Biopharmaceutical Classification of Inhaled Medicines: Modeling Approaches and the Development of an iBCS

PQRI BTC Inhalation-based Biopharmaceutical Classification System Working Group
SimInhale COST Action MP1404 October 2019
Outline

- Classification System for Oral Drugs
- Scope and Relevance of an iBCS
- The iBCS Development Process
- Operating Principles and Proposed Classification Grids
- Modelling and Simulation Approaches
- Summary, Conclusions, and Next Steps
Classification of Oral Drugs

- 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.  
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

Biopharmaceutical Classification System

Volume Required to Dissolve the Highest Dose (mL)

Permeability (1x10^{-6} cm per s)

- I: High solubility, High permeability
- II: Low solubility, High permeability
- III: High solubility, Low permeability
- IV: Low solubility, Low permeability

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.
Overall Goal and Scope of the iBCS Initiative

**Goal:**
- Develop a physiologically-based pulmonary drug product classification system based on biorelevant drug and product attributes.

**Scope:**
- The initial focus will be on locally acting therapeutics and will exclude antibiotics, systemic delivery, metabolized drugs (pro-drugs), protein and nucleic acid therapeutics.
- Until standardized methods are developed and available, for physicochemical and systemic data sets that are not available to the working group, input parameters used for modelling studies will be obtained from the literature using methods and/or media that are as similar as possible (e.g., Caco-2 for permeability, PBS for solubility).
Developing and iBCS: The 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.
The iBCS Development Plan

- Develop a pulmonary drug product classification system 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 boundaries (sensitivity) and application (validation) through simulation studies.

- Outcomes:
  - Identify attribute “Rule of Thumb” guidelines based on the classification grid and boundaries.
  - Identify modeling tools for BE assessment.
The iBCS Process Map

Physical and Biopharmaceutical Attributes – identification and range-finding

- Deposition and Dose
- Physicochemical properties – including solubility and dissolution
- Biological attributes – permeability and disposition

PK model validation

Modeling studies

Input

- PK model validation

Output

- Define an iBCS

Confirmation

- Reality and pressure checks

Industry data PK/Molecule properties

Modeling studies

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Foundational Principles of an iBCS

- 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.
  - Currently, identical regional dose deposition patterns can only be obtained by manufacturing products with similar properties and delivering with similar devices.
Peak absorption rate (Cmax) governed by solubility (driver) and permeability (barrier) – both molecular properties. Extent (AUCc) of absorption governed by the balance between absorption and MCC – dose independent

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 (AUCc) likely to be = dose in conducting airways unless permeability is very low, dose is high, or drug is metabolized

Peak absorption rate (Cmax) governed by dose and permeability. Extent (AUCc) likely to be = peripheral dose unless drug is metabolized
Proposed Regional iBCS Grids

Central Compartment

<table>
<thead>
<tr>
<th>Low Permeability</th>
<th>Low Solubility (non-sink)</th>
<th>High Solubility (sink)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete and very slow absorption</td>
<td>Mostly complete and slow absorption</td>
<td></td>
</tr>
<tr>
<td>Incomplete and slow absorption</td>
<td>Complete and fast absorption</td>
<td></td>
</tr>
</tbody>
</table>

Peripheral Compartment

<table>
<thead>
<tr>
<th>Low Permeability</th>
<th>Low Solubility (sink)</th>
<th>High Solubility (sink)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete and dissolution-rate driven absorption (very slow)</td>
<td>Complete and permeability-driven absorption (fast)</td>
<td></td>
</tr>
<tr>
<td>Complete and dissolution-rate driven absorption (very fast)</td>
<td>Complete and fast absorption (immediate)</td>
<td></td>
</tr>
</tbody>
</table>
**Grids and Compounds for iBCS Model Validation**

<table>
<thead>
<tr>
<th>giBCS Class</th>
<th>Solubility</th>
<th>Permeability</th>
<th>Oral Route</th>
<th>Pulmonary Route</th>
<th>Model Compounds for iBCS Model Validation</th>
</tr>
</thead>
</table>
| 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)  
AZD 5423 |
| III         | High       | Low          | • Sufficiently/poorly absorbed | • Available dose \(\simeq\) deposited dose  
• Long MAT | Olodaterol |
| IV          | Low        | Low          | • Poorly absorbed | • Available dose < deposited dose  
• Very Long MAT | None identified |
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

PK/Molecule properties

Input

Confirmation

SimInhale COST Action Oct 2019
Why Do We Need Computer Based Models?

**Understanding**
Multiple, kinetically competing processes 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
Computer-Based Models and the iBCS

Mechanistic deposition and pulmonary absorption software packages available to the iBCS Working Group:
- AstraZeneca LungSIM (proprietary, presented at DDL 2017)
- Merck (proprietary, presented at DDL 2016)
- SimulationsPlus Gastroplus ADRM (commercially available)
- Mimetikos Preludium (commercially available)
Validation studies will be conducted using one of the software platforms to assess the ability of the software to simulate exposure using parameters of solubility, permeability, and regional dose.

1. Collect data for each model compound/product
   - Formulation properties (i.e., aerosol performance)
   - Physicochemical and molecular properties
   - Systemic properties
   - Associated PK data set

2. Run PBPK simulations

3. Compare simulated profiles to actual profiles
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>
<td>487.5</td>
</tr>
<tr>
<td>Lipophilicity, logD</td>
<td>5.7</td>
</tr>
<tr>
<td>Permeability, P_{app} (cm/s × 10^6)</td>
<td>10.4</td>
</tr>
<tr>
<td>Solubility in PBS, pH 7.4 (μM)</td>
<td>0.6</td>
</tr>
<tr>
<td>Solubility in FASSIFv2 (μM)</td>
<td>9</td>
</tr>
<tr>
<td>Protein binding, F_{up} (%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Blood–plasma partitioning, R_{bp}</td>
<td>0.58</td>
</tr>
<tr>
<td>Density (g/mL)</td>
<td>1.4</td>
</tr>
<tr>
<td>pKa</td>
<td>Neutral</td>
</tr>
<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
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 (within ± 5-30%) of $AUC_{\text{inf}}$, $AUC_t$ and $C_{\text{max}}$ for the 6 cohorts evaluated.

- For AZD 5423, models are consistent and predictive of changes due to differences in dose, deposition pattern and dissolution rate.
The iBCS Process Map

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Reality and pressure checks
iBCS and PBPK Sensitivities Analyses

- PBPK simulations will be conducted using various software platforms and input parameters to:
  - Understand the impact of dose, solubility, and permeability on the proposed regional classification grids and boundaries
  - Identify the rate limiting processes at different conditions and in different regions of the lungs

- Conducting airways (Bb)
- Respiratory airways (Al)

Sensitivity modelling ranges:
- Doses (0.43 µg – 4.3 mg)
- Solubility (0.1 µg/mL – 100 µg/mL)
- Permeability (1x10^-4 cm/s – 1x10^-7 cm/s)
Preludium: Snapshot of Results for AI (g16-23) Deposition

- Preliminary sensitivity data from 3 software packages have been generated
- Results are currently being evaluated by the iBCS Modeling Working Group

*Unpublished data from iBCS WG*
Current Conclusions Based on PBPK Modelling

- The PK modelling validation studies, as well as other published examples suggest that computer based models based on first principles are capable of generating clinically meaningful simulations of systemic exposure in response to changes in critical product attributes.

- Validation results also indicate that all 3 models evaluated for AZD 5423 (BCS 2-like compound) 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.

- 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.

- We hypothesize that PBPK validation and sensitivity studies will enable definition of drug and/or product classes with distinct development risks.
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
The PQRI BTC iBCS Working Group Members

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- Guenther Hochhaus (University of Florida)
- Wenlei Jiang (FDA)
- Stavros Kassinos (University of Cyprus)
- Phil Kuehl (Lovelace Biomedical)
- David Prime (GSK)
- Yoen-Ju Son (Merck)
- Erika Stippler (EDQM)
- Simon Teague (GSK)
- Ulrika Tehler (Astra Zeneca)
- Jen Wylie (Merck)
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https://pqri.org/

Thank You!