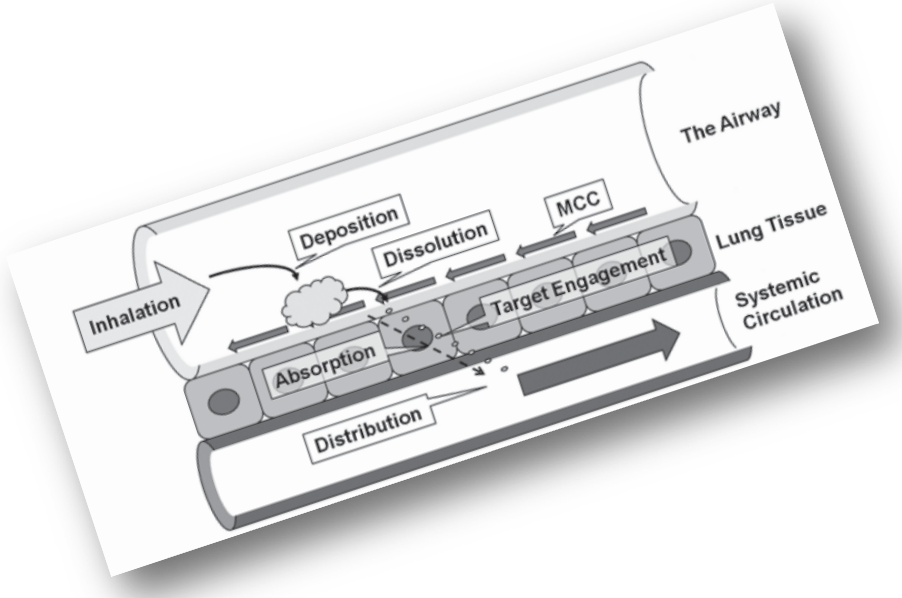
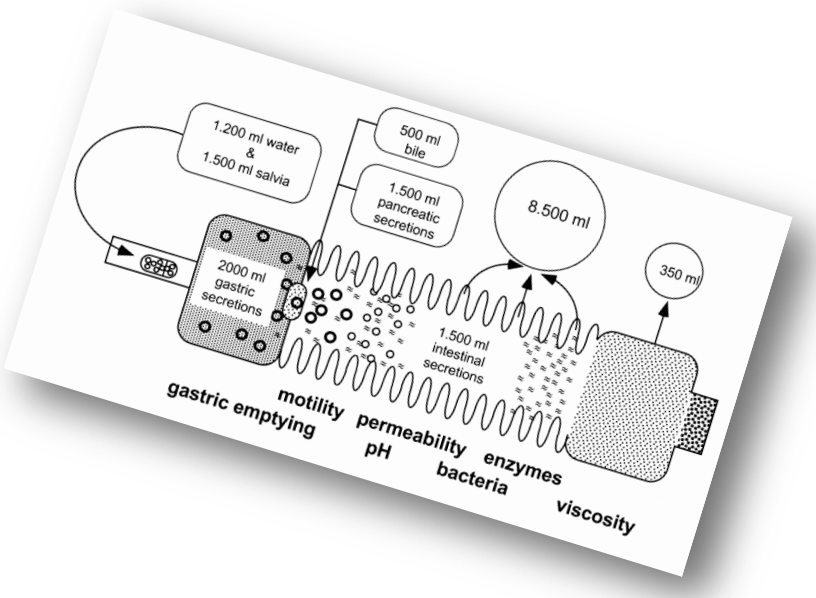
Biopharmaceutical Classification of Inhaled Medicines: Development of an iBCS

Jayne E Hastedt, PhD
Co-Chair of PQRI BTC iBCS Working Group





Outline

- The Oral BCS (giBCS)
- Developing a Classification System for Inhaled Medicines
- Determining the Classification Parameters
- Generating iBCS Classification Grids and Modelling
- Summary and Next Steps

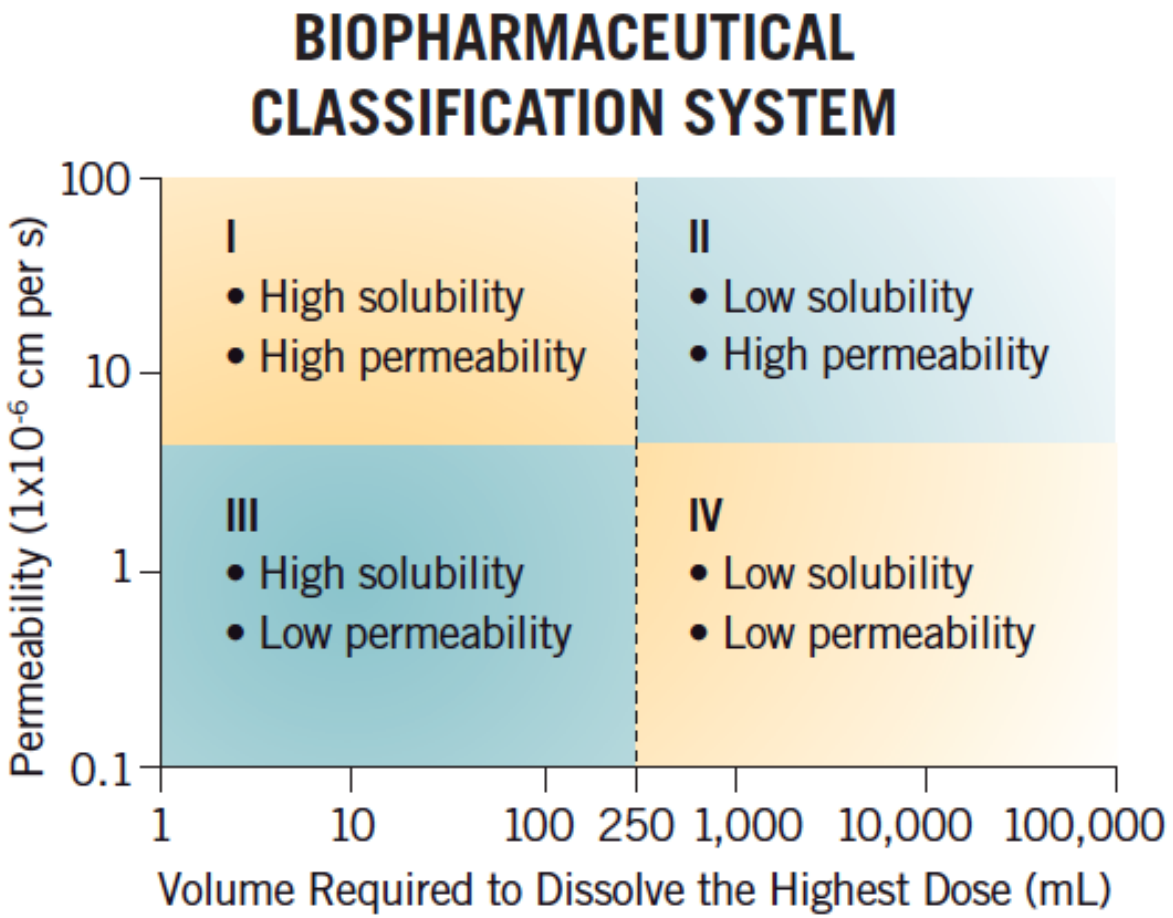
Work in Progress

What is the BCS?

- The Biopharmaceutics Classification System (oral BCS or giBCS), is a science-based classification system used and developed for orally administered, immediate release drugs.
- The giBCS uses three simple, derived dimensionless numbers that take into account the dissolution, dose, and absorption for a particular drug substance.
- The giBCS is focused on oral drugs with systemic activity.
- Using the *dose number*, *dissolution number*, and *absorption number*, one can classify drugs based on solubility and permeability.

Amidon, G. L.; Lennernas, H.; Shah, V. P.; Crison, J. R.
A Theoretical Basis for a Biopharmaceutical Drug Classification: The Correlation of in vitro Drug Product Dissolution and in vivo Bioavailability. Pharm. Res. 1995, ***12****: 413-420*

BCS For Orally Administered Drugs (giBCS)



Benefits:

- Drug discovery/design
  - Screening techniques
- Formulation strategies
  - Addressing the “lows”
- Biowaivers
  - BCS Class I
  - BCS Class III
- IVIVC Potential
  - BCS Class II
  - BCS Class I

FDA. Guidance for Industry Guidance for Industry Waiver of In Vivo Bioavailability and Bioequivalence Studies for IR Solid Oral Dosage Forms Based on BCS; 2015.

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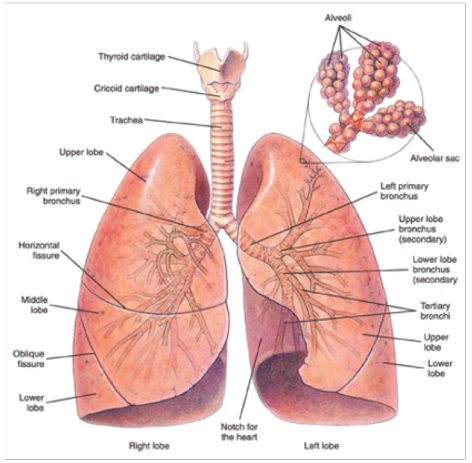
Can a BCS-like classification system be developed for inhaled medicines?



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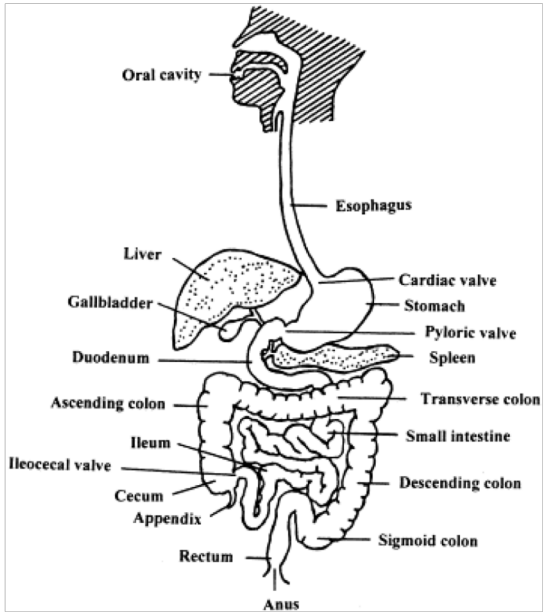


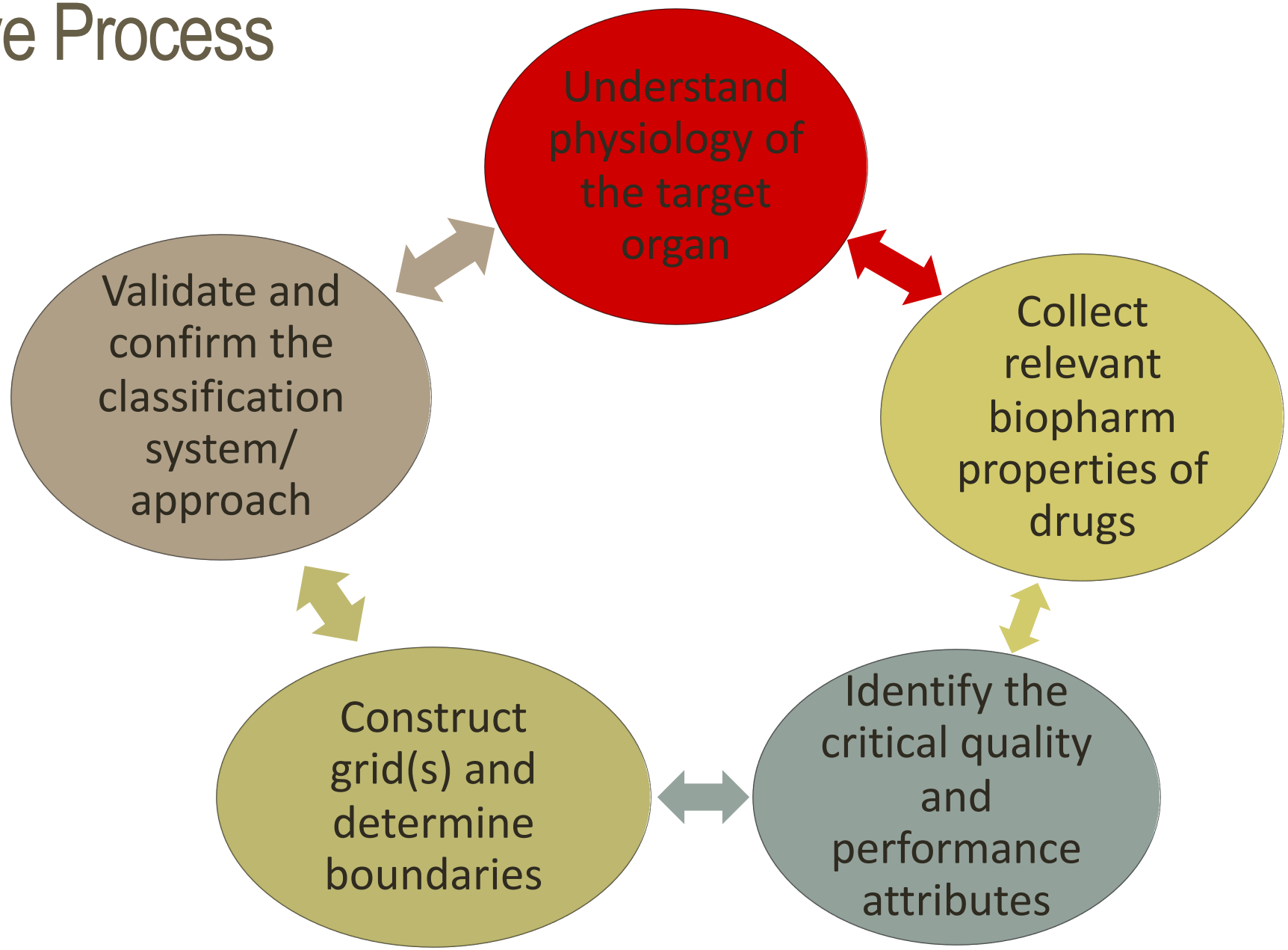
Developing a Classification System for Inhaled Medicines

- Goal:
  - Develop a physiologically-based pulmonary drug product classification system based on biorelevant drug and product attributes.
- Scope:
  - The classification system will be based on scientific principles, current understanding of pulmonary physiology, and relevant phys chem properties.
  - Initial focus will be on locally acting therapeutics and will exclude antibiotics, systemic delivery, metabolized drugs (pro-drugs), and protein therapeutics.
  - Initial drug and product attributes to be evaluated:
    - solubility and dissolution rate
    - dose and deposition
    - absorption and disposition.

Developing an iBCS for Inhaled Medicines – Value and Challenges

- Value:
  - Generate a common set of tools to aide pulmonary drug product development efforts.
  - De-risk the development of inhaled medicines.
  - Support bioequivalence assessment and generic product approvals for pulmonary drug products.
- Challenges:
  - Inability to measure local drug concentrations *in vivo*.
  - Limited data sets – the number of inhaled medicines is small compared to oral medicines and complete data sets are often not published.
  - A complete list of harmonized biorelevant testing and characterization techniques are lacking for pulmonary drugs.
  - Simulation approaches are still under development and any model will require validation.

Developing a Biopharmaceutics Classification System is an Iterative Process



Determining the Drug and Product Classification Parameters

Start with the giBCS parameters and modify based on lung physiology and product understanding

Properties of The Tube (Oral GI) and the Tube + Bucket (Lung)

Property	GI	Lung
Description	"Tube"	"Tube + Bucket"
Typical site of action	Systemic	Local
Transit or Residence time	199 minutes (mean intestinal transit time)	1 – 24 hours
"Fluid" volume	50 – 1,100 mL Average: 500 mL	15 – 70 mL
"Fluid" properties	Bulk liquid Location-specific pH	Surface fluid layers with location-specific viscosity, composition and thickness
pH Range*	Range: 1.4 – 7.4 Stomach: 1.4 – 2.1 Duodenum: 4.4 – 6.6 Ileum: 6.5 – 7.4	6.69 ± 0.07 (~5 in macrophages)
Dose	mcg – 1000mg	10 mcg – 50 mg

*fasted state

Adapted from Hastedt, J. E. Inhalation Magazine. 2014, pp. 18–22.

Rennard, S.I. et al., Estimation of volume of epithelial lining fluid recovered by lavage using urea as marker of dilution", J. Appl. Physiology, 60, 532-538.

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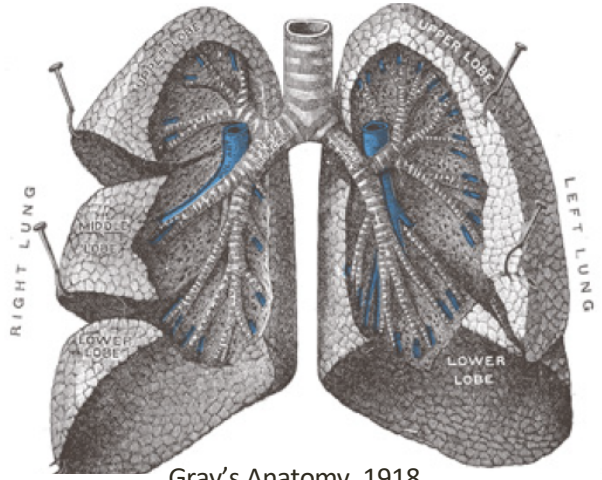
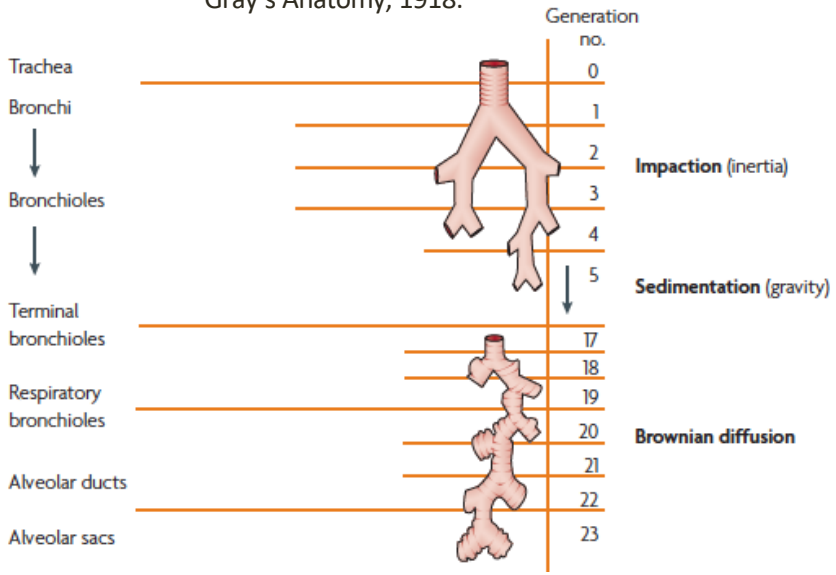
The Lung Anatomy – approximate ranges – everyone is different!



Gray's Anatomy, 1918.



Conducting (Central) Zone

- Trachea
- Bronchi
- Bronchioles
- Terminal Bronchioles
- Volume: ~175 cm^3
- Surface Area: ~1-2.5 m^2

Respiratory (Peripheral) Zone

- Respiratory Bronchioles
- Alveolar Ducts
- Alveoli
- Volume: ~5,000 cm^3
- Surface Area: ~60 – 140 m^2

Key Learning:

- The surface area of the peripheral airways >> than the central airways

These values are estimates based on various references/authors. Diseased lungs are different

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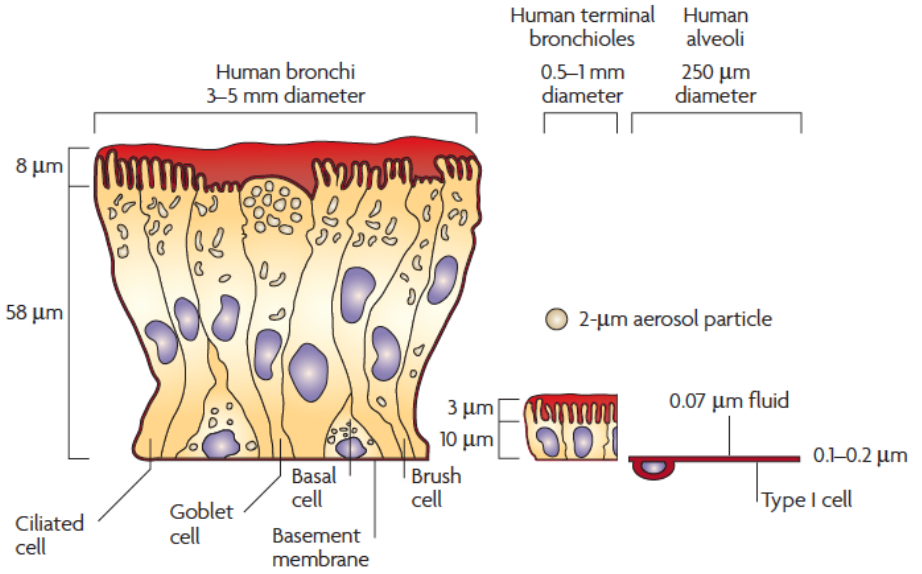
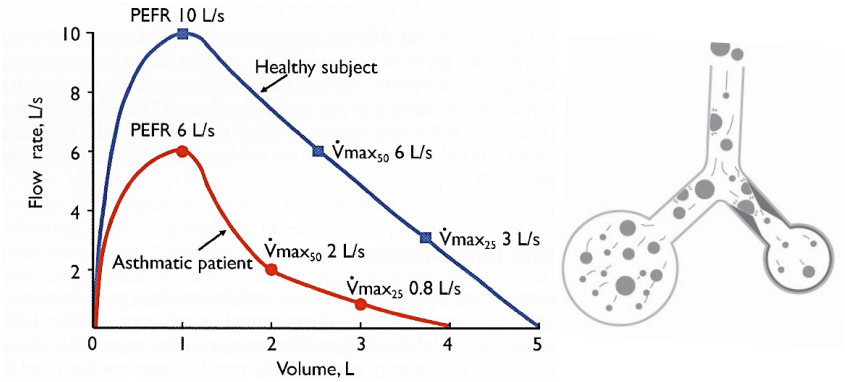
The Lung Anatomy by Region

The upper airways (conducting zone) are covered with a non-Newtonian layer of mucus – thickness varies by location.

- The upper airways are ciliated.

The lower airways (alveoli/respiratory zone) are covered with a thin layer of Newtonian lung surfactant-rich film.





Key Learnings:

- Clearance mechanisms vary by region.
- "Liquid" composition and thickness vary by region.

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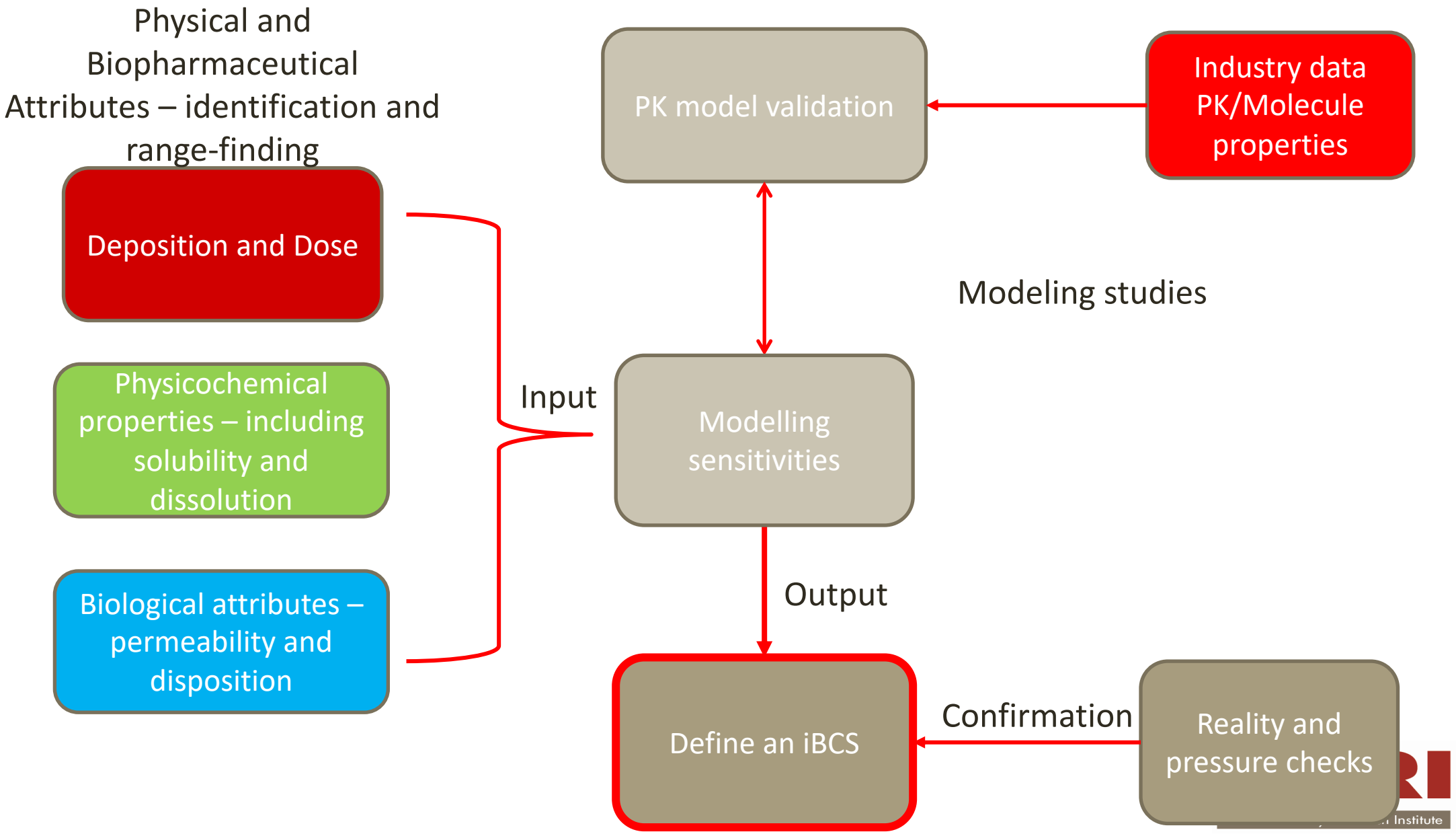
Wang, Y.-B.; Watts, A. B.; Peters, J. I.; Williams, R. O. The impact of pulmonary diseases on the fate of inhaled medicines--a review. Int. J. Pharm. 2014, 461, 112–28.

The iBCS Development Process

- Development of a pulmonary drug product classification system will be based on critical attributes for pulmonary drugs and drug products.
- Critical attributes for pulmonary drugs:
  - Dose and deposition
  - Dissolution and solubility
  - Permeability and tissue interaction (disposition)
  - General phys chem properties (diffusion, charge, partition coef, etc.)
- Classify measurable attributes onto grid(s)
  - Use PBPK and compartmental PK models to confirm classification (sensitivity) and application (validation) through simulation studies.
- Outcomes:
  - Identify attribute “Rule of Thumb” assumptions and a classification grid with defined boundaries.
  - Identify modeling tools for BE assessment.

The iBCS Process Map



Potential Classification Grids for Inhaled Medicines

Pulmonary physiology + Biopharmaceutics + CQAs

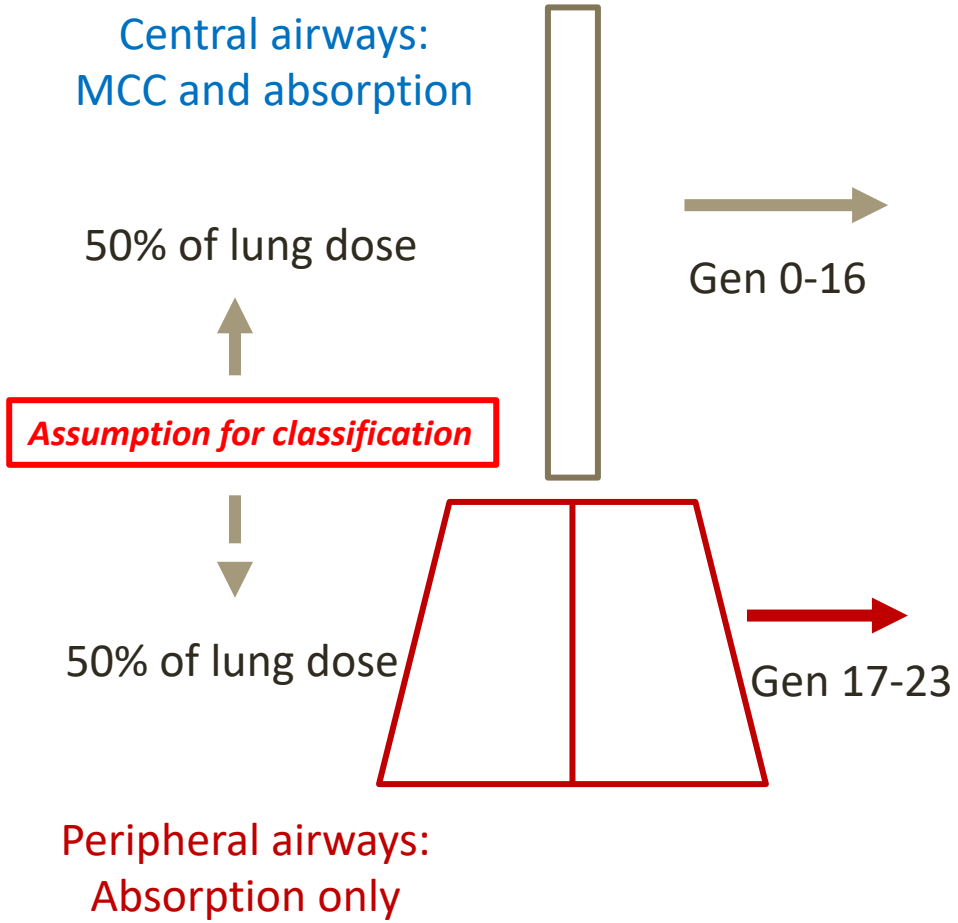
Fundamental iBCS Operating Assumptions

- For any given drug:
  - The regional dose and deposition pattern, dissolution rate, and tissue interactions (including permeability) will dictate the local concentration and retention time within the lung.
- In the case when two drug products contain the same drug and excipients:
  - Identical regional dose deposition patterns and dissolution rates will ensure the same local concentrations within the lung.

Developing the iBCS Grids – Further Assumptions

- Parameters:
  - Solubility/dissolution rate and permeability/retention time are the key properties impacting local drug concentrations and systemic exposure.
- Deposition/Dose and Clearance:
  - Deposited dose: 50% central and 50% peripheral of lung dose
  - Dissolved drug is not cleared by MCC; clearance by absorption only in peripheral airways
- Retention Time:
  - Since we cannot measure local drug concentrations and regional binding/transport, we can use MAT (Mean Absorption Time) to describe retention of drug in the lung.
- Since the central and peripheral regions of the lung have different physiological properties, we will need 2 regional classification grids (as a start).

A Conceptual Biopharmaceutics Diagram for the Lung



	Low solubility/ slow dissolution	**High solubility/ fast dissolution**
Central airways: MCC and absorption	Peak absorption rate governed by solubility (driver) and permeability (barrier) – both molecular properties. Extent (AUCc) of absorption governed by balance between absorption and MCC – dose independent	Peak absorption rate (Cmax) governed by dose and permeability. Extent (AUCc) likely to be = dose in conducting airways unless permeability is very low, dose is high, or drug is metabolized
Peripheral airways: Absorption only	Peak absorption rate (Cmax) governed by rate of dissolution, Extent (AUCp) = peripheral dose unless drug is metabolized	Peak absorption rate (Cmax) governed by dose and permeability. Extent (AUCp) likely to be = peripheral dose unless drug is metabolized

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Proposed Regional iBCS Grids

Central Compartment

	Low Solubility (non-sink)	High Solubility (sink)
Low Permeability	Incomplete and very slow absorption	Mostly complete and slow absorption
High Permeability	Incomplete and slow absorption	Complete and fast absorption

Peripheral Compartment

	Low Solubility (sink)	High Solubility (sink)
Low Permeability	Complete and dissolution-rate driven absorption (very slow)	Complete and permeability-driven absorption (fast)
High Permeability	Complete and dissolution-rate driven absorption (very fast)	Complete and fast absorption (immediate)

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Classification Grids and Compounds for iBCS Model Validation

giBCS Class	Solubility	Permeability	Oral Route	Pulmonary Route	Model Compounds for iBCS Model Validation
I	High	High	• Well absorbed	• Available dose = deposited dose • Short MAT (similar to IV bolus)	Albuterol
II	Low	High	• Sufficiently/ poorly absorbed	• Available dose < deposited dose • Long MAT	Fluticasone (FP)* AZD5423*
III	High	Low	• Sufficiently/ poorly absorbed	• Available dose ≅ deposited dose • Long MAT	Olodaterol*
IV	Low	Low	• Poorly absorbed	• Available dose < deposited dose • Very Long MAT	None identified

* Healthy and diseased data sets available

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Sensitivity Modelling: Dose, Solubility, Permeability Attributes

Conducting airways (Bb)

Respiratory airways (Al)

Sensitivity modelling by varying:

- Doses (0.43 µg – 43 mg)
- Solubility (0.1 µg/mL – 10 µg/mL)
- Permeability ($1x10^{-4}$ cm/s to $1x10^{-6}$ cm/s)

Understand the rate limiting processes at different conditions and in different regions of the lungs

Summary: Classification Approaches for Inhaled Medicines

- A process to develop a classification system for inhaled medicines has been defined.
- Classification grids based on central and peripheral regions of the lung have been proposed using parameters of solubility, permeability, and regional dose.

Summary: iBCS Challenges and Opportunities

- Challenges:
  - Lack of harmonized measurement tools
    - Local drug concentrations; dissolution test methods; permeability test methods
  - Limited number of compounds and lack of relevant published data
    - Including basic phys chem properties, published deposition data, PK data
  - Simulation approaches are still being developed
    - Sensitivity analyses to define grid boundaries will need to use a validated model – iterative process
- Opportunities:
  - A common set of tools for formulators and discovery chemists to aide pulmonary drug product development efforts.
    - Impact of phys chem properties on the fate of inhaled medicines
  - Determine approaches to assess bioequivalence
    - Based on dose, solubility, deposition, and permeability (MAT)
  - De-risk pulmonary drug development programs
    - Use of CMC data to enable successful clinical studies

Next Steps

- Sensitivity analyses to understand the impact of dose, solubility, and permeability on the proposed regional classification grids and boundaries will be conducted using PBPK simulations.
- Validation studies will be conducted using various software platforms to assess the ability of the software to simulate exposure using parameters of solubility, permeability, and regional dose.

Acknowledgements

The PQRI BTC Working Group

- Jayne Hastedt (JDP Pharma – co-chair)
- Per Bäckman (Emmace – co-chair)
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- Phil Kuehl (Lovelace Biomedical)
- Jens Markus Borghardt (Boehringer Ingelheim)
- David Prime (GSK)
- Yoen Ju Son (Merck)
- Erika Stippler (USP)
- Simon Teague (GSK)
- Ulrika Tehler (Astra Zeneca)
- Jeff Weers (Respira Therapeutics)
- Jen Wylie (Merck)

The PQRI BTC

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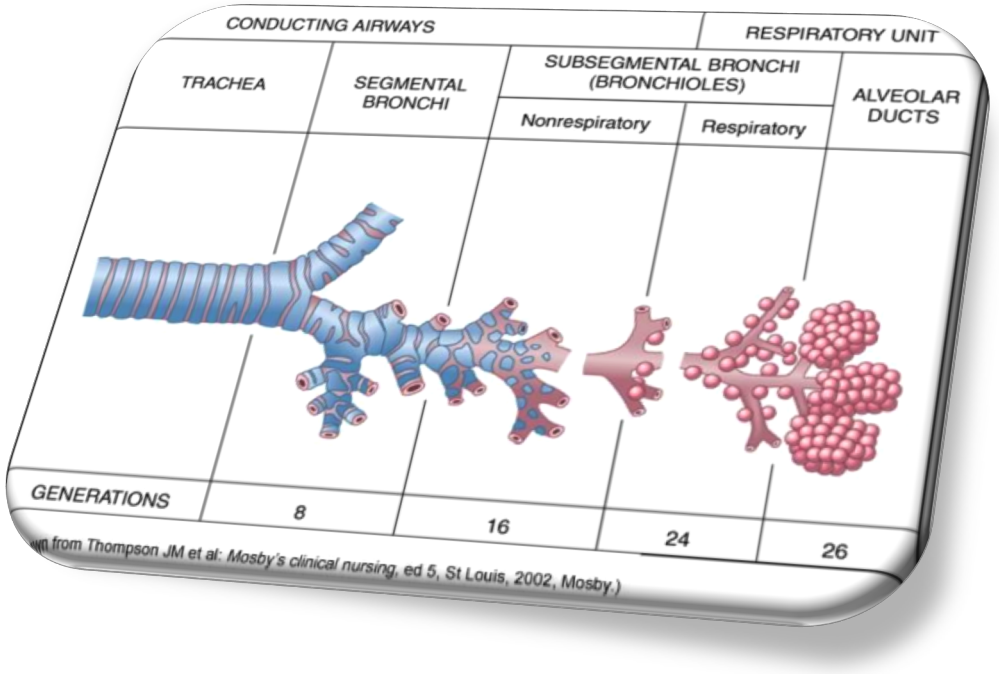
- Filippos Kesisoglou
- Mehran Yazdanian
- Dede Godstrey
- Erika Stippler
- Wenlei Jiang

The AAPS Inhalation Focus Group

Backgrounder

Pulmonary Physiology



The Lung doesn't look like the GI

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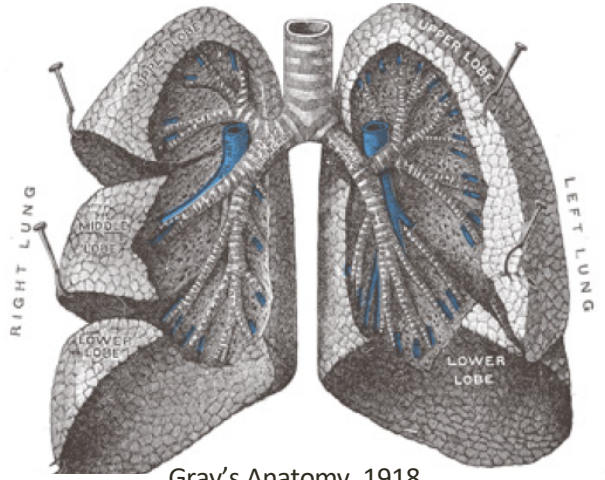

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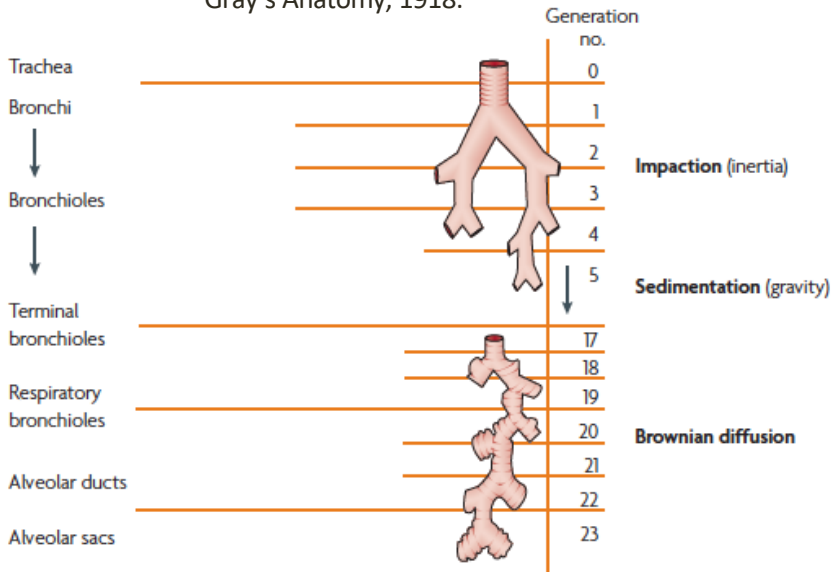

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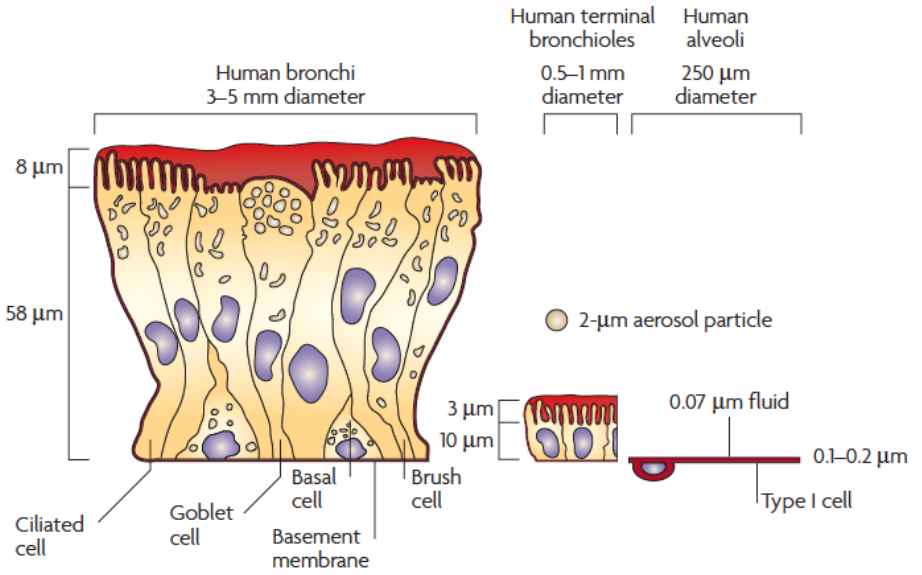
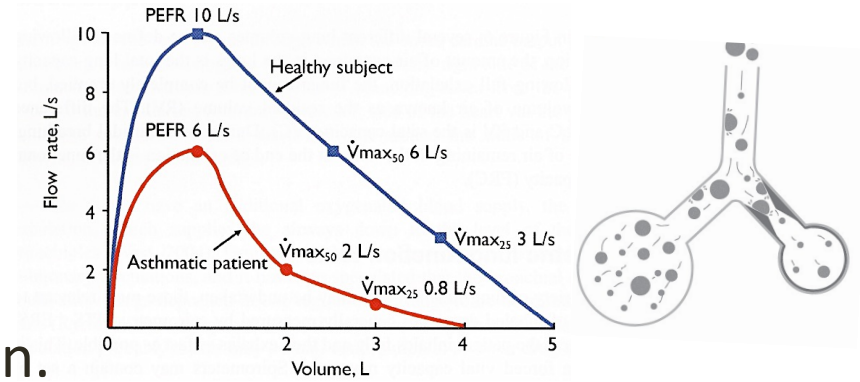
Diseased lungs are different from healthy lungs.

Key Learnings:

- Clearance mechanisms vary by region.
- "Liquid" composition and thickness vary by region.





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Lung “fluid” by Region

Conducting zone (Central)

- Non-Newtonian viscous mucus layer
- “Fluid” Composition:
  - 1% inorganic salts
  - 1% proteins
  - 2% glycoproteins (mucins)
  - 1% lipids
  - 95% water
- Volume
  - ~ 4 – 25 mL

Respiratory zone (Peripheral)

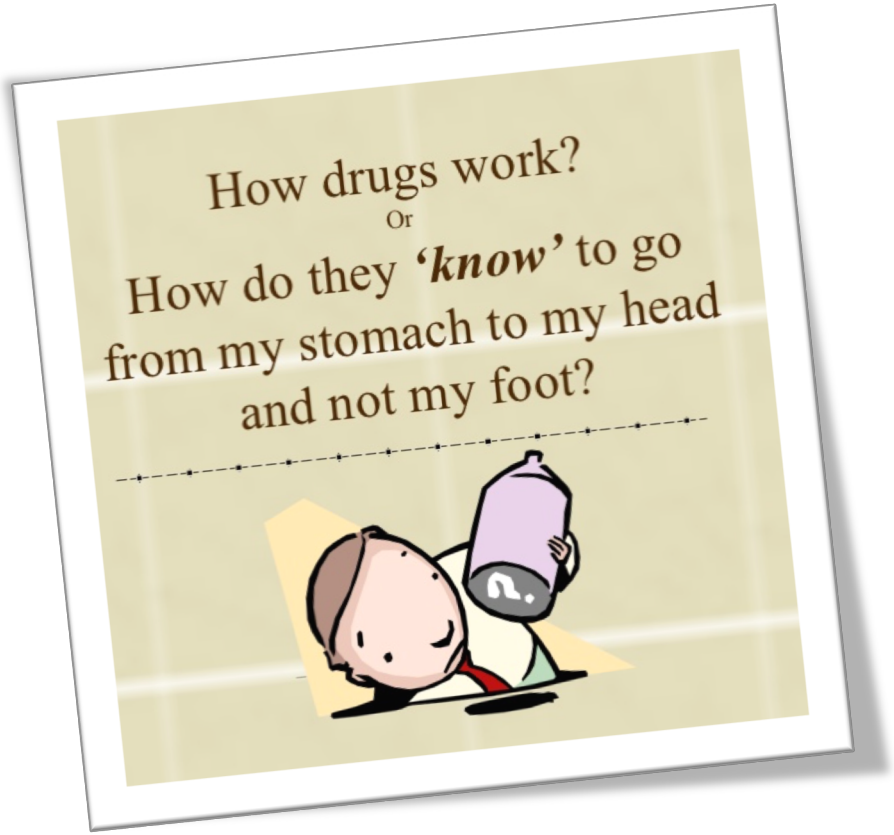
- Newtonian thin layer of surfactant
- “Fluid” Composition:
  - 85% phospholipids
  - 5% cholesterol
  - 10% proteins
- Volume:
  - ~ 7 – 20 mL

Volume and composition are also disease dependent

Eixarch, H.; Haltner-Ukomadu, E.; Beisswenger, C.; Bock, U. J. Epithel. Biol. Pharmacol. 2010, 3, 1–14.

Anderson, S.D., “Asthma provoked by exercise, hyperventilation, and the inhalation of non-isotonic aerosols”, Asthma Basic Mechanism and Clinical Management, 2nd Ed., Vol 28, pp. 473, 490, Academic Press, New York, 1992

Properties of Inhaled Medicines



Desired Properties:
Oral vs. Inhaled Therapeutics

	Oral Drugs	Inhaled Drugs with Local Target
Distribution	Systemic	Local to Lung
Systemic absorption	Rapid	Low to None
Systemic Clearance	Slow	Rapid
Protein Binding or Retention Time	Low	High
Oral BA	High	Low

Adapted from Yeadon, M. Future Med. Chem. 2011, 3, 1581–1583.

Physicochemical Properties

Class	Avg Mol. Weight (SD)	Avg. H-bond count (SD)	Avg. Polar Surface Area (Å^2) (SD)	Avg. Rotatable Bond Count (SD)
LABA	498 (80.29)	11.00 (2.12)	116.63 (28.53)	13.00 (4.30)
LAMA	385 (63.39)	3.50 (1.50)	43.15 (11.80)	6.00 (2.35)
MABA	717 (58.22)	12.82 (1.80)	148.5 (23.97)	16.73 (2.83)
PDE4 Muscarinic duals	691 (32.29)	11.25 (1.30)	122.50 (9.66)	12.25 (1.30)
Phosphate prodrugs	969 (102.88)	13.20 (2.48)	173.00 (31.72)	26.2 (2.32)
Oral	305 (91.00)	6.04 (2.92)	60.37 (32.27)	4.70 (2.69)
Inhaled	370 (103.00)	8.31 (3.25)	89.20 (38.65)	5.10 (2.76)

Selby, M. D.; de Koning, P. D.; Roberts, D. F. Future Med. Chem. 2011, 3, 1679–1701.

Inhaled Medicines are Typically More Potent than Oral Medicines

Class	Drug	Mol Wt (g/mol)	Dose (mcg)	Aqueous Solubility (mcg/mL)	Log P
ICS	Budesonide	430.5	200 - 400	16	2.8
	Fluticasone propionate	500.6	100 – 500	0.14	4.1
	Beclomethasone dipropionate*	521.0	100 – 200	0.13	1.3
	Mometasone furoate	521.4	220 – 440	0.1	4.5
	Ciclesonide*	540.7	80 – 160	<0.1	5.3
LABA	Salmeterol xinafoate	603.7	50	80	3.9
	Indacaterol maleate	508.6	75 – 300	230	3.31
	Formoterol fumarate	840.9	6 – 12	11,000	1.6

PubChem open chemistry database and Drugbank database **Prodrugs*

Adapted from Guenther Hochhaus, Jeff Weers, Hiro Sakagami as presented at iBCS Workshop in 2015 and RDD publications

The Fate of Inhaled Particles

Positively charged drugs are cleared more slowly.

Small molecules are absorbed very quickly.

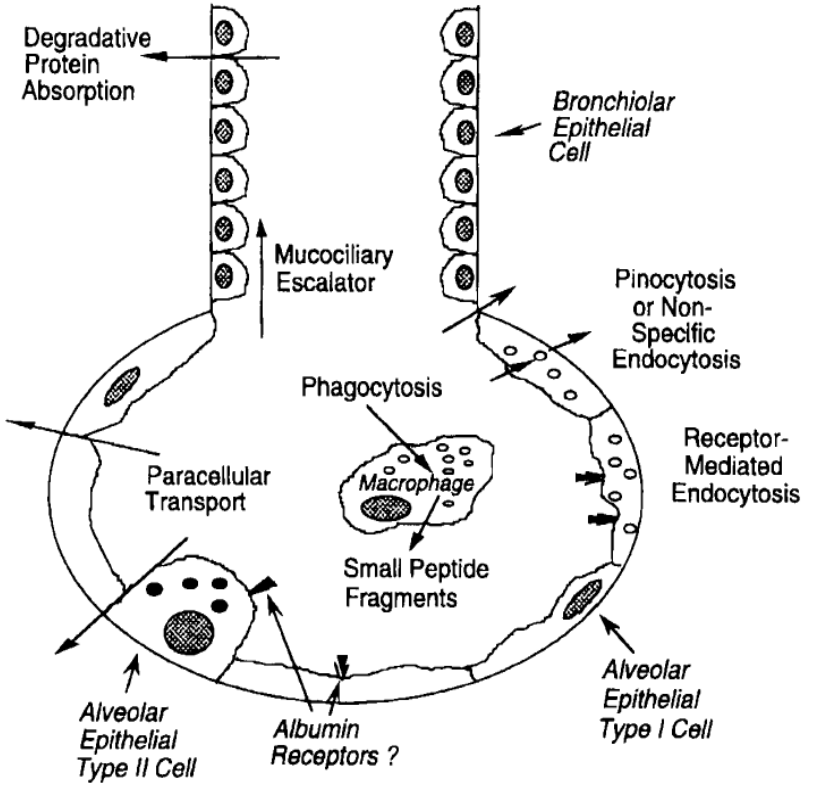
Very low water solubility and high doses may slow dissolution and produce a depot-type release.

Small peptides are rapidly absorbed, but are susceptible to peptidases and cleared rapidly.

Larger proteins are absorbed slowly.

Clearance varies by location:

- Mucociliary clearance in the upper airways
- Macrophages and dendritic cells in the lower airways



Folkesson, H.G., M.A. Matthay, B.R. Westrom, K.J. Kim, B.W. Karlsson, and R.H. Hastings.. Alveolar epithelial clearance of protein. J. Appl. Physiol. 1996 80, 1431-1445.

*Patton, J. S.; Brain, J. D.; Davies, L.; Fiegel, J.; Gumbleton, M.; Kim, K.-J.; Sakagami, M.; Vanbever, R.; Ehrhardt, C.; J. Aerosol Med. Pulm. Drug Deliv. 2010, **23**, S71–87.*

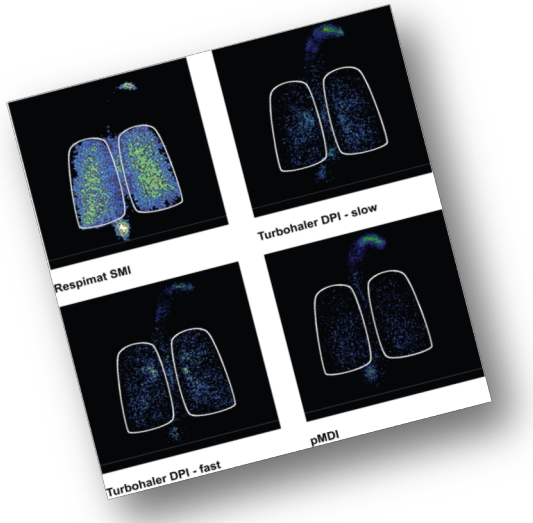
Inhaled vs. Oral Drug Properties

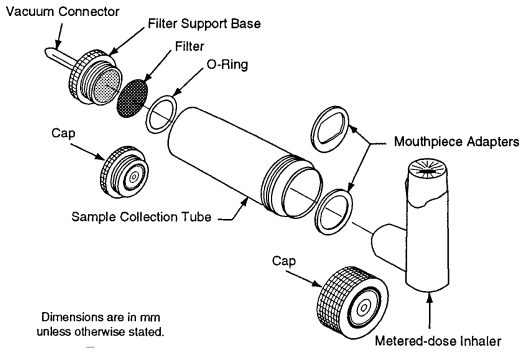
"compounds administered via the inhaled/intranasal routes have a higher polar surface area, a higher molecular weight, and a trend toward lower lipophilicity, when compared with their orally administered counterparts."

Ritchie TJ, Luscombe CN, Macdonald SJF. Analysis of the calculated properties of respiratory drugs: can we design for inhaled drugs yet? J. Chem. Inf. Model. 49(4), 1025–1032 (2009).

The Pulmonary Dose

Delivered dose is an important CQA for inhaled drugs along with aerodynamic particle size and distribution.





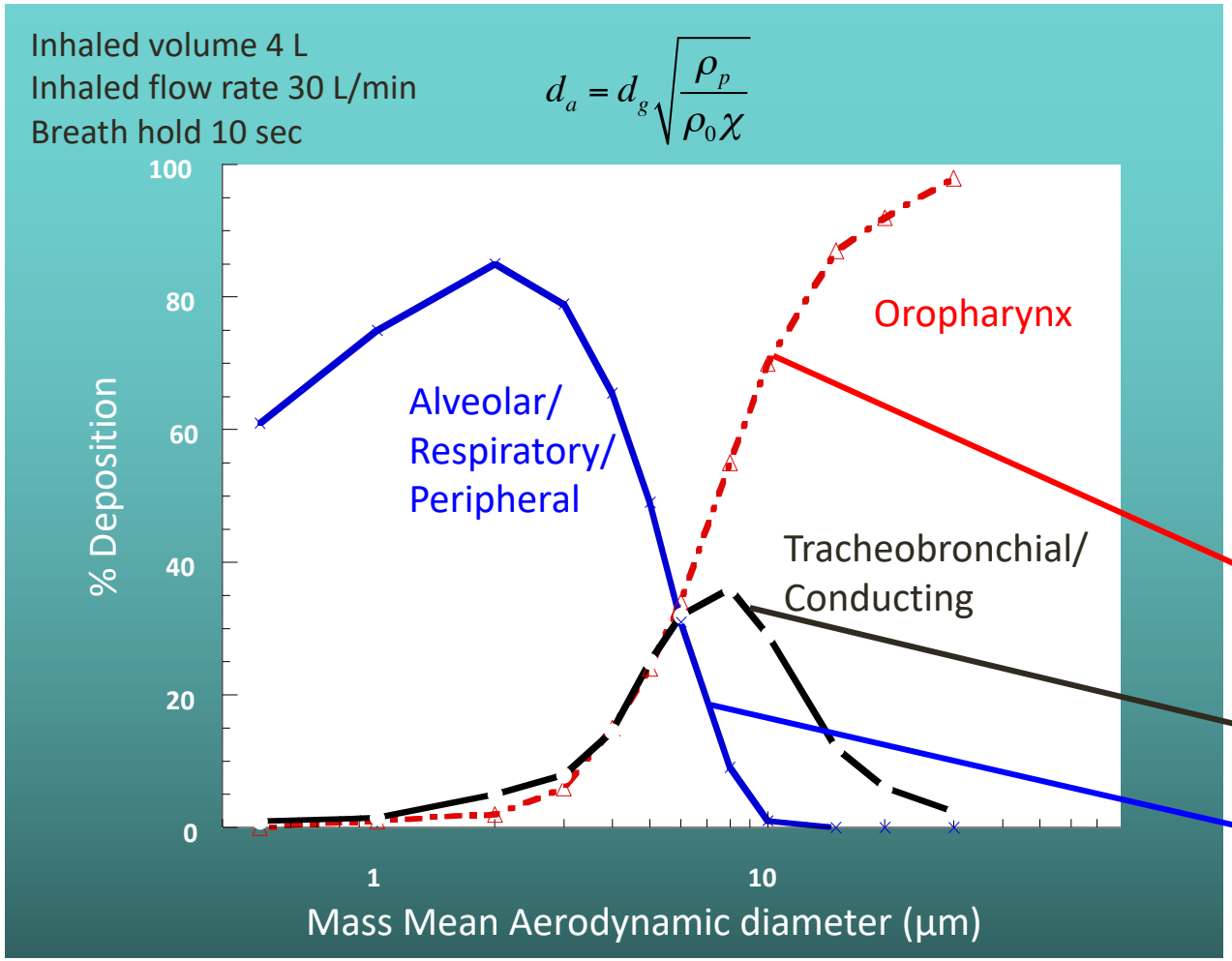
The Pulmonary Dose

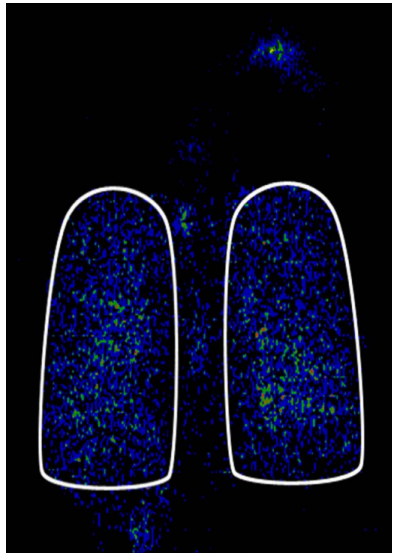
- Clinical safety and efficacy of inhaled drugs are influenced by the total aerosolized dose delivered to the lungs and by the aerodynamic particle size distribution.
  - The lung dose is less than the amount of drug in the dosage unit and is dependent upon the device used.
  - Both dose content uniformity and aerodynamic particle size distribution are CQAs for inhaled drugs.
  - The device matters!

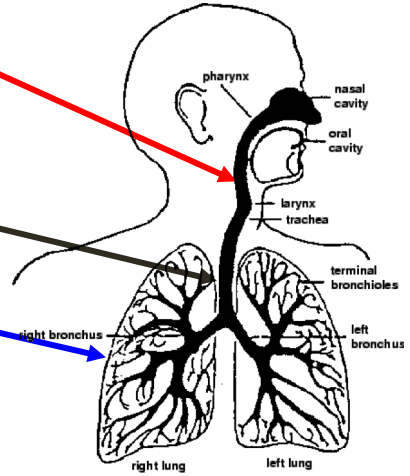
Particle size and Lung deposition: The Aerodynamic Diameter

Inhaled volume 4 L
Inhaled flow rate 30 L/min
Breath hold 10 sec

$$d_a = d_g\sqrt{\frac{\rho_p}{\rho_0 \chi}}$$







Clark, A. R.; Egan, M. Modelling the deposition of inhaled drug aerosols. J. Aerosol Sci. 1994, 25, 175–186.

Regional Deposition & Dose

The head, mouth, and throat dictate the total lung dose.
The particle size of the “true” aerosol impacts the deposition pattern (P/C).
Empirical - Dose and deposition pattern (P/C ratios); 45-65% slow clearance for most products

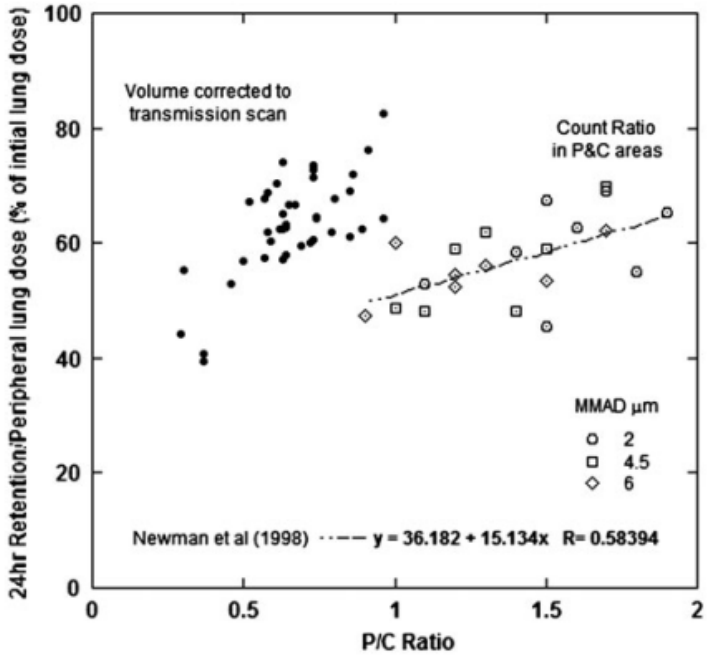


FIG. 1. Twenty-four-hour retention versus P/C ratio for studies by Newman et al.[18] and Clark et al.[19] The equation shown are least squares fit line to the data of Newman et al.[18]

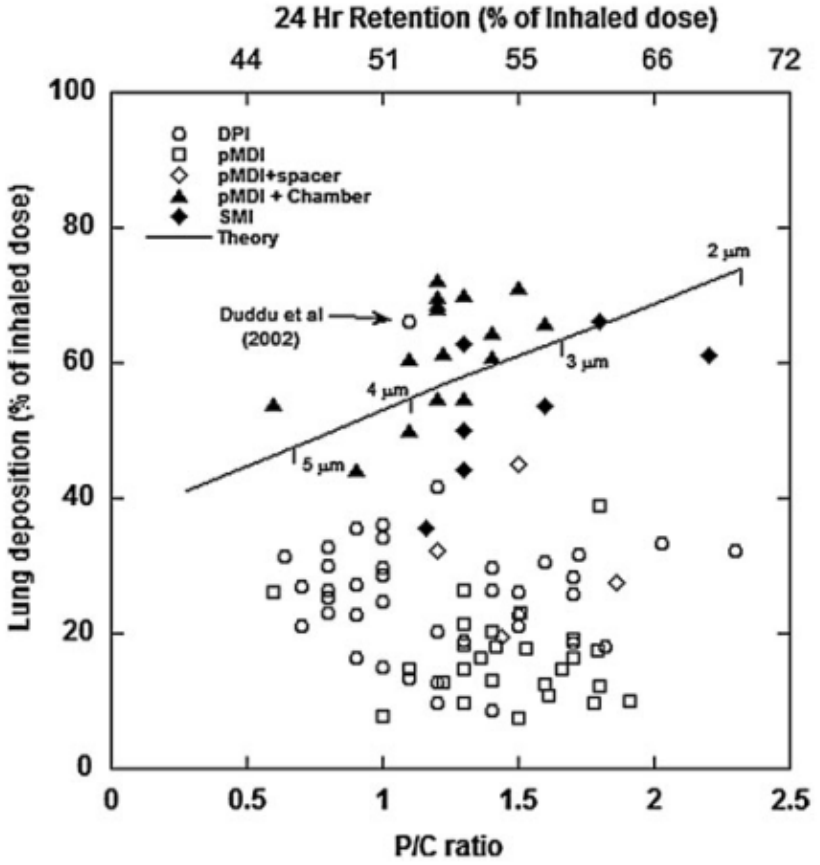


FIG. 2. A plot of lung deposition versus P/C ratio for data from 37 papers (containing 97 study arms) published by Newman and coworkers[18] between 1982 and the present. The theoretical line was derived using the algebraic representation of Sthalhofen's model[7] given by Rudolf.[8] The upper abscissa is 24-h retention calculated using the model. The MMAD values placed on the theory line correspond to an inhaled flow rate of 60 L/min. The equivalent D^2Q values are 25,000, 16,000, 9000, and 4000 $\mu m^2 \cdot mL \cdot s$ and diameters corresponding to other inhalation flow rates can be readily calculated using these d^2Q values.

PQRI
Product Quality Research Institute

Central and Peripheral Regions of the Lung

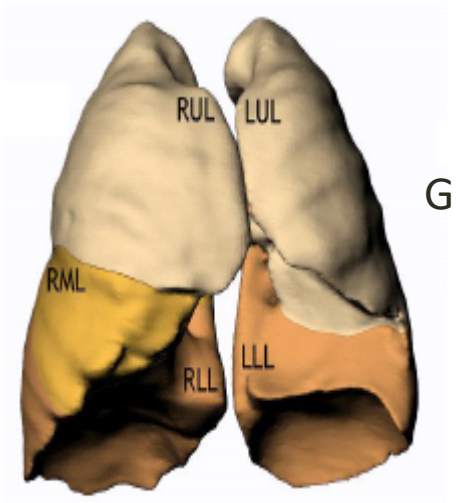
Central Airways
~ 50% of drug reaching
the upper respiratory tract

Generations 0-16

Competition between dissolution and absorption and Mucocillary Clearance (MCC). Ciliated region.

Assumption for Classification

Peripheral Airways
~ 50% of drug reaching
the lower respiratory tract



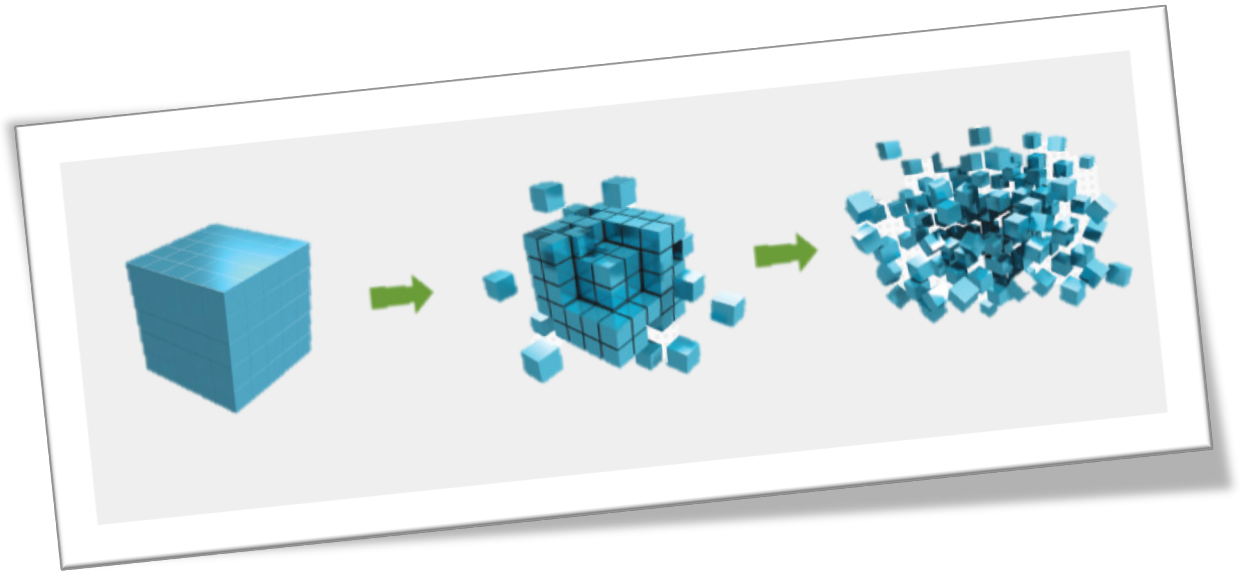
Generations 17-23

"Clearance" by absorption only. Non-ciliated region.

The surface area of the peripheral airways >> than the central airways

Particle Dissolution In the Lung

Currently, there are no regulatory requirements or USP techniques for dissolution testing of inhaled drugs.



Impact of solubility on particle dissolution – ICS drugs

There is a good correlation between Do and MDT for ICS drugs

ICS	C_S (µg/ml)	Do	Mean Dissolution Time (hr)
Fluticasone propionate	0.14	27	>8
Beclomethasone dipropionate	0.13	15	>5
Budesonide	16	0.375	~ 0.1
Flunisolide	140	0.01	< 0.03

Source: *Högger P, Bonsmann U, Rohdewald P. Efflux of glucocorticoids from human lung tissue to human plasma in vitro [Abstract P1735]. Eur Respir J 1994;**7**:382s.*

J. Weers, AAPS/FDA/USP iBCS Workshop, March 2015.

Estimated Pulmonary Dose Numbers, Central Deposition

$$Do = DoseNumber = \frac{Mo/Vo}{C_S}$$

Dose adjusted for device and estimated deposition pattern (P/C)

$$Mo = central\ lung\ dose = M_{nom} \times \eta_{lung} \times \eta_{central}$$

$$Vo = volume = 10ml$$

$$C_s = solubility\ in\ water$$

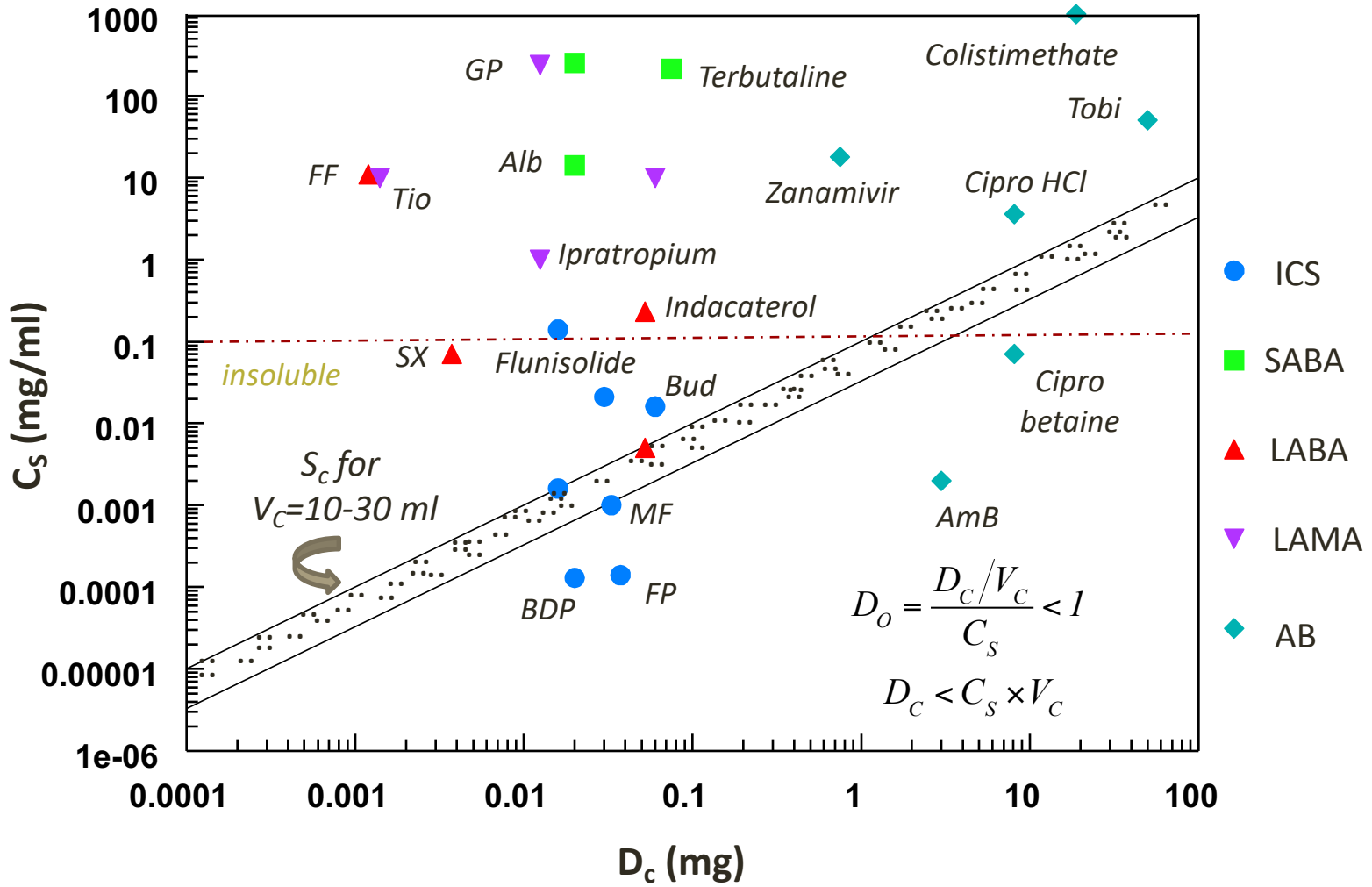
If Do is < 1, the delivered dose is assumed to be fully dissolved

Drug	Class	Do
Amphotericin B	AB	150
Fluticasone propionate	ICS	27
Beclomethasone dipropionate	ICS	15
Ciprofloxacin betaine	AB	12
Mometasone furoate	ICS	3
Tobramycin sulfate	AB	0.1
Salmeterol xinafoate	LABA	0.005
Albuterol sulfate	SABA	0.0001
Ipratropium bromide	SAMA	0.00002
Formoterol fumarate	LABA	0.00001
Tiotropium bromide	LAMA	0.00001

Adapted from J. Weers, AAPS/FDA/USP iBCS Workshop, March 2015.

Impact of solubility and dose on particle dissolution in the Central Airways

Dissolution becomes important for drugs that are considered “insoluble”



Adapted from Hastedt, J. E.; Bäckman, P.; Clark, A. R.; Doub, W.; Hickey, A.; Hochhaus, G.; Kuehl, P. J.; Lehr, C.-M.; Mauser, P.; McConville, J.; Niven, R.; Sakagami, M.; Weers, J. G. *AAPS Open* 2016, 2, 1.

Dissolution – No standardized methods for inhaled medicines exist – FDA list of completed grants

- An Optimized Dissolution Test System for Orally Inhaled Drugs: Development and Validation
  - Site PI: Guenther Hochhaus (University of Florida)
  - Grant #: 1U01FD004950-01
  - 09/15/2013- 08/31/2016

In Vitro Fluid Capacity-limited Dissolution Testing and Its Kinetic Relation to in Vivo Clinical pharmacokinetics for orally inhaled drug products

  - Site PI: Masahiro Sakagami (Virginia Commonwealth University)
  - Grant #: 1U01FD004941-01
  - 09/15/2013-02/28/2018
- Development of in Vivo Predictive Dissolution Technique to Understand the Clinical Based
  - Site PI: Robert Price (University of Bath)
  - Grant #: 1U01FD004953-01
  - 09/15/2013- 10/31/2016

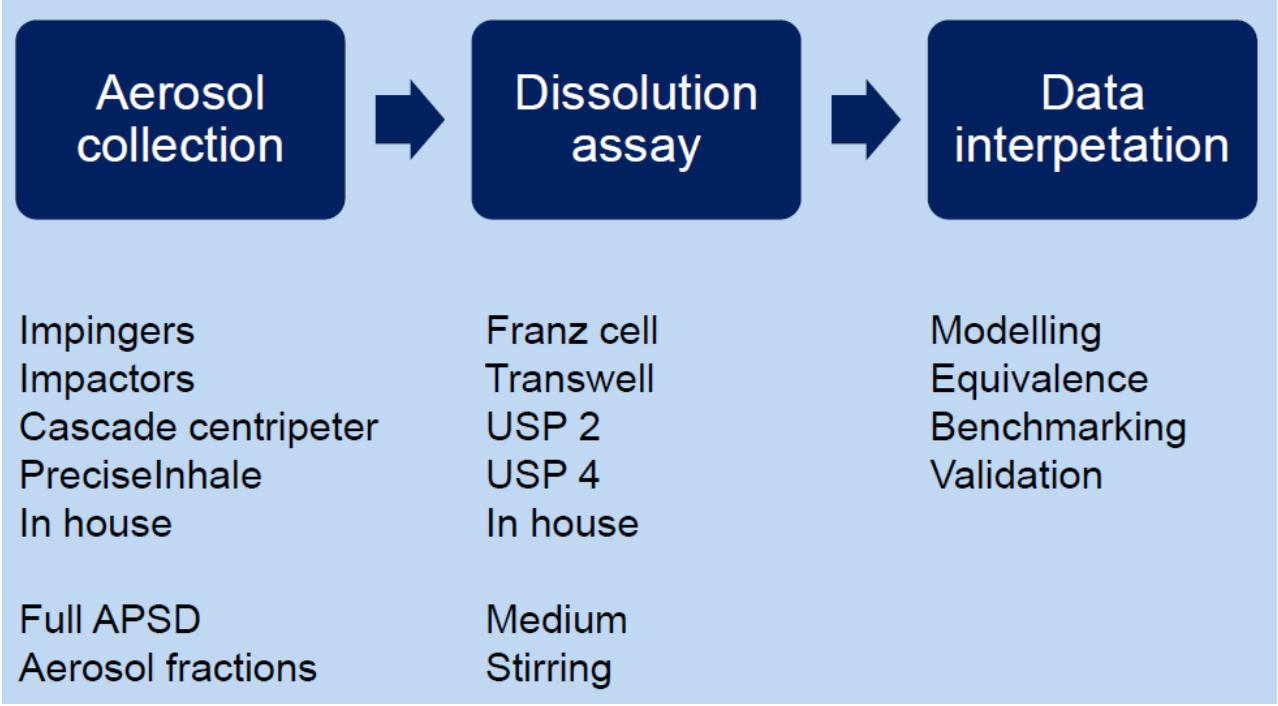
Ongoing FDA Funded Project

- **A Multiscale Computational Framework for Bioequivalence of Orally Inhaled Drugs**
  - Awarded to CFD Research Corporation (CFDRC) (HHSF223201810182C)
  - Linking deposition models for inhalation delivery to PBPK models is a key step to more efficient bioequivalence methods for OIDPs. This type of model can help determine if bioequivalence for OIDPs can be evaluated by pharmacokinetic and in vitro studies without the need for comparative clinical endpoint studies.

Dissolution – No standardized methods for inhaled medicines exist – Collaborations

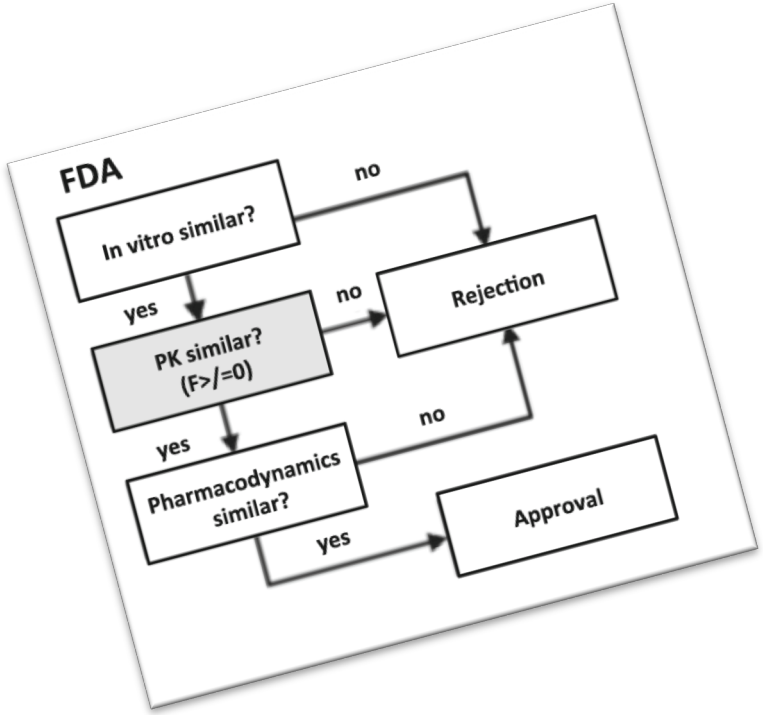
- Evaluate experimental dissolution set-ups with a view to validation/standardisation

- Set criteria regarding solubility/dissolution for classification purposes

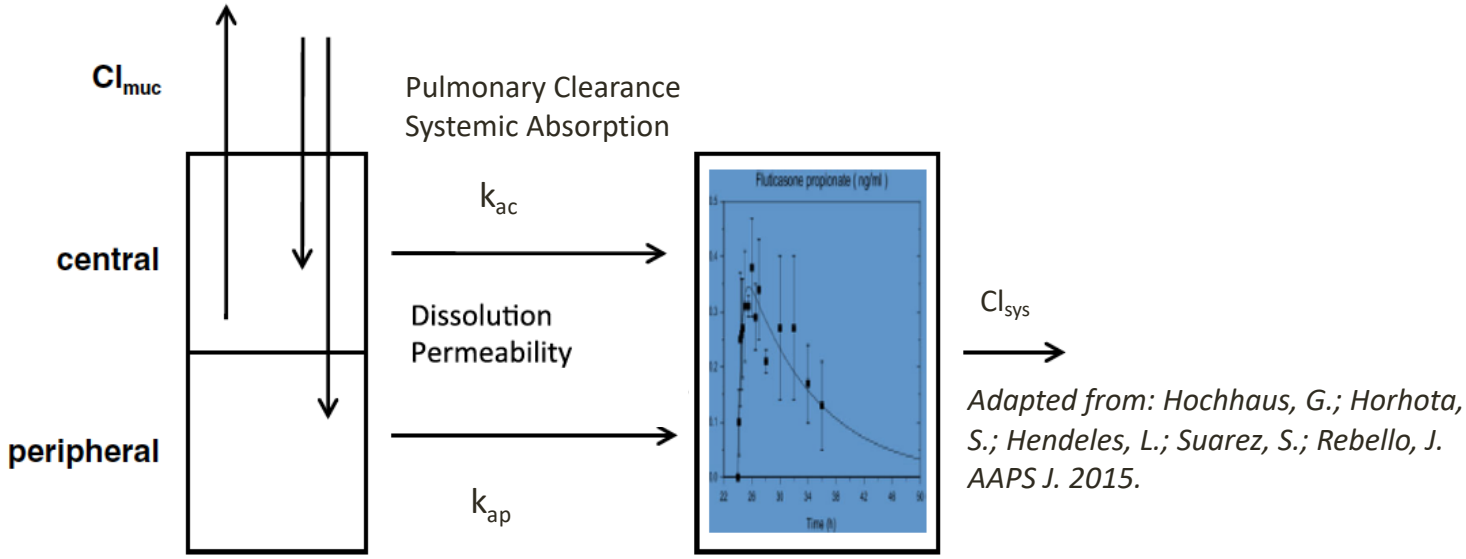


Tissue Interaction and Residence Time

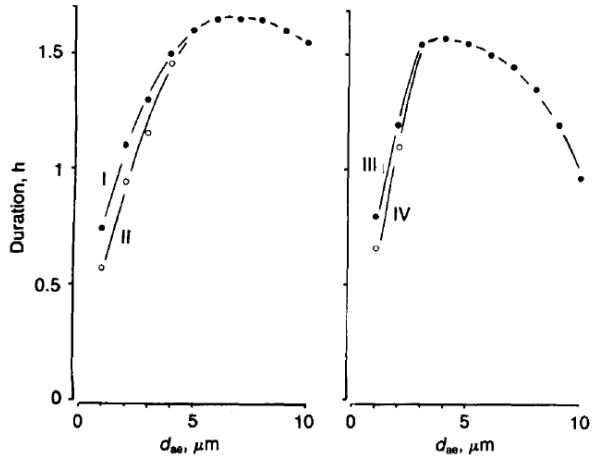
Using PK to understand local effects



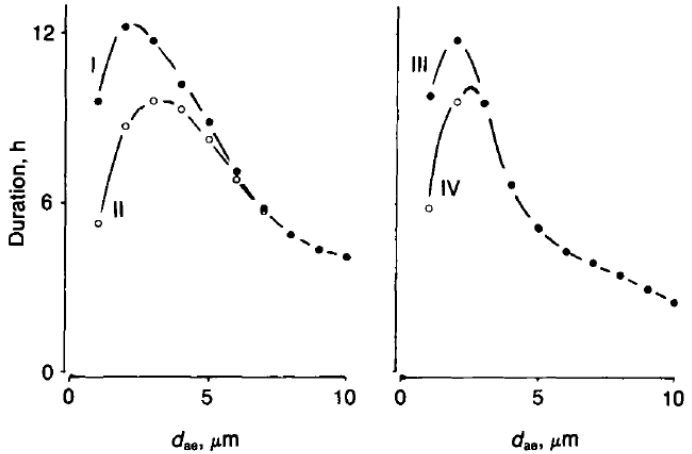
Understanding PK, Permeability, and Residence Time



Adapted from: Hochhaus, G.; Horhota, S.; Hendeles, L.; Suarez, S.; Rebello, J. AAPS J. 2015.



Soluble and highly permeable

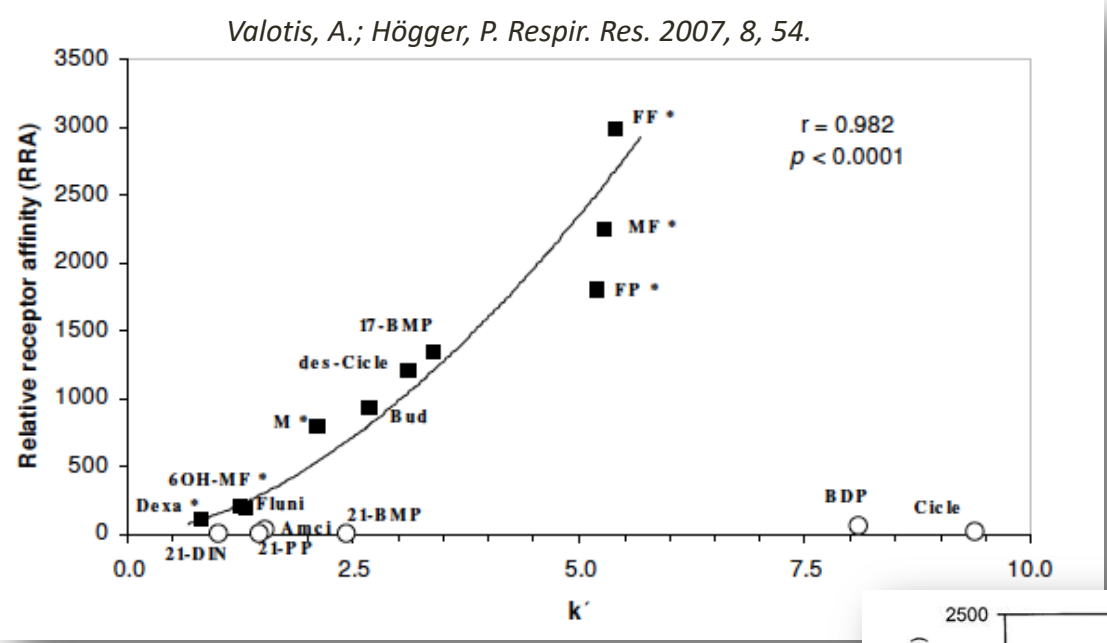


Insoluble and low permeability

Byron, P. R. J. Pharm. Sci. 1986, 75, 433–438.

Relative Receptor Affinities – ICS Drugs

Valotis, A.; Högger, P. Respir. Res. 2007, 8, 54.



Winkler, J.; Hochhaus, G.; Derendorf, H. Proc. Am. Thorac. Soc. 2004, 1, 356–363.