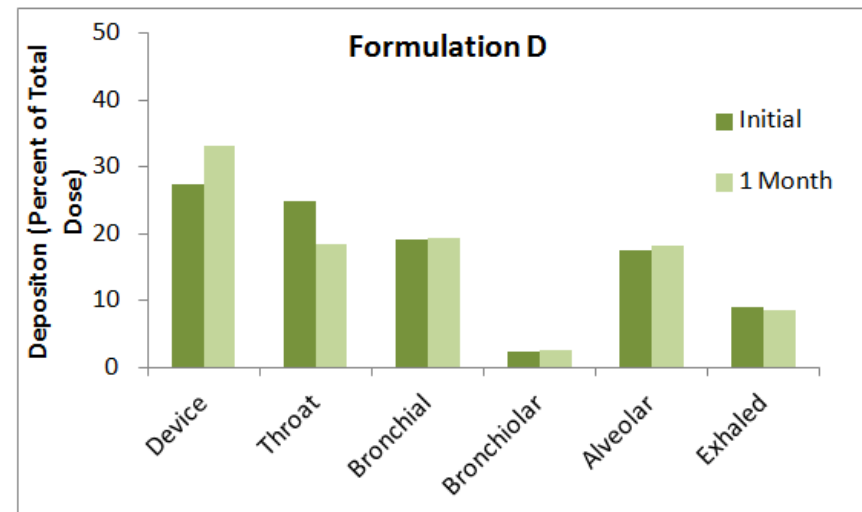
NGI Particle Size Data

Predicted Lung Deposition
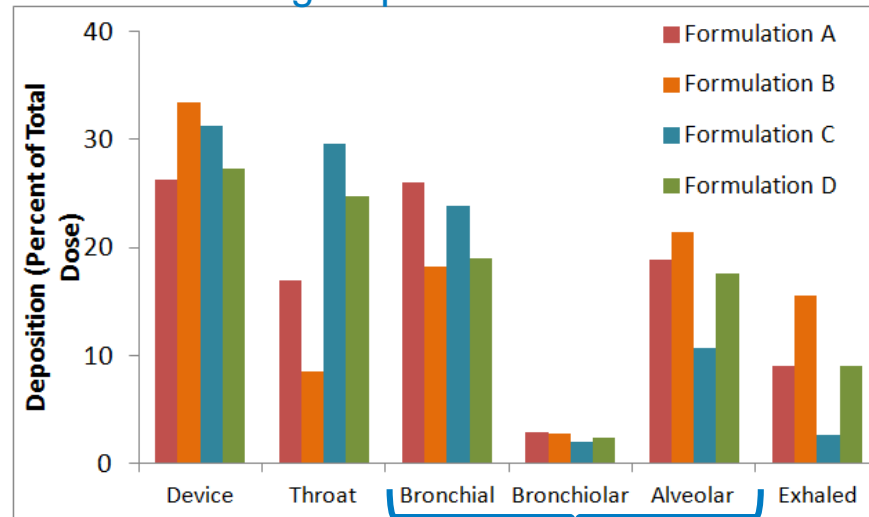
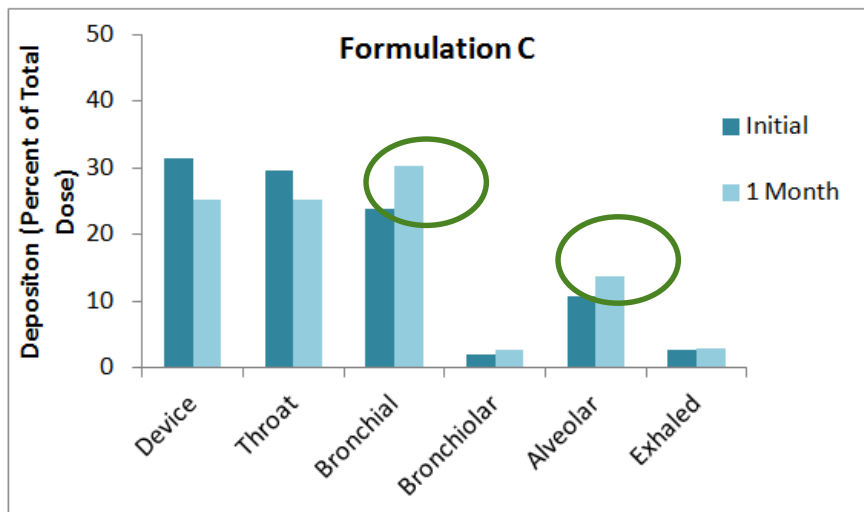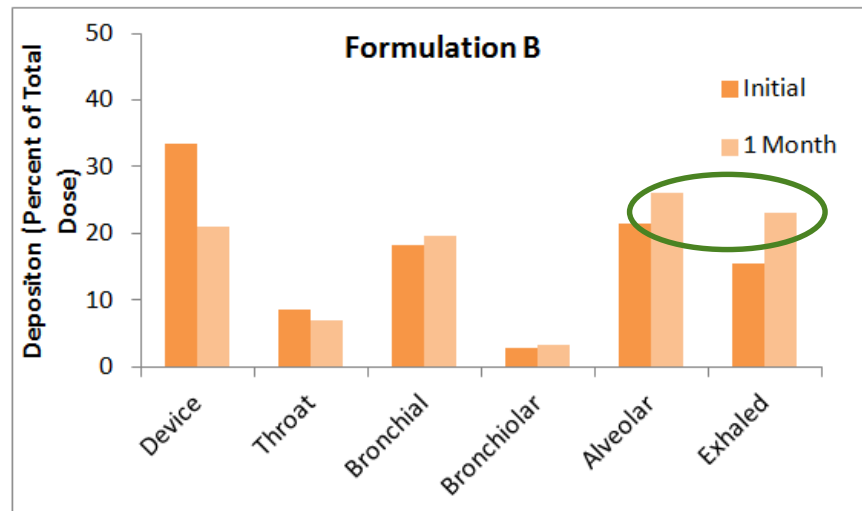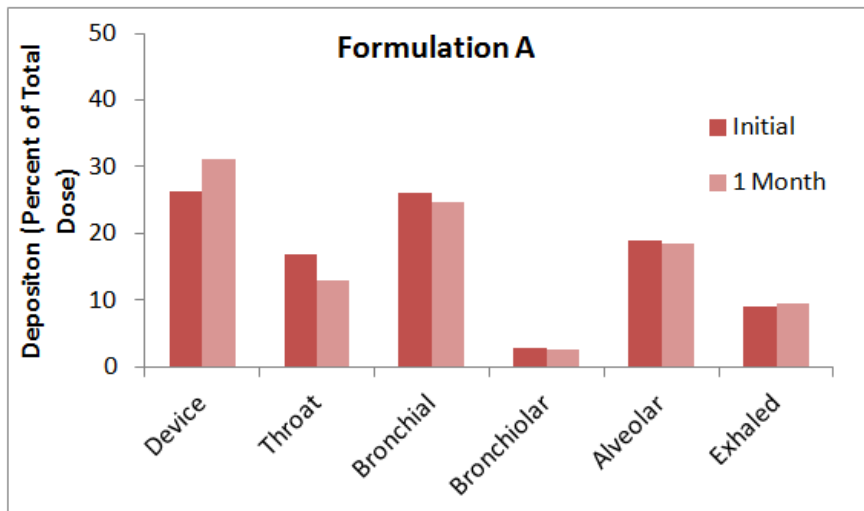## Particle Size Distribution
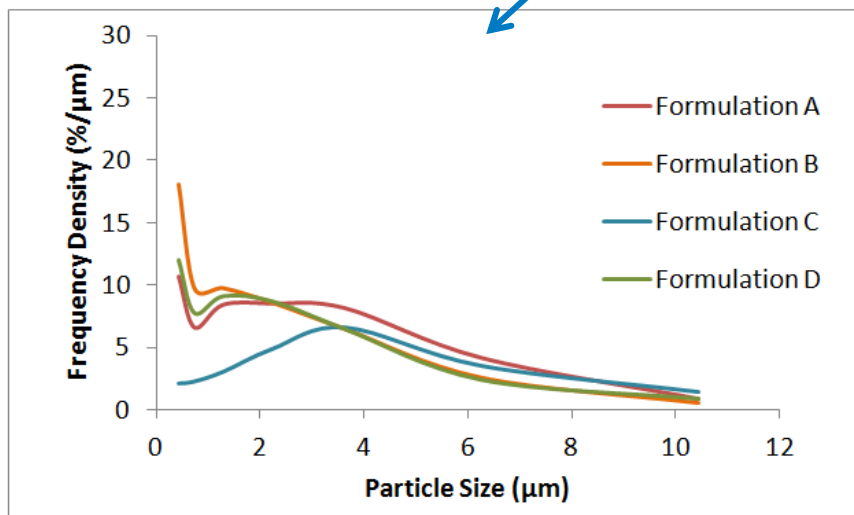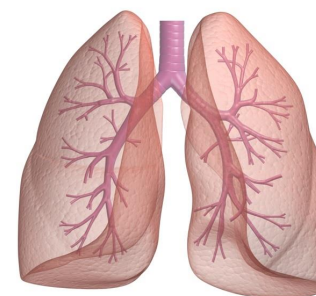
Lung Deposition Detailed View

Impact of Stability on Particle Size

Impact of Stability on Lung Delivery

Summary

- The lung is an important means of delivery for biopharmaceuticals.

- Understanding lung delivery is challenging since our understanding of the highly variable processes of powder aerosolisation and lung deposition are incomplete.

- However math models provide a helpful guide in interpreting experimental data and giving an estimate of lung deposition trends that are based on underlying physics rather than intuitive judgements.

- The impact of factors such as formulation choices or long-term storage can be investigated and help guide product design decisions.

Thank you

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do more
feel better
live longer