Modelling aspects related to inhaled medicines

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Co-Chair of PQRI BTC iBCS Working Group
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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
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Why do We Need Computer Based Models?

**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)

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Modified from Olsson and Bäckman, Respiratory Drug delivery 2014
When do We Need Computer Based Models?

Dx → Ph1 → Ph2 → Ph3 → Ph4

Compound Design → Device Bridging → IVIVC → Product Design

BE Design
Examples of Computer-Based Models (Q4-2017)

- 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

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: \( \frac{dn_{ET}}{dt} \propto k_{MCC} \times n_{BB} \)
- Dissolution: \( \frac{dn_{sol}}{dt} \propto D/h \times A_s \times (C_s-C_{ALF}) \)
- Permeation into Tissue: \( \frac{dn_{tis}}{dt} \propto P_{eff} \times A_{epi} \times (C_{ALF}-C_{epi}) \)
- Perfusion into System*: \( \frac{dn_{sys}}{dt} \propto Q \times V_{tis} \times R_{bp} / F_{up} \times [C_{tis} - C_{sys}] \)

*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
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The iBCS Process Map

Physical and Biopharmaceutical Attributes – identification and range-finding

Deposition and Dose

Physicochemical properties – including solubility and dissolution

Biological attributes – including tissue interaction

PK model validation

Input

Modelling sensitivities

Output

Define an iBCS

Compounds for Model Validation:
1. Albuterol (BCS1)
2. Fluticasone (BCS2)
3. AZD5423 (BCS2)
4. Olodaterol (BCS3)

Industry data PK/Molecule properties

Confirmation

Reality and pressure checks

Input

Removal of biological attributes – including tissue interaction

Output

Define an iBCS

Compounds for Model Validation:
1. Albuterol (BCS1)
2. Fluticasone (BCS2)
3. AZD5423 (BCS2)
4. Olodaterol (BCS3)

Industry data PK/Molecule properties

Confirmation

Reality and pressure checks

Input
Validation – The AZD 5423 Example
Clinical data and model inputs from Bäckman, Tehler and Olsson, JAMP 2017

Compound Properties

<table>
<thead>
<tr>
<th>Property (units)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight (g/mol)</td>
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<tr>
<td>Lipophilicity, logD</td>
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<td>Permeability, $P_{app}$ (cm/s x 10^6)</td>
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<td>Solubility in PBS, pH 7.4 (µM)</td>
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<td>Solubility in FASSIFv2 (µM)</td>
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<tr>
<td>Protein binding, $F_{up}$ (%)</td>
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<tr>
<td>Blood–plasma partitioning, $R_{bp}$</td>
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<tr>
<td>Density (g/mL)</td>
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<tr>
<td>$pK_a$</td>
<td>Neutral</td>
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<tr>
<td>Particle Size, MMD (GSD), Study 1 (µm)$^a$</td>
<td>1.3 (3.2)</td>
</tr>
<tr>
<td>Particle Size, MMD (GSD), Study 2 (µm)$^a$</td>
<td>3.1 (1.8)</td>
</tr>
</tbody>
</table>

- 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
Impact of deposition pattern

- 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?

Impact of dissolution rate (VMD)

- Flow = 15 l/min
- Flow = 43 l/min
- VMD = 1.3 um
- VMD = 3.1 um
Validation – Gastroplus ADRM™ (w AZ deposition)

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

Impact of deposition pattern

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

Impact of dissolution rate (VMD)

- Flow = 15 l/min
- Flow = 43 l/min
- VMD = 1.3 um
- VMD = 3.1 um
Validation – Mimetikos Preludium™

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

Impact of deposition pattern

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

Impact of dissolution rate (VMD)

- Flow = 15 l/min
- Flow = 43 l/min
- VMD = 1.3 µm
- VMD = 3.1 µm
Validation – Simulations of AUC & $C_{\text{max}}$

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

- All three models give reasonable simulations of $\text{AUC}_{\text{inf}}$, $\text{AUC}_t$ and $C_{\text{max}}$ 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 $\text{AUC}_{\text{inf}}$, $\text{AUC}_t$ and $\text{C}_{\text{max}}$ for the 6 cohorts evaluated within $\pm$ 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

Physical and Biopharmaceutical Attributes – identification and range-finding

Deposition and Dose

Physicochemical properties – including solubility and dissolution

Biological attributes – including tissue interaction

PK model validation

Input

Modelling sensitivities

Output

Define an iBCS

Confirmation

Industry data PK/Molecule properties

Modeling studies

Reality and pressure checks

The iBCS Process Map

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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

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<th>Property</th>
<th>Value</th>
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<td>pKa</td>
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<tr>
<td>Peff</td>
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<td>Rbp</td>
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<td>Peak Flux into Tissue</td>
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<td>Pulmonary Region</td>
<td>AUC</td>
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<td>Output Parameters</td>
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</table>
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

Unpublished Data, iBCS PQRI Working Group

- At lower doses, (Do’s <100), $C_{\text{max}}$ is dissolution-rate driven and directly correlated to total specific surface area (dose)
- At higher doses, (Do’s >100), $C_{\text{max}}$ becomes permeability-rate driven and uncorrelated to dose (saturation)
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 $P_{\text{eff}}$ and $C_s$ on AUC$_{\text{inf}}$

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

Unpublished Data, iBCS PQRI Working Group
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

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

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

Unpublished Data, IBCS PQRI Working Group
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.
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Batch Variability - Advair Diskus 100/50™, (FP/SX)

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

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

Simulated Impact of ± 15% variation in FPM*

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

Adapted from: Bäckman and Olsson, RDD Asia 2018

*Mimetikos Preludium™

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

Simulated Impact of ± 15% variation in VMD*

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

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™
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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?
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- Dede Godstrey
- Erika Stippler
- Wenlei Jiang
Backups
Heterogeneous organ:

- **Conducting Airways:**
  - Small surface
  - T2 epithelium
  - Mucociliary clearance

- **Alveolar interstitial region**
  - Large surface
  - T1 epithelium
  - Particle clearance by alveolar macrophages
Aerosol Deposition

Impaction

\[(\text{particle size})^2, \text{velocity}, \text{density}\]

Sedimentation

\[(\text{particle size})^2, \text{residence time}, (\text{tube diameter})^{-1}\]

Diffusion

\[(\text{particle size})^{-\frac{1}{2}}, (\text{residence time})^{\frac{1}{2}}, (\text{tube diameter})^{\frac{1}{2}}\]

- 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

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

Adapted from: Harrison and Tattersfield (Thorax,2003)
Impact of Disease - FP in Accuhaler™ vs Bud in Turbuhaler™

Simulated deposition pattern suggests:
- Same lung dose
- Disease driven shift from Al to Bb

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

Mechanistic Simulations

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

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).

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