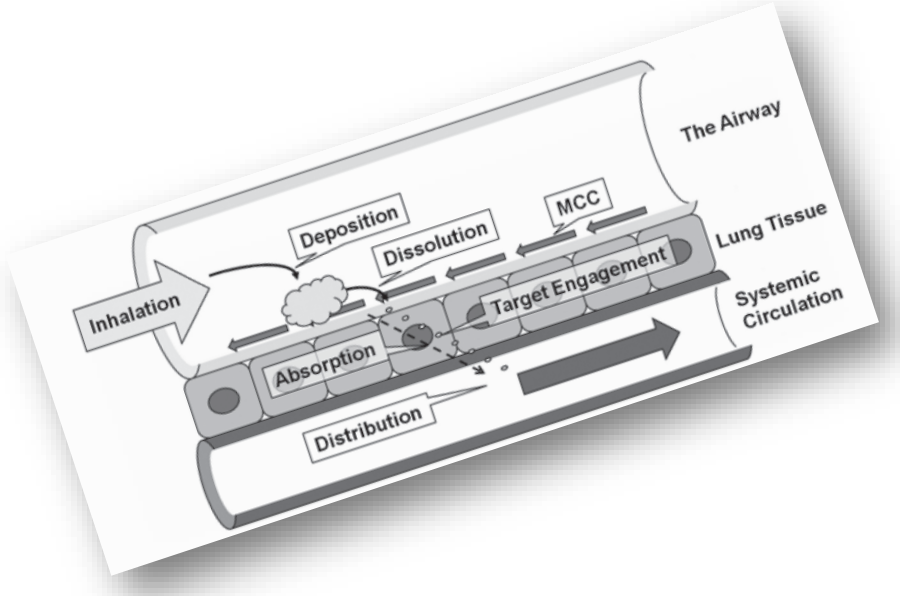
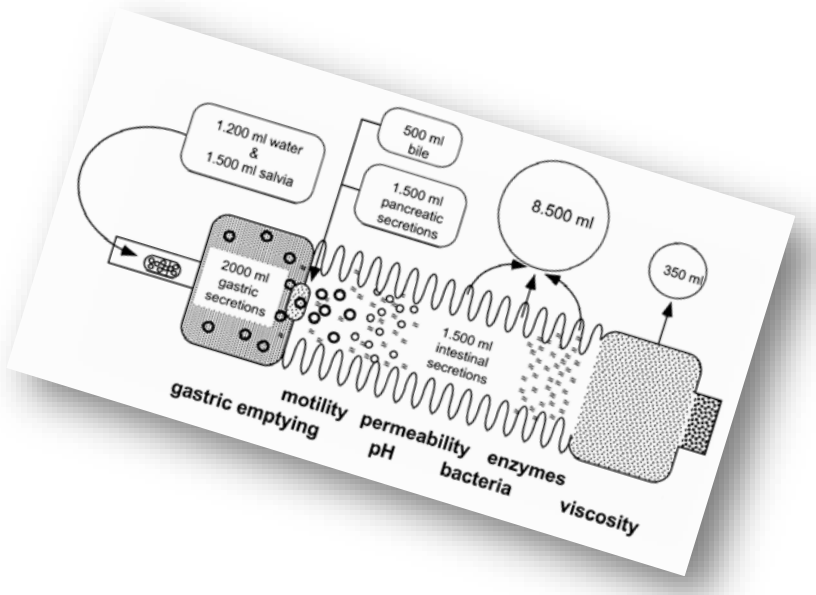
Modelling aspects related to inhaled medicines

Per Bäckman, PhD

Co-Chair of PQRI BTC iBCS Working Group





Disclaimer

The following presentation includes the personal views of the presenter and does not necessarily represent the official views of Emmace Consulting.

The mention of commercial products (including software), their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by Emmace Consulting.

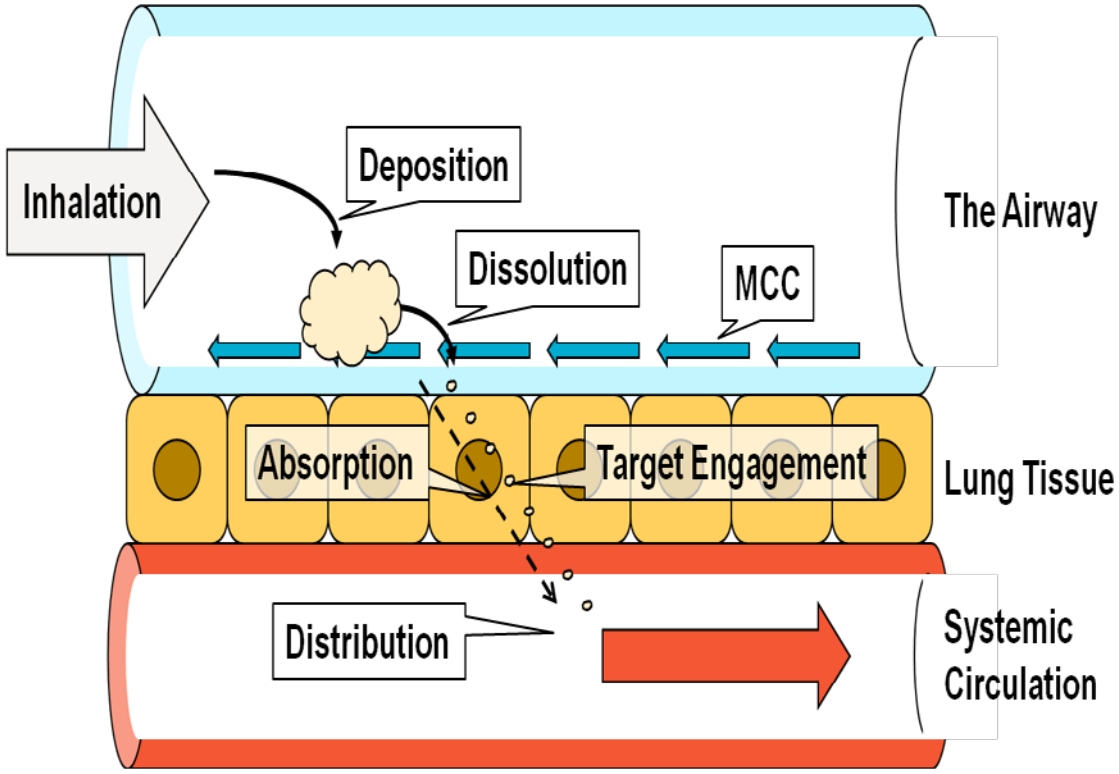
Outline

- Introduction to computer-based models
  - Model applications and general design principles
- Applications within the PQRI iBCS project
  - General outline and validation of approach (work in progress)
  - Identifying classifiers - Sensitivity Modelling (work in progress)
- General Applications to Inhaled Drug Product Development
  - Example: Advair Batch-to-Batch Variability
- Conclusions – opportunities and challenges

Outline

- Introduction to computer-based models
  - Model applications and general design principles
- Applications within the PQRI iBCS project
  - General outline and validation of approach (work in progress)
  - Identifying classifiers - Sensitivity Modelling (work in progress)
- General Applications to Inhaled Drug Product Development
  - Example: Advair Batch-to-Batch Variability
- Conclusions – opportunities and challenges

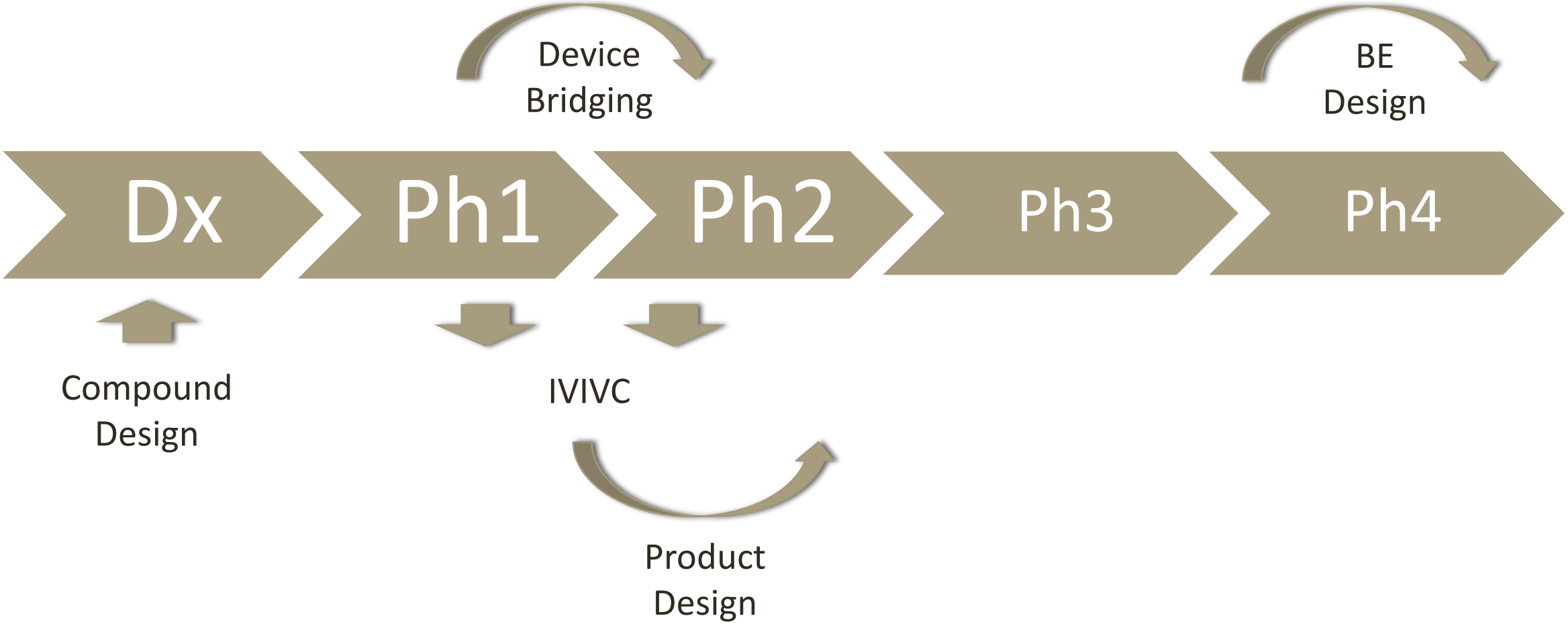
Why do We Need Computer Based Models?



Modified from Olsson and Bäckman, Respiratory Drug delivery 2014

- Understanding
  - Multiple, kinetically competing processed sensitive to changes in drug and product attributes
- Compound and product design
  - Now: Product/compound specific (e.g. design for BE)
  - Future: Generalized rules (*e.g.* iBCS)

When do We Need Computer Based Models?

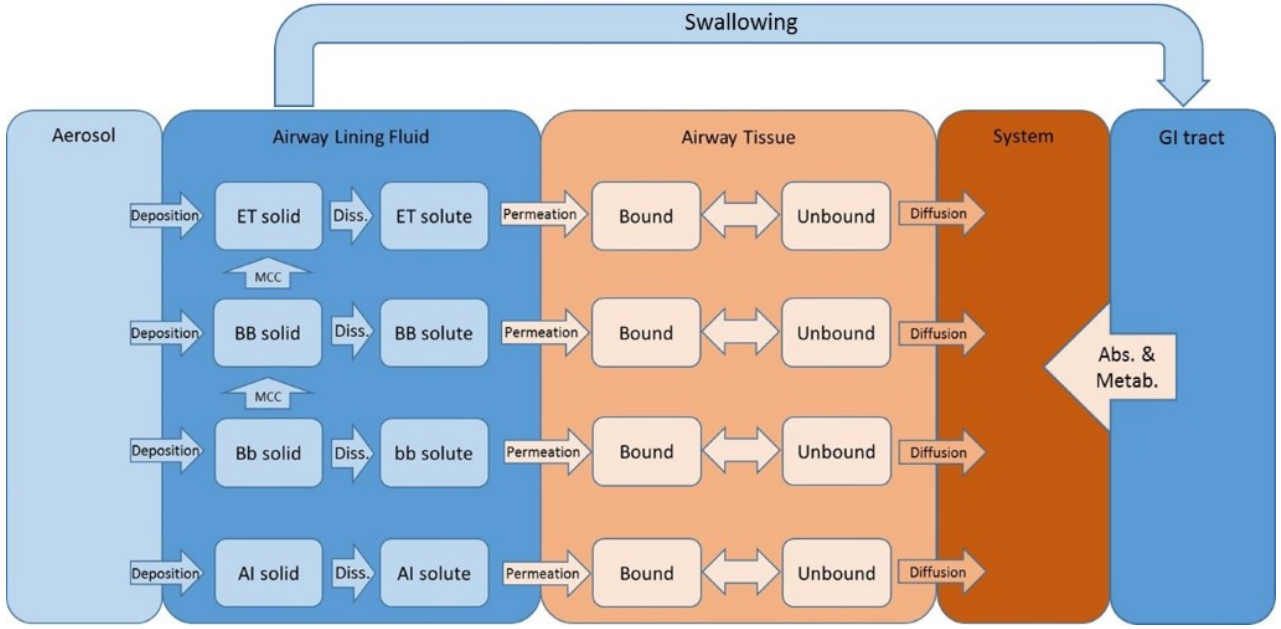


Examples of Computer-Based Models (Q4-2017)

Bäckman et al, Eur J Pharm Sci. 2018 Feb 15;113:41-52

- Mechanistic deposition and pulmonary absorption:
  - AstraZeneca LungSIM (proprietary, presented at DDL 2017)
  - Merck (proprietary, presented at DDL 2016)
  - SimulationsPlus Gastroplus ADRM (commercially available)
  - Mimetikos Preludium (commercially available)

Design Principles



From: Bäckman et al, Eur J Pharm Sci. 2018 Feb 15;113:41-52

- Process Flow:

1. Deposition
2. Non-absorptive Clearance
3. Dissolution
4. Permeation into Tissue
5. Perfusion into System
6. Systemic disposition*

- *non-mechanistic

The Model: A System of Differential Equations

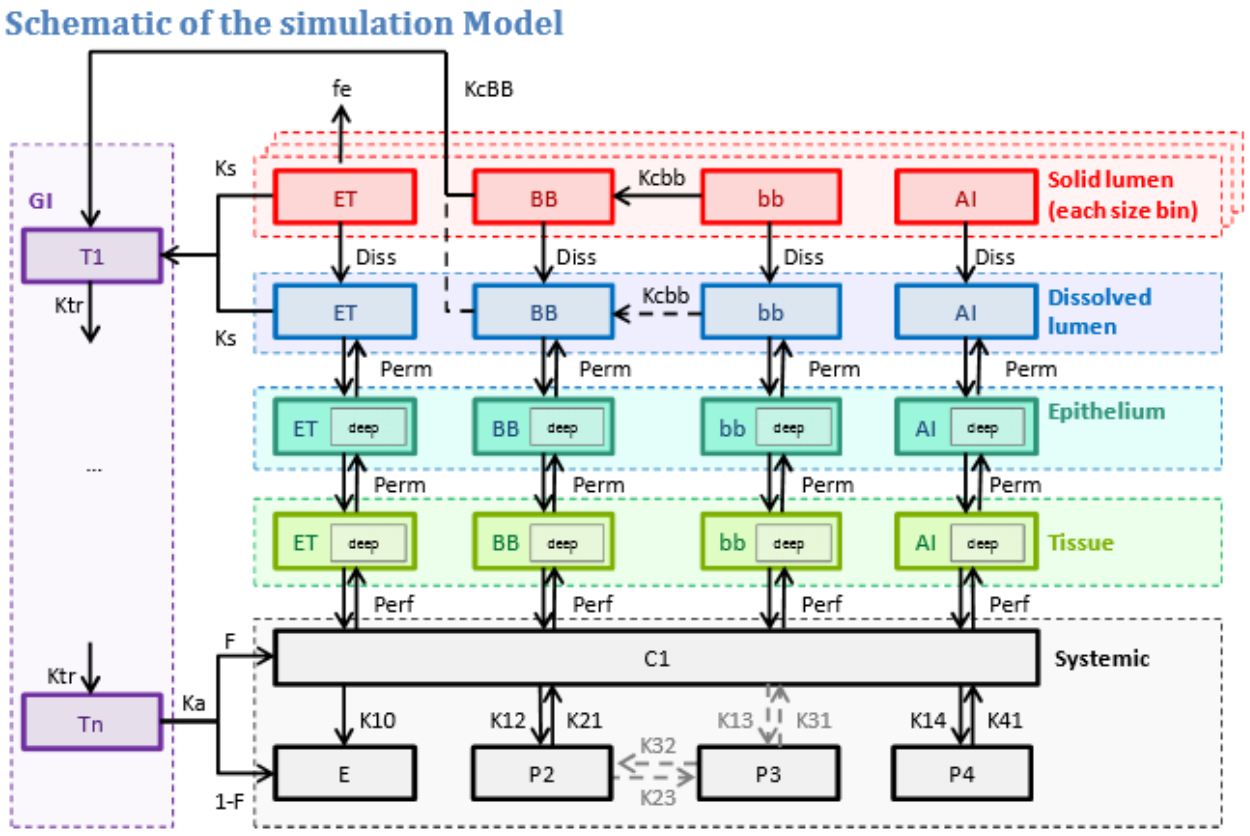
- **Mathematical description** (generalized and simplified examples):
  - Deposition Probability: $\eta_g = 1 - (1-\eta_g^i)(1-\eta_g^s)(1-\eta_g^d)$
  - Non-Absorptive Clearance: $dn_{ET}/dt \propto k_{MCC} \times n_{BB}$
  - Dissolution: $dn_{sol}/dt \propto D/h \times A_s \times (C_s - C_{ALF})$
  - Permeation into Tissue: $dn_{tis}/dt \propto P_{eff} \times A_{epi} \times (C_{ALF} - C_{epi})$
  - Perfusion into System*: $dn_{sys}/dt \propto Q \times V_{tis} \times R_{bp}/F_{up} \times [C_{tis} - C_{sys}]$

- *Systemic disposition is described by a non-mechanistic compartmental PK model based on IV PK data

- Critical Product Attributes: Deposition, Dissolution Rate, Permeation & Tissue Interaction

The Mimetikos Preludium™ Model

Modified from Olsson and Backman, RDD18



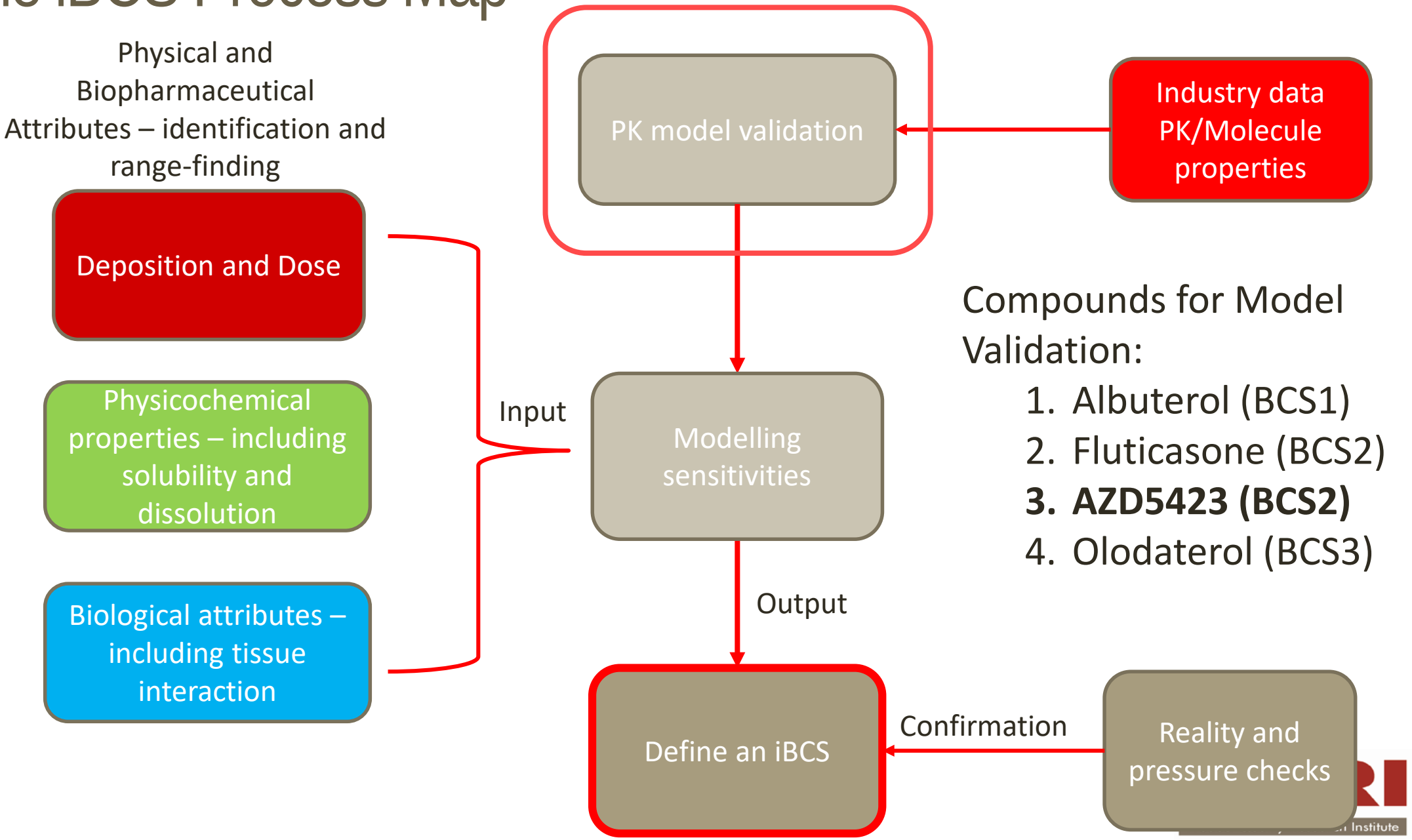
Model Inputs

- Dose Deposition (1D): APSD, DD, Inhalation flow…
- Dissolution: VMD, D, C_s,…
- Permeation: P_{eff}
- Tissue interaction: logD, pK_a, R_{bp}…
- Systemic compartmental PK model: IV data

Outline

- Introduction to computer-based models
  - Model applications and general design principles
- Applications within the PQRI iBCS project
  - General outline and validation of approach (work in progress)
  - Identifying classifiers - Sensitivity Modelling (work in progress)
- General Applications to Inhaled Drug Product Development
  - Example: Advair Batch-to-Batch Variability
- Conclusions – opportunities and challenges

The iBCS Process Map



Compounds for Model Validation:

1. Albuterol (BCS1)
2. Fluticasone (BCS2)
3. **AZD5423 (BCS2)**
4. Olodaterol (BCS3)

Validation – The AZD 5423 Example

Clinical data and model inputs from Bäckman, Tehler and Olsson, JAMP 2017

JOURNAL OF AEROSOL MEDICINE AND PULMONARY DRUG DELIVERY
Volume 30, Number 2, 2017
© Mary Ann Liebert, Inc.
Pp. 106–117
DOI: 10.1089/jamp.2016.1306

Predicting Exposure After Oral Inhalation of the Selective Glucocorticoid Receptor Modulator, AZD5423, Based on Dose, Deposition Pattern, and Mechanistic Modeling of Pulmonary Disposition

Per Bäckman, PhD,* Ulrika Tehler, PhD, and Bo Olsson, PhD†

Compound Properties

TABLE 1. PHYSICOCHEMICAL PROPERTIES OF AZD5423

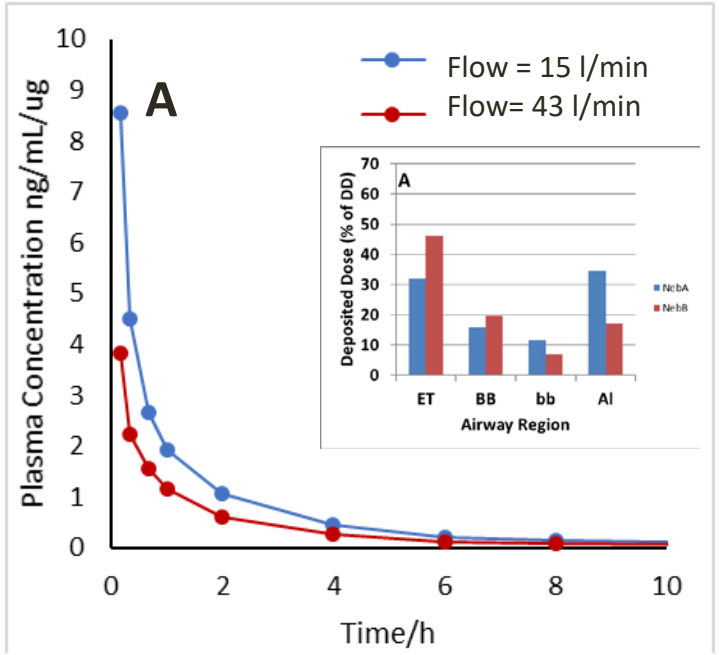
Property (units)	
Molecular weight (g/mol)	487.5
Lipophilicity, logD	5.7
Permeability, P_{app} ($cm/s \times 10^6$)	10.4
Solubility in PBS, pH 7,4 (μM)	0.6
Solubility in FASSIFv2 (μM)	9
Protein binding, F_{up} (%)	0.02
Blood–plasma partitioning, R_{bp}	0.58
Density (g/mL)	1.4
pKa	Neutral
Particle Size, MMD (GSD), Study 1 (μm)[a]	1.3 (3.2)
Particle Size, MMD (GSD), Study 2 (μm)[a]	3.1 (1.8)

- BCS 2-type compound
  - Low Solubility
  - High Permeability
- In vitro and In vivo data available for 6 products
  - 2 Nebulizers (Spira & iNeb)
  - 2 Dry Powder Inhalers
  - 2 Particle sizes (disso)
- Useful for testing model capability

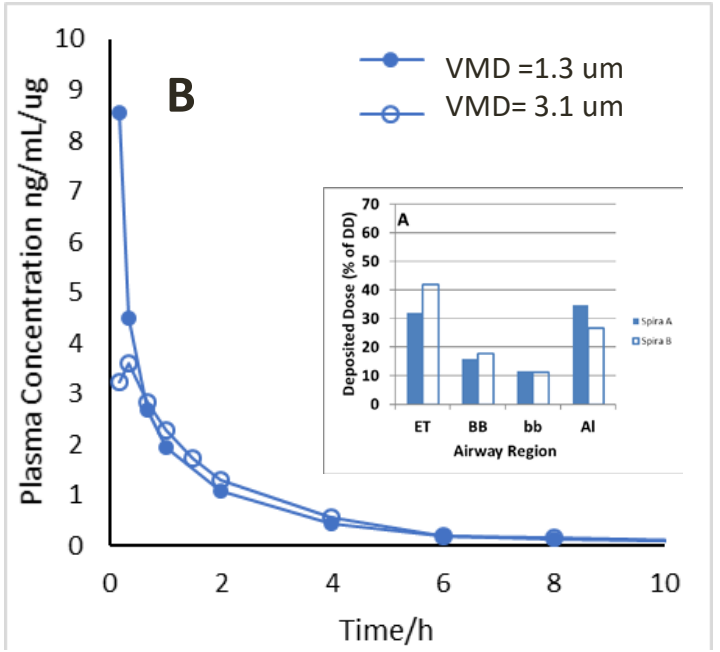
Validation – The AZD 5423 Example

Pharmacokinetic data and model inputs from Bäckman, Tehler and Olsson, JAMP 2017

Impact of deposition pattern



Impact of dissolution rate (VMD)

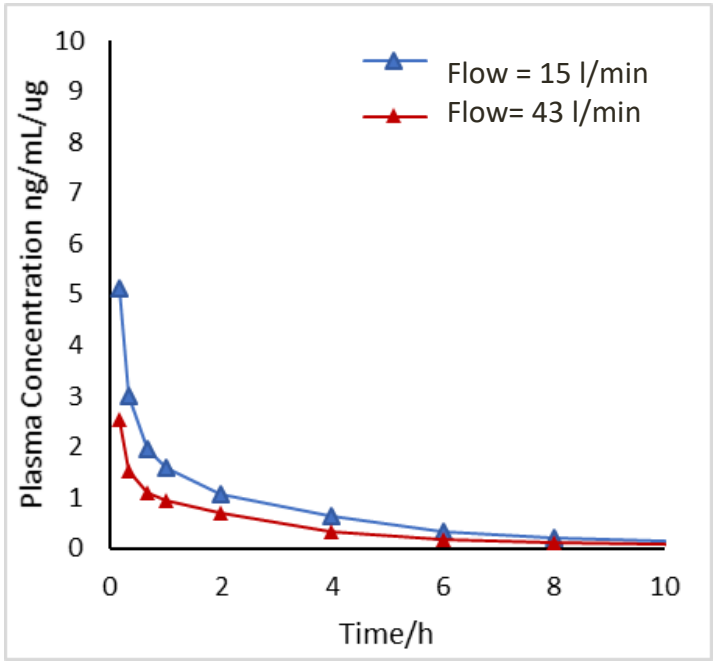


- Nebulized suspensions with: **A**: same VMD and different deposition (inhalation flow); and **B**: different VMD and same deposition (inhalation flow)
- Can the models simulate these changes to exposure based on first principles?

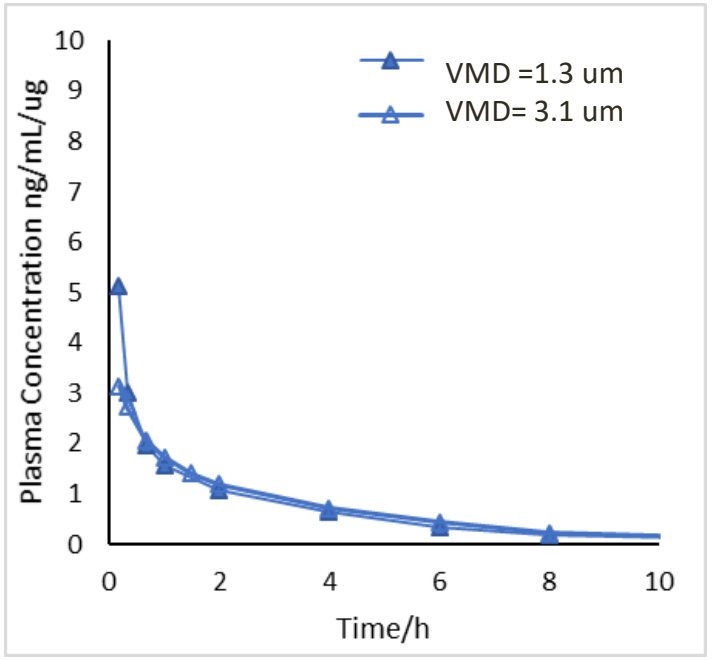
Validation – Gastroplus ADRM™ (w AZ deposition)

Pharmacokinetic data and model inputs from Bäckman, Tehler and Olsson, JAMP 2017

Impact of deposition pattern



Impact of dissolution rate (VMD)

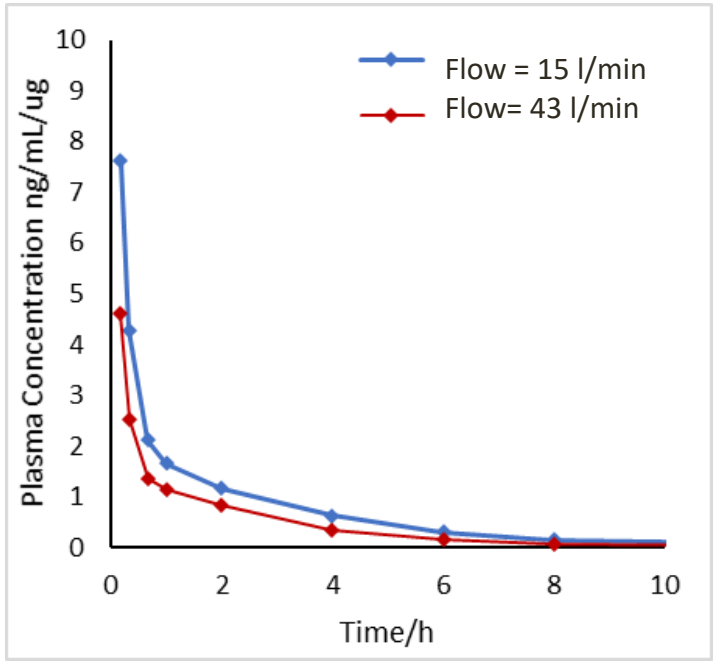


- General changes to AUC C_{max} and t_{max} predicted, some absolute errors identified

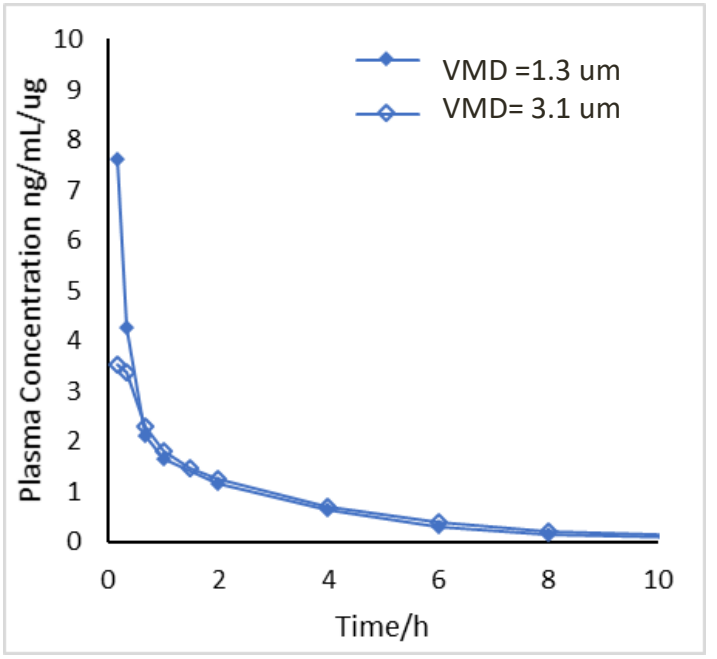
Validation – Mimetikos Preludium™

Pharmacokinetic data and model inputs from Bäckman, Tehler and Olsson, JAMP 2017

Impact of deposition pattern



Impact of dissolution rate (VMD)

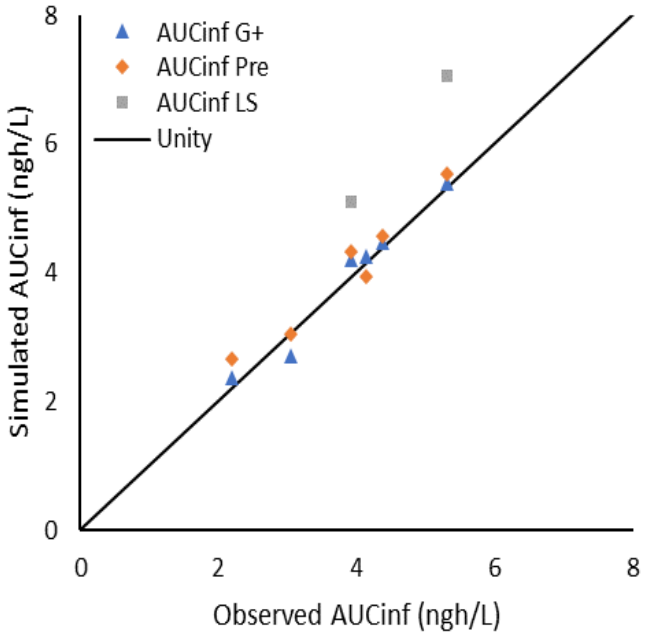


- General changes to AUC C_{max} and t_{max} predicted, minor absolute errors identified

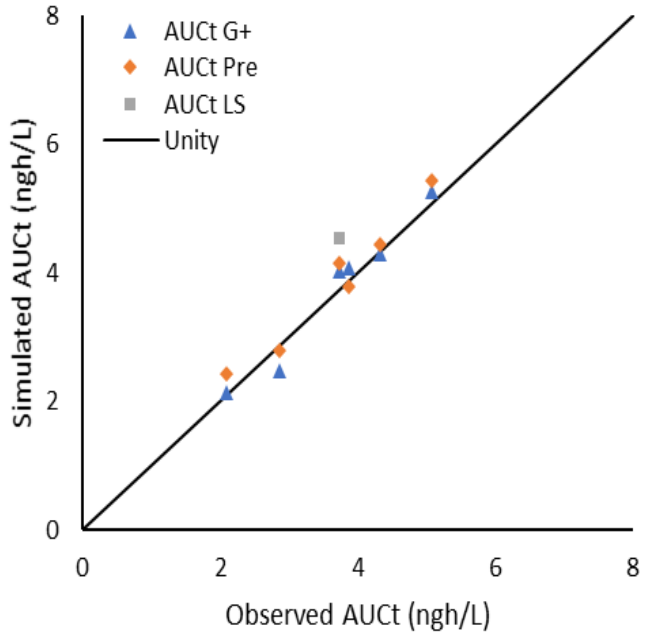
Validation – Simulations of AUC & C_{max}

Pharmacokinetic data and model inputs from Bäckman, Tehler and Olsson, JAMP 2017

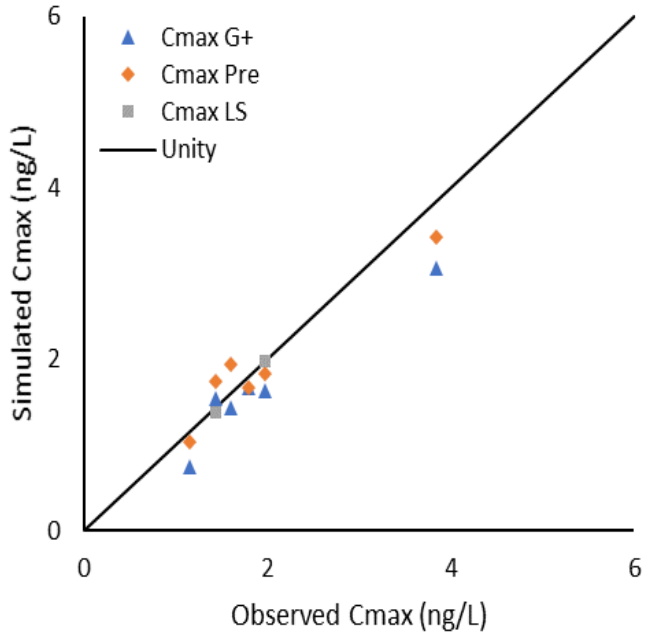
AUC_{inf}



AUC_t



C_{max}



- All three models give reasonable simulations of AUC_{inf}, AUC_t and C_{max} for the 6 cohorts evaluated
- For AZD5423, models are consistent and predictive of changes due to differences in dose, deposition pattern and dissolution rate

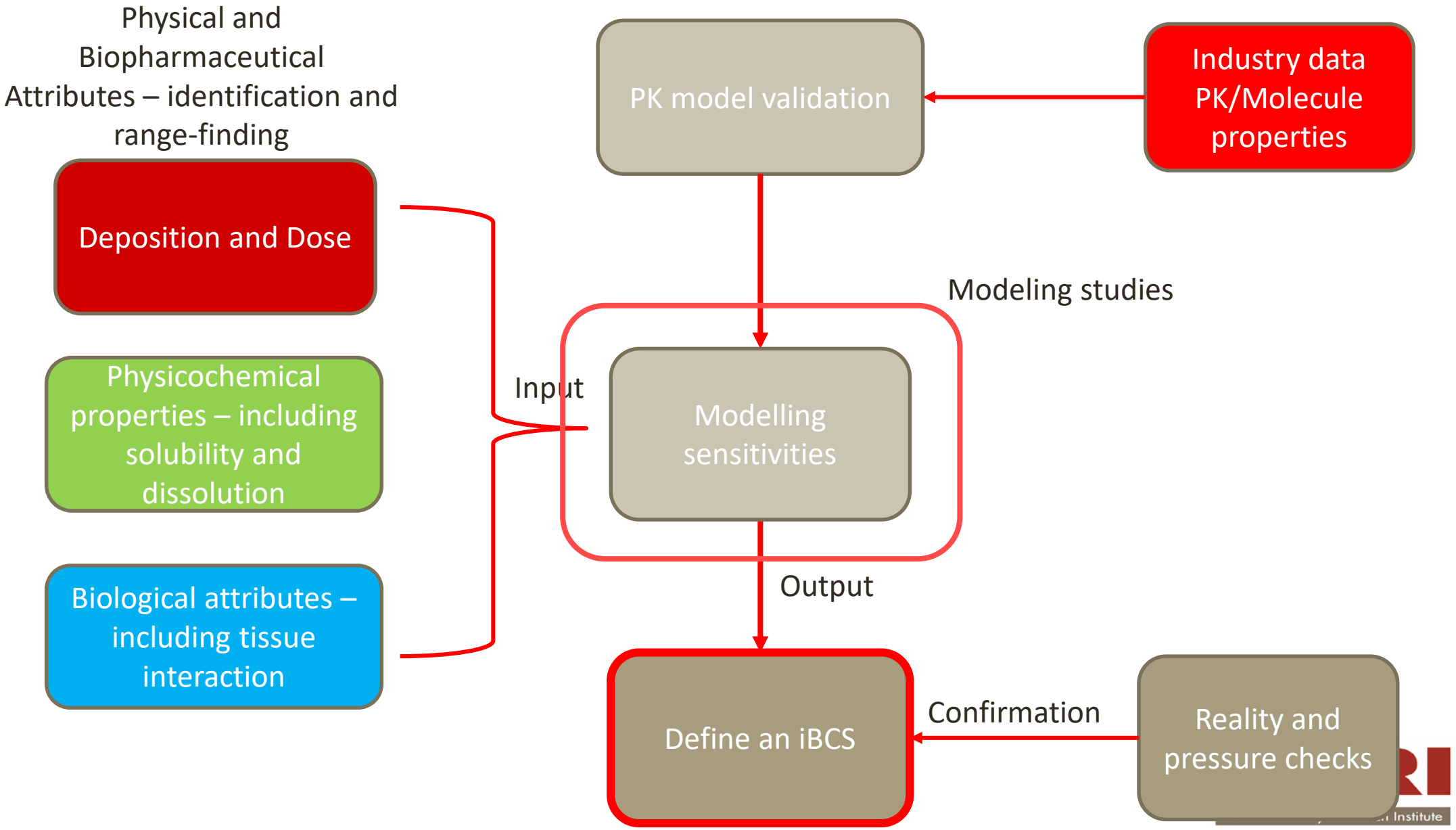
Validation – Summing Up (for a BCS 2-type drug)

work in progress

- All three models are capable of:
  - Simulating the overall shape of the plasma profile and how it qualitatively responds to changes in dose deposition and dissolution rate
  - Predicting absolute values of AUC_{inf}, AUC_t and C_{max} for the 6 cohorts evaluated within ± 5-30% (model and product dependent)

- Suggests that computer based simulations based on first principles are capable of clinically meaningful predictions of local and systemic PK for this type of drug
- Also, that these models are capable of simulating clinically meaningful changes in local and systemic PK in response to changes in critical product attributes such as dose, deposition and dissolution

The iBCS Process Map



Sensitivity Modelling – Outline

(work in progress)

Conducting airways (Bb)

Respiratory airways (Al)

Sensitivity modelling by varying:

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

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

Sensitivity Modelling – Test Grid & Drug Attributes

(work in progress)

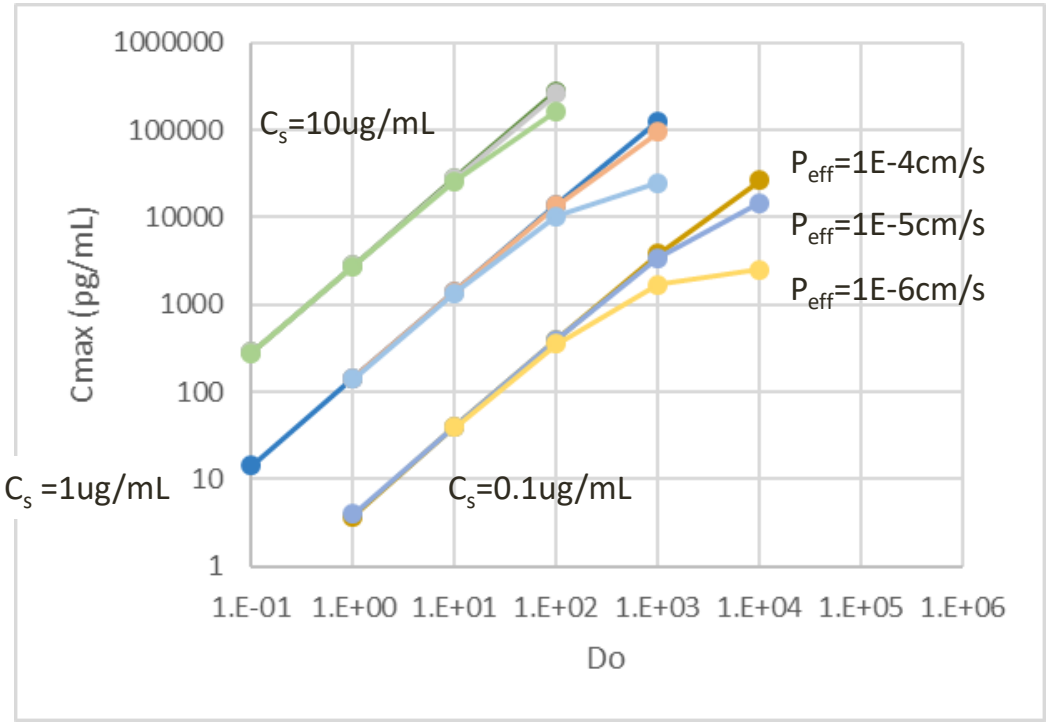
Hypothetical drug – Properties	
Mw	500 g/mol
logP	0
Diffusivity	3 E-4 cm^2/min
Solubility	**0.1-10 µg/mL**
pKa	Neutral
Peff	**1E-4 – 1 E-6 cm/s**
Rbp	1
Kp	1
Fup	1
VMD	**1-3µm**
GSD	2
Dose	0.43-4300 ug
CL	80L/h
Vc	10L

Do (V_{ASL}=4.3 mL)	Peff (cm/s)	Solubility (ug/mL)	VMD (GSD) (um)	Pulmonary Region	Output Parameters
0.1	1E-4	0.1	1 (2)	AI	T1/2 in Lumen
1	1E-5	1	2 (2)	Bb	Peak Flux into Tissue
10	1E-6	10	3 (2)		Cmax
100	1E-7	100	4 (2)		AUC
1 000					F
10 000					

Sensitivity Modelling – Respiratory Region (AI)

Doses (DD) ranging from 0.43 ug to 43 mg; Solubility (Cs) 0.1-10 ug/mL; Permeability (Peff) 1E-4 to 1E-6 cm/s

Impact of P_{eff} and C_s on C_{max}



Unpublished Data, iBCS PQRI Working Group

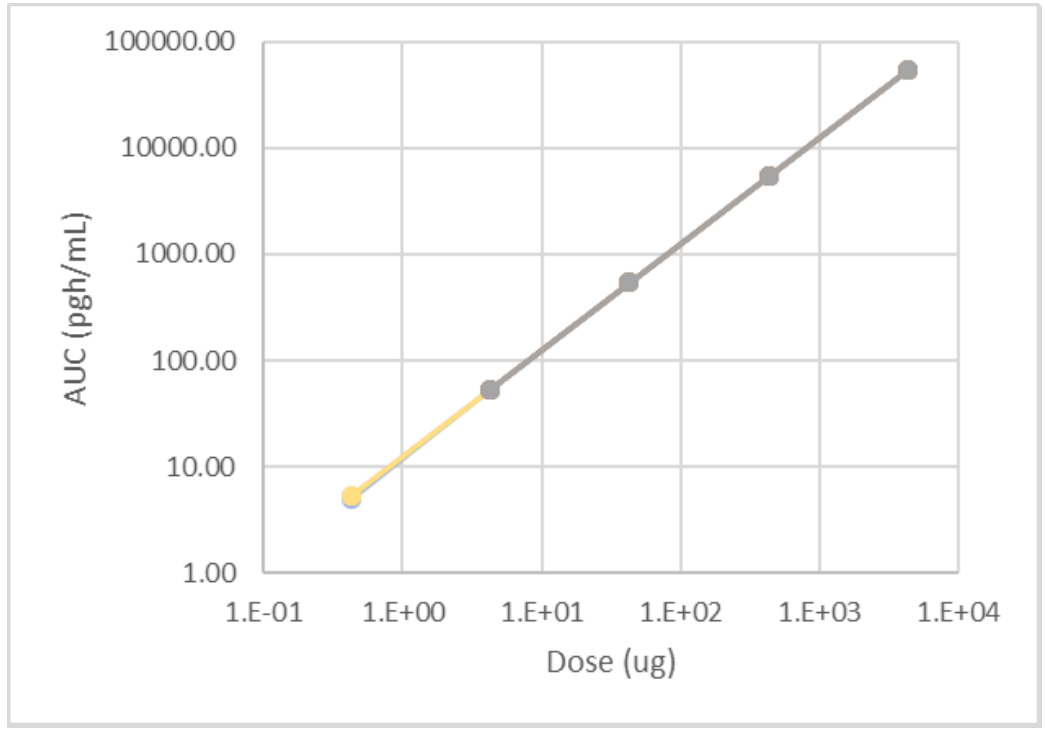
- At lower doses, (Do's <100), C_{max} is dissolution-rate driven and directly correlated to total specific surface area (dose)
- At higher doses, (Do's >100), C_{max} becomes permeability-rate driven and uncorrelated to dose (saturation)

22

Sensitivity Modelling – Respiratory Region (AI)

Doses (DD) ranging from 0.43 ug to 43 mg; Solubility (Cs) 0.1-10 ug/mL; Permeability (Peff) 1E-4 to 1E-6 cm/s

Impact of P_{eff} and C_s on **AUC_{inf}**



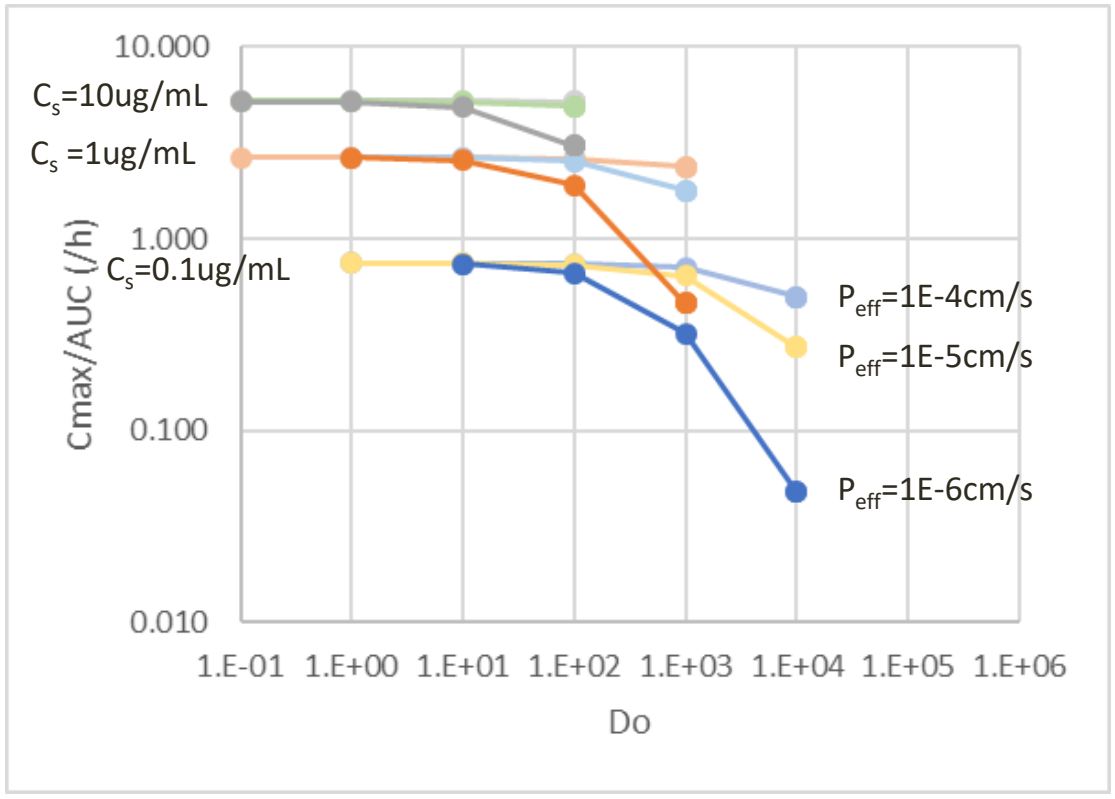
Unpublished Data, iBCS PQRI Working Group

- At all doses, AUC_{inf} is directly correlated to dose (F=1) and independent of C_s and P_{eff}
- Therefore, at same dose, neither changes in P_{eff}, nor in C_s impacts ~~on~~ AUC_{inf}

Sensitivity Modelling – Respiratory Region (AI)

Doses (DD) ranging from 0.43 ug to 43 mg; Solubility (Cs) 0.1-10 ug/mL; Permeability (Peff) 1E-4 to 1E-6 cm/s

Impact of P_{eff} and C_s on C_{max}/ AUC_{inf}

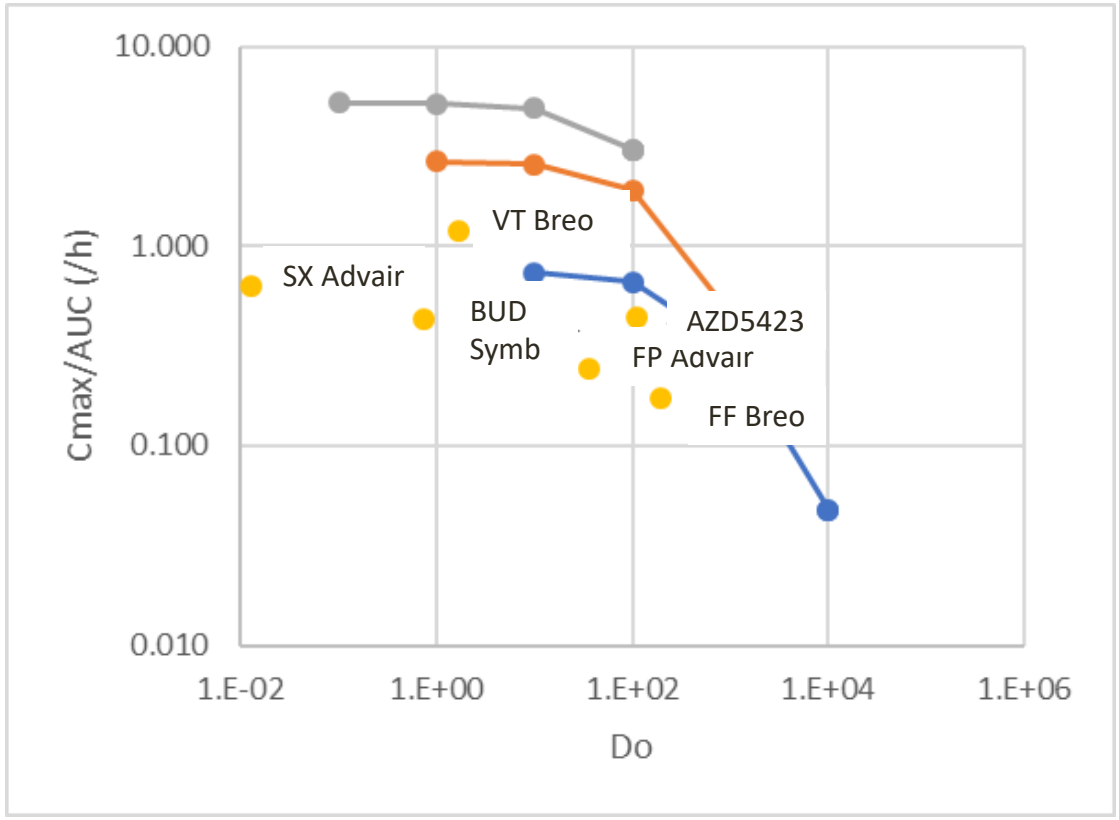


- The ratio of C_{max}/AUC_{inf} is used to assess equivalence of relative absorption rates
- The ratio of C_{max}/AUC_{inf} changes as the rate limiting step changes from dissolution to permeation

Unpublished Data, iBCS PQRI Working Group

Sensitivity Modelling – Actual Products?

C_{max}/ AUC_{inf} for a set of inhaled drugs



- Respiratory region dose numbers for actual products fall roughly within the investigated range
- A downward tendency can be observed as Do's increase despite differences in tissue interactions

Unpublished Data, iBCS PQRI Working Group

Sensitivity Modelling – Summing Up

- Sensitivity modelling suggests that computer based models may help identify rate limiting steps and critical attributes, as well break-points where they change
- Results also indicate that parameter sensitivity will change with region and dose for a given compound
- **Today**, sensitivity modelling could support understanding the clinical impact of changes in product attributes – possibly aiding the definition of specification limits on such attributes
- **Tomorrow**, sensitivity modelling could help define general classifiers to identify development risks for product classes – an iBCS

Outline

- Introduction to computer-based models
  - Model applications and general design principles
- Applications within the PQRI iBCS project
  - General outline and validation of approach (work in progress)
  - Identifying classifiers - Sensitivity Modelling (work in progress)
- General Applications to Inhaled Drug Product Development
  - Example: Advair Batch-to-Batch Variability
- Conclusions – opportunities and challenges

Batch Variability - Advair Diskus 100/50 ™, (FP/SX)

Plasma Profiles of FP(A) and SX(B)

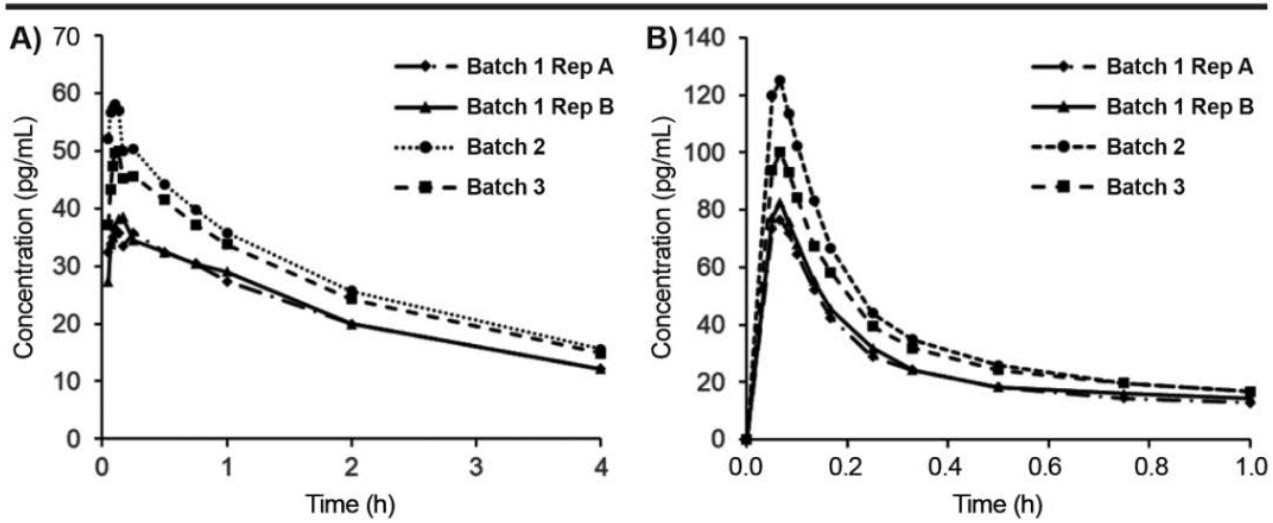


Figure 1. Mean plasma concentration vs. time profiles for: A) fluticasone propionate (100µg) and B) salmeterol xinafoate (50 µg) from three batches (Batch 1 replicated twice) following inhalation to healthy volunteers using the Advair Diskus 100/50. (Data from Reference 16, Figure 1).

Adapted from: Bäckman and Olsson, RDD Asia 2018
***Burmeister Getz et al, CPT, 2016**

- Significant batch to batch variability observed for Advair Diskus 100/50*
- Age difference 1 yr – Impact on FPM and/or Dissolution?

Batch Variability - Advair Diskus 100/50 ™, (FP/SX)

Simulated Impact of ± 15% variation in FPM*

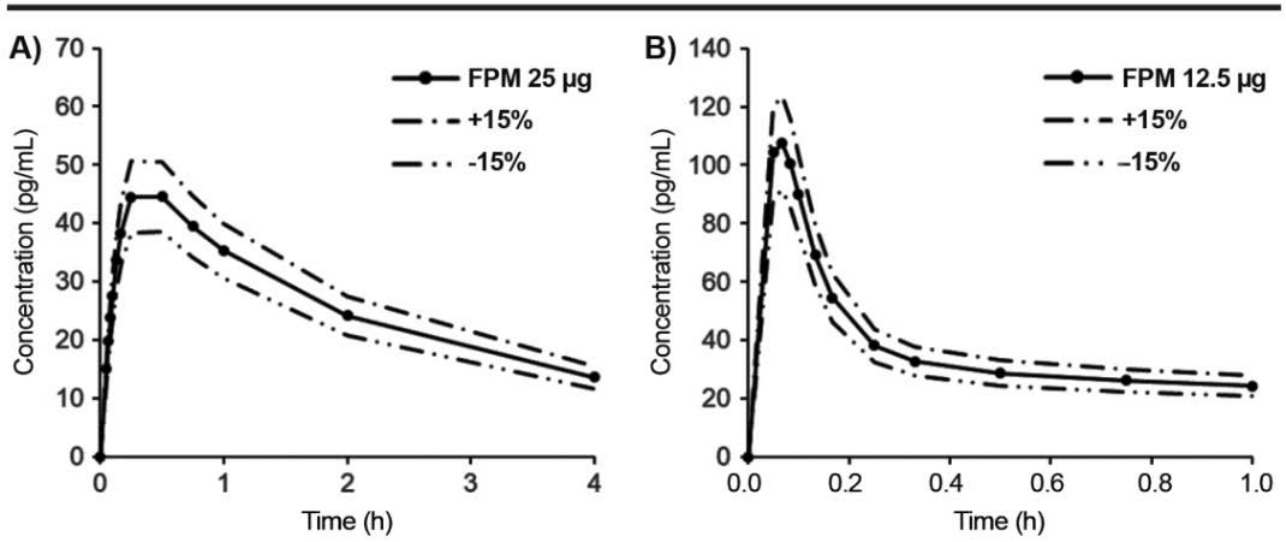


Figure 2. Simulated plasma-concentration vs time profiles for: A) fluticasone propionate and B) salmeterol xinafoate, illustrating the impact of a ± 15% variation in fine particle mass (FPM).

Adapted from: Bäckman and Olsson, RDD Asia 2018
***Mimetikos Preludium™**

- Good correlation between simulated and observed profiles
- Simulated variation in C_{max} and AUC corresponds to observed variation

Batch Variability - Advair Diskus 100/50 ™, (FP/SX)

Simulated Impact of ± 15% variation in VMD*

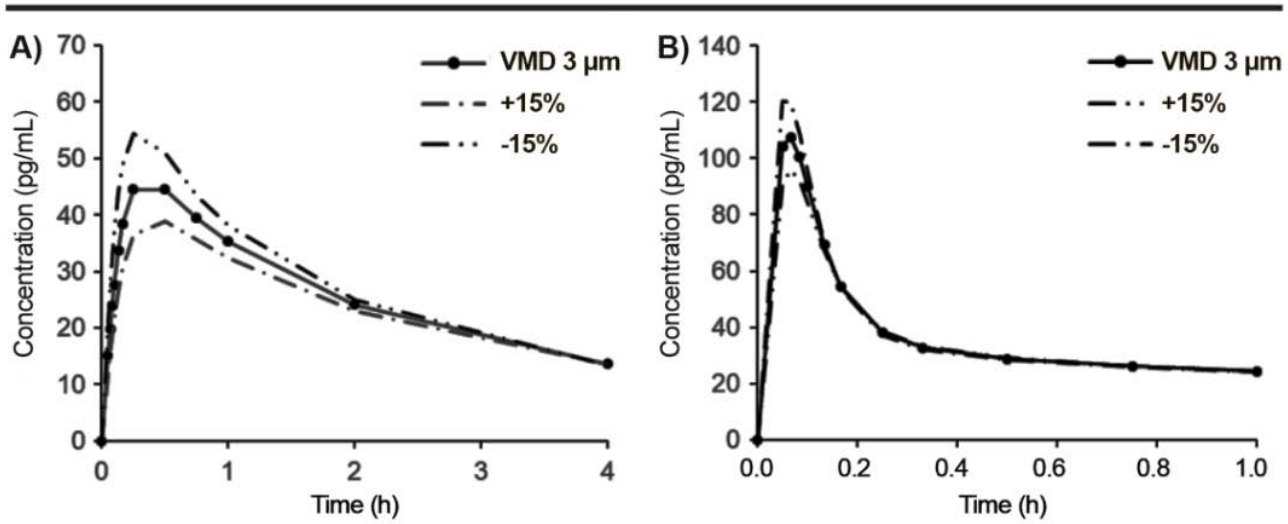


Figure 4. Simulated plasma-concentration vs time profiles for: A) fluticasone propionate and B) salmeterol xinafoate, illustrating the impact of ± 15% variation in volume mean diameter (VMD) of the fine particle mass (FPM).

Adapted from: Bäckman and Olsson, RDD Asia 2018
***Mimetikos Preludium™**

- Simulated variability impacts on C_{max}, not AUC
- Observed batch to batch variability in AUC is likely a result of variations in FPM, not in dissolution

Outline

- Introduction to computer-based models
  - Model applications and general design principles
- Applications within the PQRI iBCS project
  - General outline and validation of approach (work in progress)
  - Identifying classifiers - Sensitivity Modelling (work in progress)
- General Applications to Inhaled Drug Product Development
  - Example: Advair Batch-to-Batch Variability
- Conclusions – opportunities and challenges

Conclusions

- The validation studies, as well as other published examples suggests that computer based models based on first principles are capable of clinically meaningful simulations of systemic exposure in response to changes in critical product attributes
- Sensitivity modelling suggests that computer based models may provide insights into the rate limiting steps as a function of critical product attributes and phys chem properties.
- We hypothesize that this will enable definition of drug and/or product classes with distinct development risks
- **Today**, computer-based modelling and compound classifiers could support development of inhaled drugs and products, helping developers define specifications to meet demands on lung targeting, lung retention, and therapeutic equivalence with the minimum amount of studies
- **Tomorrow**, these tools could perhaps influence the regulatory landscape for inhaled products?

Acknowledgements

The PQRI BTC Working Group

- Jayne Hastedt (JDP Pharma – co-chair)
- Per Bäckman (Emmace – co-chair)
- Tony Cabal (Merck)
- Andy Clark (Aerogen Pharma)
- Carsten Ehrhardt (Trinity College Dublin)
- Ben Forbes (King's College London)
- Tony Hickey (USP/RTI)
- Guenther Hochhaus (University of Florida)
- Wenlei Jiang (FDA)
- Stavros Kassinos (University of Cyprus)
- 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

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

The AAPS Inhalation Focus Group

Backups

PQRI
Product Quality Research Institute

The Respiratory Tract

Hastedt et al AAPS Open 2016

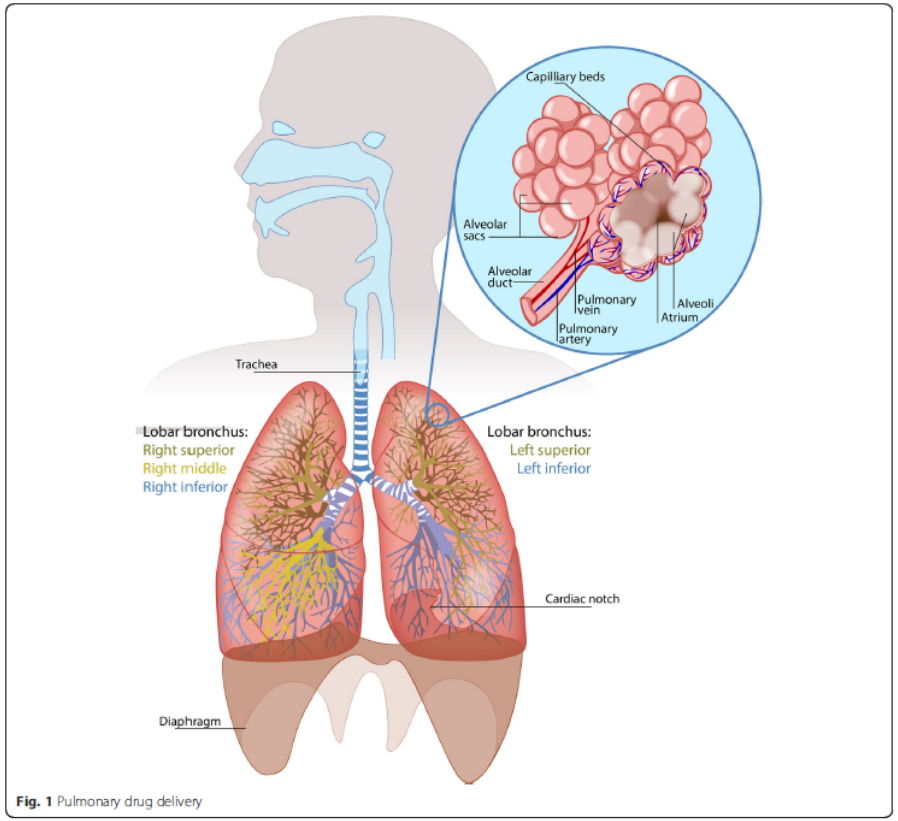


Fig. 1 Pulmonary drug delivery

	generation		d (cm)	l (cm)	number	cross-section area (cm2)	cartilage	epithelial cell type
conducting zone	trachea	0	1.8	12.0	1	2.54	open rings	columnar ciliated
	bronchi	1	1.22	4.8	2	2.33		
		2	0.83	1.9	4	2.13	plates	
		3	0.56	0.8	8	2.00		
	bronchioles	4	0.45	1.3	16	2.48		
	terminal bronchioles	5	0.35	1.07	32	3.11		
		↓	↓	↓	↓	↓		
		16	0.06	0.17	$6x10^4$	180.0		cuboidal
respiratory zone	respiratory bronchioles	17					absent	cuboidal to alveolar
		18	↓	↓	↓	↓		
		19	0.05	0.10	$5x10^5$	10^3		
	alveolar ducts	20						alveolar
		21						
		22	↓	↓	↓	↓		
	alveolar sacs	23	0.03	0.03	$8x10^6$	10^4		

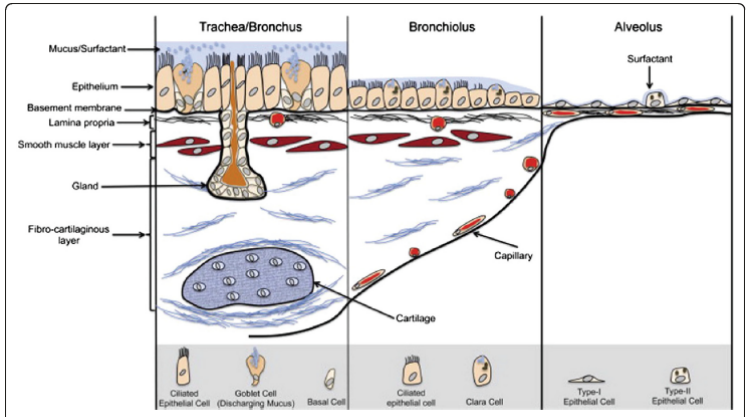


Fig. 2 Throughout the respiratory tract, the cell type and morphology changes in concert with their physiological function (Hittinger et al. 2015), adapted from (Klein et al. 2011)

Heterogeneous organ:

- Conducting Airways:
  - Small surface
  - T2 epithelium
  - Mucociliary clearance
- Alveolar interstitial region
  - Large surface
  - T1 epithelium
  - Particle clearance by alveolar macrophages

Aerosol Deposition

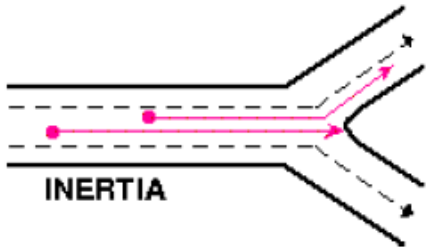
Courtesy of Bo Olsson (Lung Deposition 2016.ppt)

Impaction

(particle size)^2

velocity

density

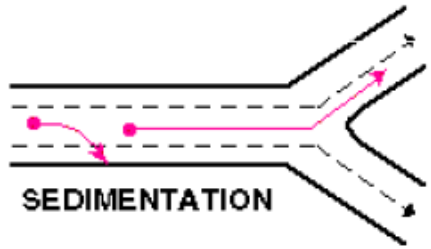


Sedimentation

(particle size)^2

residence time

(tube diameter)$^{-1}$

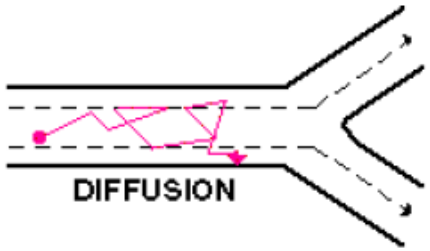


Diffusion

(particle size)$^{-½}$

(residence time)^{½}

(tube diameter)^{½}



- Large particles (>10 µm) end up in mouth throat due to high impaction
- Smaller particles (~3 µm) penetrate into lung
- Even smaller particles (~0.5 µm) may be exhaled

- All numbers influenced by inhalation manoeuvre and lung physiology

Impact of Disease
- FP in Accuhaler™ vs Bud in Turbuhaler™

Plasma Profiles HV and Moderate Asthma

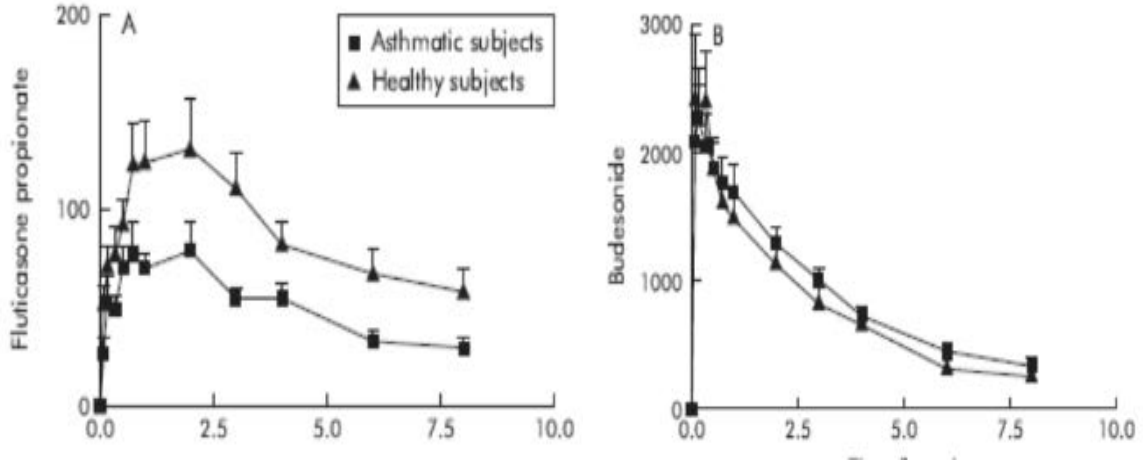


Figure 1 Mean (SE) plasma concentrations of (A) fluticasone propionate and (B) budesonide in healthy subjects and subjects with moderately severe asthma.

Adapted from: Harrison and Tattersfield (Thorax,2003)

- Moderate asthma reduced systemic exposure (AUC) for FP but not for Bud
- Why?

Impact of Disease
- FP in Accuhaler™ vs Bud in Turbuhaler™

Impact of large airway constriction? (FP(A); Bud(B))

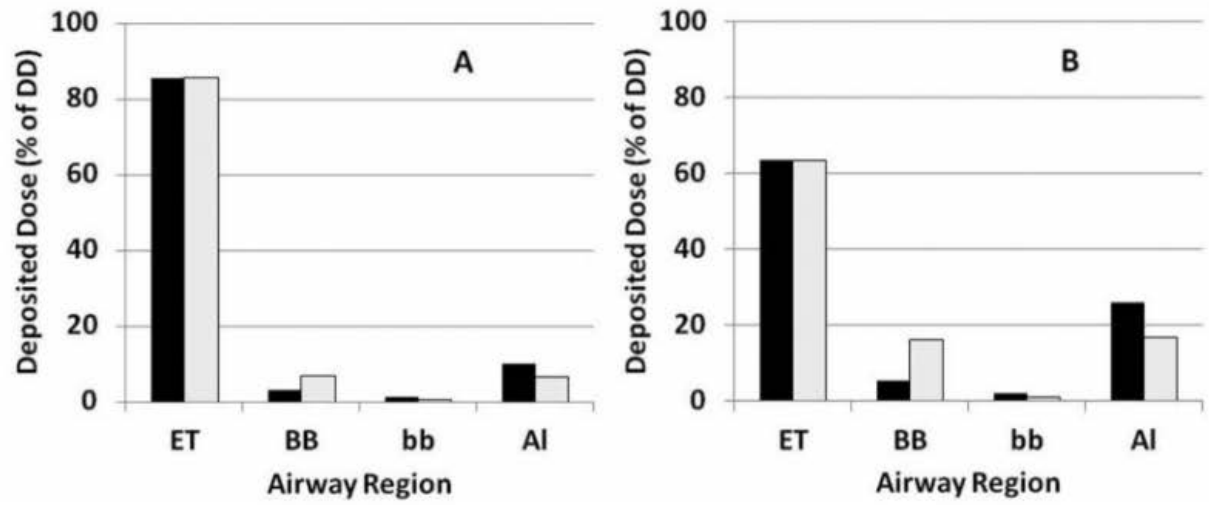


Figure 1. Predicted deposition patterns for fluticasone propionate administered via Accuhaler™ (A) and budesonide administered via Turbuhaler® (B) in healthy volunteers (black) and asthma patients (gray). ET = extra-thoracic, BB = large bronchi, bb = small bronchi, AI = alveolar interstitium.

Adapted from: Bäckman and Olsson, RDD, 2016

Simulated deposition pattern suggests:

- Same lung dose
- Disease driven shift from AI to Bb

Impact of Disease
- FP in Accuhaler™ vs Bud in Turbuhaler™

Mechanistic Simulations[1]

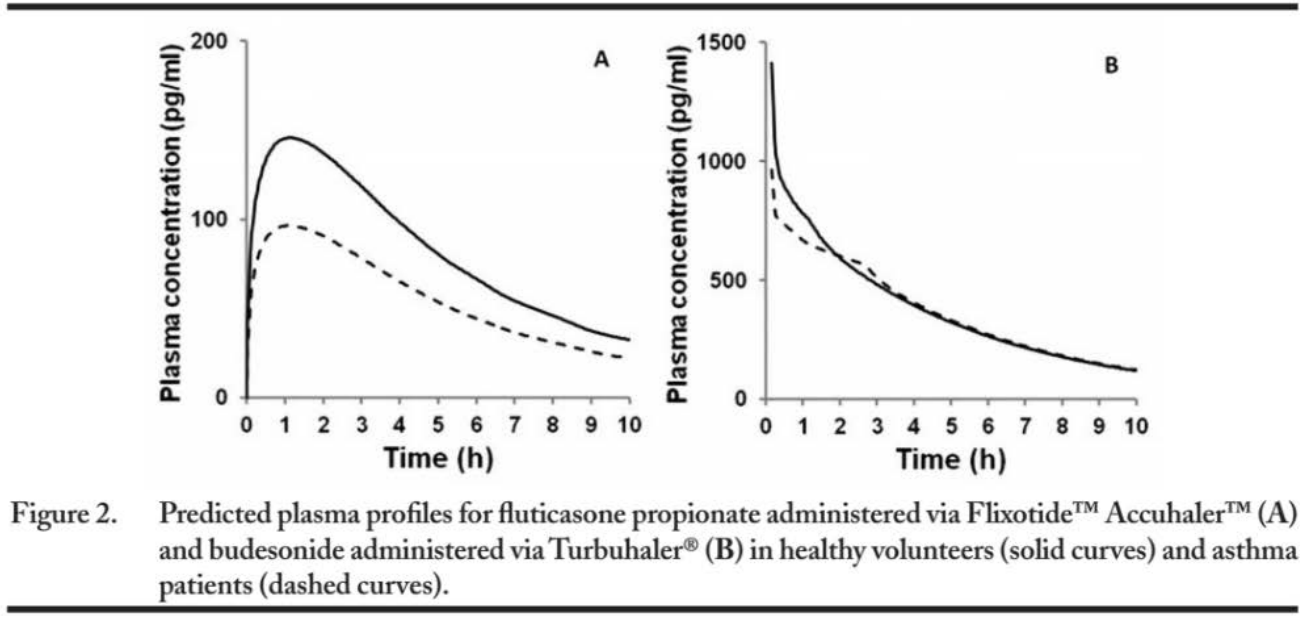


Figure 2. Predicted plasma profiles for fluticasone propionate administered via Flixotide™ Accuhaler™ (A) and budesonide administered via Turbuhaler® (B) in healthy volunteers (solid curves) and asthma patients (dashed curves).

- Reasonable correlations between simulated and observed C_{max} and AUC
- **Low FP bioavailability in Bb results in significant AUC reduction**

Adapted from: Bäckman and Olsson, RDD, 2016, [1] Gastroplus ™, ver 9.0, Simulations Plus Inc. Lancaster CA, US