Conventional versus Physiologically-Based (PB)-IVIVC: Revisiting Some Successful and Failed Conventional IVIVC Cases with PB-IVIVC

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Simcyp (a Certara Company)

AAPS Annual Meeting, 4th November 2014
How to Develop IVIVC?

- **In Vivo Dissolution**
  - Graph showing % Dissolved vs Time (h)

- **In Vitro Dissolution**
  - Graph showing % Dissolved vs Time (h)

- **Plasma Concentration**
  - Graph showing Plasma Conc vs Time (h)

**DECONVOLUTION**

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What is Deconvolution?

\[ \text{Response} = \text{Input} \times \text{System behaviour} \]

If you know \( R \) and \( S \), you can find \( I \)

Input is the rate of release/dissolution from administered formulation

System behaviour is how the human body processes the drug (Disposition)

Response is the result (Plasma Concentration-time profile) of what happens (system behaviour) to the drug after a particular input (formulation) is given to the system

What you deconvolute and its quality depends on how you define the system and parameterise it
Deconvolution: Limitations of Conventional Methods

- Wagner-Nelson and Loo-Riegelman Methods
  - Assumes human body (system) as one or two compartments
  - Cannot be used for nonlinear elimination
  - Deconvolutes systemic input rate which is a composite function of dissolution + GI Transit + Permeation + First Pass

- Numerical Methods
  - No physiological assumptions but mathematical assumptions: input site is the same for all formulations and input rate is constant (infusion) between two time points
  - Depending on the UIR used, it deconvolutes a composite function of dissolution + GI Transit + Permeation + First Pass

Langenbucher (2003) EJPB 56(3), 429
Mechanistic Deconvolution: e.g. ADAM Model

- in vivo dissolution is deconvoluted separately from GIT transit, permeation, gut wall metabolism and first pass liver extraction

- Gastric Emptying

- Luminal Transit

- PBPK DISTRIBUTION MODEL

- Portal Vein

- LIVER

- Duodenum, Jejunum I, Jejunum II, Ileum I, Ileum II, Ileum III, Ileum IV, Colon

- Dissolution

- Absorption Efflux/Influx

- Metabolism

- Degradation
Advantages of Physiologically-based IVIVCs

Mechanistic Deconvolution

In vitro

Simple IVIVC Function

In vivo

Conventional Deconvolution

In vitro

Complex IVIVC Function

In vivo

Simple IVIVCs are easy-to-interpret and important during formulation optimisation

Dissolution  Permeation  Systemic Input
Case study 1: IVIVC for Metoprolol ER formulations

Reported Model 1: Numerical Deconvolution with Oral Solution as UIR

In vitro in vivo correlation

Reported Model 2: FPE Parent / Metabolite Model

In vitro in vivo correlation

Two-Stage Sequential Approach using Linear IVIVC

A. Physiologically based Method (%Dissolved)

\[ y = 0.95x + 2.7809 \]
\[ R^2 = 0.9883 \]

B. FPE method Sirisuth & Eddington 2002

\[ y = 1.1579x - 0.2493 \]
\[ R^2 = 0.9244 \]

C. ND Method Eddington et al. 1998

\[ y = 1.1402x - 0.201 \]
\[ R^2 = 0.9592 \]

<table>
<thead>
<tr>
<th>Validation</th>
<th>Formulation</th>
<th>%PE in AUC</th>
<th>%PE in Cmax</th>
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</thead>
<tbody>
<tr>
<td>Internal</td>
<td>Fast</td>
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<td></td>
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<td></td>
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<td></td>
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<td>IV (80 kg)</td>
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<tr>
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<td>AAPE</td>
<td>2.69</td>
<td>10.69</td>
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</tbody>
</table>

Patel et al. 2014 9th W PBP meeting, Lisbon
Deconvolution methods comparison

A. Physiologically based Method (%Dissolved)

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ND method deconvolutes fraction absorbed (Fa(t)) rather than fraction dissolved (F_diss(t)) even when oral solution is used as UIR whereas PB method deconvolutes all processes involved in absorption – F_diss(t), Fa(t), F_pv(t) and F(t)
Why fast release formulation not deconvoluted well with ND?

A. Physiologically based Method (%Dissolved)

\[ y = 0.95x + 2.7809 \]
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\[ R^2 = 0.9592 \]

Gastric emptying controls significant proportion of absorption profile region for Fast formulation.
Physiologically Based Deconvolution at a Population Level

- Exploratory analysis of the individual subject PK data of the Metoprolol oral formulations indicated significant BS and WS variability
- PBPK to identify sources of variability
  - Given the small duration of the clinical study, only BS variability and assumed the WS variability in disposition parameters to be negligible.
  - WS as well as BS variability in dissolution and GI transit was considered

Deconvolution with WS and BS variability included

UIR Characterisation

Disposition BS Variability

Peff  CL  Vss

In vivo release/dissolution from Medium formulation is more variable which corresponds to partial AUC analysis of PK profiles

Poster Number **M1328 – B Mistry et al, AAPS AM, 2014**

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Physiologically Based Deconvolution at a Population Level

Assuming individual subject GI Transit (GET) is equal to Pop. Mean

Considering WS and BS variability in GI Transit (GET) for population

Poster Number M1328 – B Mistry et al, AAPS AM, 2014
Case Study 2: Diltiazem (BCS I, BDDCS II) CR products

- Complexities involved
  - Gut-wall metabolism (formulation-dependent non-linearity)
  - Auto-inhibition of CYP3A4 by DTZ and its metabolite

### Numerical Deconvolution IVIVC

- Formula: $y = 0.9765x + 2.7752$
- $R^2 = 0.9202$

### PB-IVIVC

- Formula: $y = 0.9544x + 0.7355$
- $R^2 = 0.9942$

<table>
<thead>
<tr>
<th>Formulation</th>
<th>%PE in AUC PB</th>
<th>%PE in Cmax PB</th>
<th>%PE in AUC ND*</th>
<th>%PE in Cmax ND*</th>
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<tbody>
<tr>
<td>Fast</td>
<td>8.33</td>
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<td>8.63</td>
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<tr>
<td>Slow</td>
<td>-13.65</td>
<td>47.5</td>
<td>-5.05</td>
<td>65.9</td>
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</table>

**Type of IVIVC**

- Linear (PB) and Non-linear (ND)

*When all 3 formulations were used for IVIVC development.*

Sirisuth et al, 2002 Biopharm Drug Dispos
Diltiazem IVIVC: Analysis of Results

Fast - Deconvoluted in vivo profiles

Medium - Deconvoluted in vivo profiles

Slow - Deconvoluted in vivo profiles

Formulation Fast - IVIVC Chart

Formulation Medium - IVIVC Chart

Formulation Slow - IVIVC Chart

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Diltiazem: Considering auto-inhibition

- Is auto-inhibition clinically significant?

Tsao et al. 1990 “DTZ half-life was 50-100% higher after MD than SD”

Is an IVIVC or bio-equivalence established based upon a single dose valid at steady state for a drug with formulation-dependent first-pass and mechanism-based enzyme auto-inhibition?
Multi-dose studies for MR formulations

- The CHMP NfG on Modified Release Oral and transdermal Dosage Forms requires a multiple dose study for prolonged release products for drugs expected to show accumulation*

- For Diltiazem, accumulation is expected due to reduced first-pass and systemic clearance due to auto-inhibition but the dissolution is not expected to accumulate for Fast and Medium Release formulations

- PBPK models dissolution and absorption as separate processes hence allows simulation of MR formulation at steady state scenario after multi-dosing and estimate accumulation

- Can PB-IVIVC help to simulate such studies?

Simulating SS exposure of ER-Diltiazem

Such IVIVC linked PBPK simulations could help to evaluate exposure at steady state for ER products based upon single dose clinical studies.
Case study 3: IVIVC for Tramadol ER Formulation

In Vitro In Vivo Correlation

Failed to predict lower bioavailability of slow formulation

Linear Model - Time scaled Extended Model

US Patent 8158147; CDER, 2004, Tramadol Extended release tablets
**PB-IVIVC:** Two-Stage Sequential Approach using Linear IVIVC

### Internal Validation

<table>
<thead>
<tr>
<th>Validation</th>
<th>Formulation</th>
<th>AUC(_{0-t}) (ng/mL.h)</th>
<th>Cmax (ng/mL)</th>
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<tr>
<td></td>
<td>Obs/ Pred/ %PE</td>
<td>Obs/ Pred/ %PE</td>
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### External Validation

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<td>Obs/ Pred/ %PE</td>
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### UL & LL Dissolution Specifications

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<th>Prediction</th>
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**Poster Number T3273 – S Pathak et al, AAPS AM, 2014**
Application of Absorption Modelling to Predict Virtual Bioequivalence

Upper, Target and Lower dissolution profiles of Tramadol ER Formulation

Predicted Plasma profiles in virtual population using SimCYP PBPK Modelling

Inter-occasional variability incorporated before subjecting it to BE

Bioequivalence was determined using Phoenix BE module
Objections to More Mechanistic Models

1 – Data hungry!  
System vs drug/formulation data?

2- Makes many assumptions!  
Assumptions are declared; unlike other models

3- It is not transparent!  
Contradiction with previous item!

4- Does not add too much value!  
Most of the value is in “internal facilitation” and “informed decision making”

5- Other modelling types can be done too!  
Other models by their nature cannot go beyond the data which is used to drive them (no extrapolation)

Slide Courtesy - Amin Rostami Hodjegan (Uni Manchester)
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Thank you for your attention