Mechanistic IVIVC Using the Simcyp ADAM Model

Make SCIENCE out of IVIVC
**IVIVC and Its Components**

**IVIVC (In Vitro-In Vivo Correlation):** A predictive mathematical model describing the relationship between an in vitro property (usually drug dissolution or release) and a relevant in vivo response, e.g., amount of drug absorbed.

**IVIV Relationships:** The in vitro dissolution and in vivo input curves may be directly superimposable or may be made to be superimposable by the use of a scaling factor/function. Nonlinear correlations, while uncommon, may also be appropriate.
Deconvolution in simplified terms is the method to estimate the rate of input in the system that produces the observed response (PK profile).

**Model Dependent Methods**
- Algebraic Equation Based
  - Wagner Nelson
  - Loo Riegelman
- Differential Equation Based
  - DE Compartmental Model
  - Physiological (ADAM) Model

**Model Independent Methods**
- Direct Numerical Deconvolution
- Numerical Deconvolution Through Convolution
Deconvolution: Mechanistic ADAM Model

**Deconvolution: Mechanistic ADAM Model**

*in vivo* dissolution is deconvoluted separately from GIT transit, permeation, gut wall metabolism and first pass liver extraction.
Mechanistic vs. Conventional IVIVC

CR BCS I OR BCS II Low Extraction
- In vivo
- In vitro
- Conventional Deconvolution

CR BCS I OR BCS II High Extraction
- In vivo
- In vitro
- Conventional Deconvolution

CR BCS III OR BCS IV Low Extraction
- In vivo
- In vitro
- Conventional Deconvolution

CR BCS III OR BCS IV High Extraction
- In vivo
- In vitro
- Conventional Deconvolution

Differing Permeation/Metabolism in GIT
- In vivo
- In vitro
- Conventional Deconvolution

Drugs with Enterohepatic Recirculation
- In vivo
- In vitro
- Conventional Deconvolution

Dissolution
Permeation
Systemic Input
Mechanistic IVIVC Case Study Using Simcyp

- Metoprolol is a BCS Class I (High Solubility High Permeability) High First Pass Extraction Drug
- Relatively short half life and sufficient absorption from colon makes it suitable candidate for extended release formulation
- ER formulations of BCS Class I drug are Dissolution/Release Controlled Absorption

**ER BCS I OR BCS II High Extraction**

Conventional methods may require IVIVR function with lag time, sigmoid or power function to accommodate delay and slowness of *in vivo* availability as compared to *in vitro* conditions
The IVIVR was sigmoid or with lag time.

FRA -> FRD graphs shown here used all three formulation data to establish IVIVC. No graphs are shown when one of the formulations is used as external.

In spite of using parent and metabolite data and lag time IVIVR, prediction errors were higher. No graphs or results are shown when one of the formulations is used as external.
Mechanistic IVIVC Case Study Using Simcyp

Slow and Fast Formulations Used for IVIVC and Medium as External

- PK Data after oral solution were used to estimate permeability, distribution and elimination parameters
- in vivo dissolution profiles that produce observed PK profiles of each formulation were estimated

**Linear IVIVC without Lag**

- \( y = 0.8684x \quad R^2 = 0.9675 \)
- \( y = 0.0021x^2 + 0.6925x \quad R^2 = 0.9782 \)

**IVIVR Predictivity**

- \( y = 0.9941x \quad R^2 = 0.9703 \)

Deconvolution of *in vivo* dissolution rather than input rate allowed the establishment of IVIV Relationship without lag time and superior correlation (\( R^2 = 0.98 \)).
Understanding Bio-relevance of dissolution media

- The *in vitro* dissolution media used is more bio-relevant to medium release formulation but not for the fast and slow release formulations.

- Thus, Medium and Fast/Slow release formulations based IVIVC will lead to very good statistics ($R^2$) however confidence in prediction for new formulation beyond used range is questionable.

- Using two extremes (fast and slow) to develop model and test the model for medium also conforms to the idea of domain of applicability.
**Mechanistic IVIVC Using Simcyp: Internal and External Validations**

![Plasma Concentration vs. Time](image)

<table>
<thead>
<tr>
<th>Formulation ID</th>
<th>Cmax (ng/mL)</th>
<th>AUC (ng/mL*h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs</td>
<td>Pred</td>
</tr>
<tr>
<td><strong>Internal Validation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast</td>
<td>108.00</td>
<td>109.61</td>
</tr>
<tr>
<td>Slow</td>
<td>63.70</td>
<td>69.54</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>-5.33</td>
</tr>
<tr>
<td><strong>External Validation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>86.30</td>
<td>83.51</td>
</tr>
</tbody>
</table>
### Designing a new once-daily formulation of Metoprolol

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Fast Formulation</th>
<th>Medium Formulation</th>
<th>Slow Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.0</td>
<td>39.61</td>
<td>26.16</td>
<td>18.55</td>
</tr>
<tr>
<td>1.5</td>
<td>69.30</td>
<td>46.13</td>
<td>31.71</td>
</tr>
<tr>
<td>2.0</td>
<td>92.84</td>
<td>60.91</td>
<td>40.50</td>
</tr>
<tr>
<td>3.0</td>
<td><strong>118.68</strong></td>
<td>87.56</td>
<td>56.94</td>
</tr>
<tr>
<td>4.0</td>
<td><strong>107.25</strong></td>
<td>90.39</td>
<td>61.71</td>
</tr>
<tr>
<td>6.0</td>
<td>69.16</td>
<td>78.23</td>
<td>63.00</td>
</tr>
<tr>
<td>8.0</td>
<td>45.98</td>
<td>59.26</td>
<td>53.11</td>
</tr>
<tr>
<td>10.0</td>
<td>28.14</td>
<td>39.16</td>
<td>36.24</td>
</tr>
<tr>
<td>12.0</td>
<td><strong>18.08</strong></td>
<td>26.83</td>
<td>26.99</td>
</tr>
<tr>
<td>14.0</td>
<td>11.91</td>
<td><strong>17.91</strong></td>
<td><strong>17.26</strong></td>
</tr>
<tr>
<td>16.0</td>
<td>8.66</td>
<td>13.20</td>
<td>11.58</td>
</tr>
<tr>
<td>20.0</td>
<td>4.27</td>
<td>7.19</td>
<td>5.89</td>
</tr>
<tr>
<td>24.0</td>
<td>2.79</td>
<td>3.76</td>
<td>2.95</td>
</tr>
</tbody>
</table>

Therapeutic Cp range of metoprolol is 20-100 ng/mL

- All three formulations lead to Cp below 20 ng/mL after 12 h
- Thus they require administration every 12 h (twice daily)
- The Fast formulation leads to Cp beyond maximum tolerable Cp (100 ng/mL)

**How can you use Simcyp to design new once-daily (24 h) formulation?**
**Designing a new once-daily formulation: Generating desired Cp Profile**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Fast Cp (ng/mL)</th>
<th>Medium Cp (ng/mL)</th>
<th>Slow Cp (ng/mL)</th>
<th>New Cp (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>1.0</td>
<td>39.61</td>
<td>26.16</td>
<td>18.55</td>
<td><strong>25.00</strong></td>
</tr>
<tr>
<td>1.5</td>
<td>69.30</td>
<td>46.13</td>
<td>31.71</td>
<td>34.00</td>
</tr>
<tr>
<td>2.0</td>
<td>92.84</td>
<td>60.91</td>
<td>40.50</td>
<td>42.00</td>
</tr>
<tr>
<td>3.0</td>
<td><strong>118.68</strong></td>
<td>87.56</td>
<td>56.94</td>
<td>54.00</td>
</tr>
<tr>
<td>4.0</td>
<td><strong>107.25</strong></td>
<td>90.39</td>
<td>61.71</td>
<td>62.00</td>
</tr>
<tr>
<td>6.0</td>
<td>69.16</td>
<td>78.23</td>
<td>63.00</td>
<td>70.00</td>
</tr>
<tr>
<td>8.0</td>
<td>45.98</td>
<td>59.26</td>
<td>53.11</td>
<td>72.00</td>
</tr>
<tr>
<td>10.0</td>
<td>28.14</td>
<td>39.16</td>
<td>36.24</td>
<td>70.00</td>
</tr>
<tr>
<td>12.0</td>
<td><strong>18.08</strong></td>
<td>26.83</td>
<td>26.99</td>
<td>65.00</td>
</tr>
<tr>
<td>14.0</td>
<td>11.91</td>
<td><strong>17.91</strong></td>
<td><strong>17.26</strong></td>
<td>56.00</td>
</tr>
<tr>
<td>16.0</td>
<td>8.66</td>
<td>13.20</td>
<td>11.58</td>
<td>48.00</td>
</tr>
<tr>
<td>20.0</td>
<td>4.27</td>
<td>7.19</td>
<td>5.89</td>
<td>34.00</td>
</tr>
<tr>
<td>24.0</td>
<td>2.79</td>
<td>3.76</td>
<td>2.95</td>
<td><strong>24.00</strong></td>
</tr>
</tbody>
</table>

- Intuitively design a desired PK profile keeping in mind the disposition kinetics of the drug

**How to decide the dose??***

- Calculate AUC of the known formulation and newly designed PK profile
- Now estimate required dose assuming linear dose-proportionality

**Estimated Dose of New Formulation is 200 mg**
Designing a new once-daily formulation: Optimising dose to get desired Cp Profile

- Use disposition parameters obtained previously in IVIVC exercise and estimate required dissolution profile to obtain desired Cp profile

The best fit was able to achieve desired absorption phase but not the disposition
This indicates that amount of drug is not sufficient to maintain desired Cp until 24 h
More dose should be administered to achieve desired total exposure

How much is the desired dose???
Designing a new formulation: Optimise the desired dose to achieve desired Cp profile

The dose required to achieve the desired Cp profile is 250 mg
Now predict the required in vivo dissolution to achieve desired Cp profile
Designing a new formulation: Estimate required dissolution profile to achieve desired Cp profile

• This is the required \textit{in vivo} dissolution profile

• Use the established and validated IVIVC to obtain required \textit{in vitro} dissolution profile from estimated \textit{in vivo} dissolution profile

\begin{verbatim}
<table>
<thead>
<tr>
<th>Time</th>
<th>%Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>6.29</td>
</tr>
<tr>
<td>2</td>
<td>8.98</td>
</tr>
<tr>
<td>4</td>
<td>16.31</td>
</tr>
<tr>
<td>6</td>
<td>23.33</td>
</tr>
<tr>
<td>8</td>
<td>30.40</td>
</tr>
<tr>
<td>12</td>
<td>46.36</td>
</tr>
<tr>
<td>16</td>
<td>63.69</td>
</tr>
<tr>
<td>24</td>
<td>99.89</td>
</tr>
</tbody>
</table>
\end{verbatim}
Designing a new formulation: Assessing the population variability of designed formulation

• Simulation trials 10X10 with healthy volunteers aged 20-50

In none of the trials, \( C_P \) has exceeded MTC (100 ng/mL) and maintained \( C_P \) of more than MEC (20 ng/mL)
Designing a new formulation: Assessing the steady state performance of designed formulation

- Simulated PK profile in healthy volunteers aged 20-50 for 7 days

At steady state, Cp level was maintained within the therapeutic range of metoprolol.
• Simcyp can also help to evaluate performance of this new formulation in elderly, paediatric and specific age groups

• Performance on various disease groups, ethnicity, etc. can be studied using Simcyp

• Metabolic DDIs could be evaluated for the designed formulation

• The simulated PK profiles could be linked to pharmacodynamics models to estimate and understand the efficacy of the designed formulation
THANK YOU
Advantages of Mechanistic IVIVC

Differing Permeation/Metabolism

Mechanistic Deconvolution

Conventional Deconvolution

Simple IVIVC Function

Complex IVIVC Function

Simple IVIVRs are important during formulation optimisation
IVIVC and BCS Classes

<table>
<thead>
<tr>
<th>BCS Class</th>
<th>Solubility</th>
<th>Permeability</th>
<th>Controlling Factor</th>
<th>IVIVC Expectation for IR Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>High</td>
<td>High</td>
<td>Gastric Emptying</td>
<td>IVIVC expected, if dissolution rate is slower than gastric emptying rate</td>
</tr>
<tr>
<td>Class II</td>
<td>Low</td>
<td>High</td>
<td>Dissolution/Sol</td>
<td>IVIVC expected</td>
</tr>
<tr>
<td>Class III</td>
<td>High</td>
<td>Low</td>
<td>Permeability</td>
<td>Permeability is rate determining and limited or no IVIVC with dissolution</td>
</tr>
<tr>
<td>Class IV</td>
<td>Low</td>
<td>Low</td>
<td>Diss/Sol/Perm</td>
<td>Limited or no IVIVC is expected</td>
</tr>
</tbody>
</table>

IVIVC is expected and is used to obtain ‘Biowaiver’ for CR/ER products of Class I drugs as the release/dissolution becomes the rate limiting step.

Mechanistic IVIVC models are useful for class III/IV drugs as they distinguish dissolution, GI transit and permeation processes and avoids confounding.

IVIVC for drugs with nonlinearity in $F_g$, $F_a$ and systemic clearance can not be modelled using conventional methods but can be effectively modelled using mechanistic models.

Why IVIVC?

- Current Simcyp Implementation: Predict PK profile of Oral formulation from *in vitro* dissolution, $P_{eff}$ and disposition parameters

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>%Diss</td>
<td>0</td>
<td>25</td>
<td>50</td>
<td>75</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

- *In vitro* dissolution profiles vary depending on the media, type of formulation and other experimental conditions used.
- If validated relationship between in vitro and in vivo dissolution (IVIVC) is obtained, it could be used to effectively predict PK/(PD) profiles new formulations

**Assumption: in vitro dissolution == in vivo dissolution**
Why IVIVC

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>%Diss</td>
<td>0</td>
<td>25</td>
<td>50</td>
<td>75</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

What IVIVC Relationship to use and How to Establish/Validate it?
**IVIVC and Its Components**

**IVIVC**: A predictive **mathematical model describing the relationship** between an *in vitro* property (usually drug dissolution or release) and a relevant *in vivo* response, *e.g.*, amount of drug absorbed/dissolved.

**VALIDATION**

**DECONVOLUTION MODELS**

**CONVOLUTION MODELS**

**Validation**: External validation is recommended when only 2 formulations are used to establish IVIVC.

**IVIVC**: The *in vitro* dissolution and *in vivo* input curves may be directly superimposable or may be made to be superimposable by the use of a scaling factor/function. Nonlinear correlations, while uncommon, may also be appropriate.
Simcyp IVIVC – Two Stage

**STAGE 1**
ADAM + PBPK Parameters

**In vivo** %D

**Observed**

Cp

t

**IVIVC**

Vivo %D

Vitro %D

**STAGE 2**
Establish IVIVC

In vitro %D

In vitro

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>%Diss</td>
<td>0</td>
<td>25</td>
<td>50</td>
<td>75</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

In vitro Input Discrete Data

© Copyright 2012 Certara, L.P. All rights reserved.
Single Stage IVIVC

- **In vitro Dissolution**
- **Time Table**
<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>%Diss</td>
<td>0</td>
<td>25</td>
<td>50</td>
<td>75</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
- **IVIVC Predicted**
- **Observed**
- **ADAM + PBPK Parameters**
- **IVIVC Function**
  - Predicted
  - In vivo
  - And Initial Parameters
  - Interpolation
- **Iteratively estimate IVIVC Function Parameters**
  - Which give best fit of predicted PK profile to the observed PK Profile