The Utility of Level C IVIVC for Setting Clinically Relevant Specifications: Case Studies and Implications

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Outline

• Level C and Level A IVIVC
• Case study 1 – Impact of polymer on MR product
• Case study 2 – Impact of API PSD on IR product
• Case study 3 – Impact of tablet hardness of IR product
• Level C vs Level A IVIVC – A theoretical exercise (PQRI project)
• Conclusions
IVIVC guidance: If such a multiple Level C correlation is achievable, then the development of a Level A correlation is likely.

Is this statement always true? Is it accurate for IR products? And is the Level A model always needed?
Case Study 1 - IVIVC for Niacin ER

- Extremely complex metabolism, dependent on rate of absorption
Multiple Level C IVIVC Models

With the exception of first timepoint (0.5 hrs), P.E. < 5%
Similar correlation seen for total urinary excretion
Level A Model

• Impossible to obtain for Niacin (multiple methodologies attempted)

• Traditional (time scale/shift/cutoff) or compartmental based for NUA was successful for AUC but ~33% P.E. on Medium formulation $C_{\text{max}}$

• Level A model obtained for NUA using a correlation between dissolution in vitro fit parameter (Makoid-Banakar TMAX) and in vivo absorption parameter (Hill function Finf and MDT)
Multiple Level C Model Application

NUA AUC used as an example

% Dissolved vs Time (hr)

Medium batch +/- 10% AUC projections
Case Study 2 - Impact of API PSD on IR Product

- BCS II
- IR formulation (crystalline API)
- Dissolution sensitive to API PSD

Dissolution for experimental batches of varying API

Relative Bioavailability Study

Plasma Concentration

Time (hr)

% Dissolved

Time (hr)

0 0.25 0.5 0.75 1 1.25 1.5

0 5 10 15 20 25 30 35 40 45 50

0 10 20 30 40 50 60 70 80 90 100
Multiple Level C IVIVC

Dissolution correlated with $C_{\text{max}}$

Linear regressions against $C_{\text{max}}$ explained observed data

As expected, later dissolution time points show somewhat lower $R^2$ values (formulations close to complete release)

Dashed lines indicate $\pm$ 10% prediction error bounds around regression line
Cross-study Multiple Level C IVIVC

\[ C_{\text{max}} = \text{intercept } (\theta_1) + \text{slope } (\theta_2) \times D_{15} + \theta_3 \times \text{ind} + \theta_4 \times D_{15} \times \text{ind} \]

*where \( D_{15} = \% \text{ Dissolution after 15 minutes.} \)

Blue diamonds: observed data with \( \text{ind} = 0 \).

Purple squares: observed data with \( \text{ind} = 1 \).

Purple line: linear regression for data with \( \text{ind} = 1 \).

Blue line: linear regression for data with \( \text{ind} = 0 \).

\*ind = 1 for the data from Part I in Study P06328 and \( \text{ind} = 0 \) for the rest of the data.
Traditional Level A model with original method narrowly failed external validation.
A slower dissolution method to reduce time-scaling resulted in successful IVIVC model.
Level C vs Level A BE Prediction

- Predictions of independent relative BA study

<table>
<thead>
<tr>
<th></th>
<th>Observed $C_{\text{max}}$ GMR</th>
<th>Level A predicted $C_{\text{max}}$ GMR</th>
<th>Level C (D15) predicted $C_{\text{max}}$ GMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch A vs Batch B</td>
<td>1.12</td>
<td>1.14</td>
<td>1.07</td>
</tr>
<tr>
<td>Batch A vs Batch C</td>
<td>1.38</td>
<td>1.35</td>
<td>1.51</td>
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Case study 3 – IR Solid Dispersion Tablets
Multiple Level C IVIVC

• Formulations (manufactured by varying compression force) selected to cover a wide dissolution range
  • All dissolution curves outside F2 bounds
  • No meaningful differences in AUC observed – Some Cmax differences seen
Develop Correlations (IVIVC)
Disintegration and Dissolution

- Disintegration Time (minutes)
  - Batch: A, C, D, E
  - Individual Values
  - Observed Arithmetic Mean
  - Predicted (Linear Model)

- % Dissolved at 10 Minutes
  - Batch: E, D, C, A

- % Dissolved at 15 Minutes
  - Batch: E, D, C, A

- % Dissolved at 20 Minutes
  - Batch: E, D, C, A

- % Dissolved at 30 Minutes
  - Batch: E, D, A, C

- $C_{max}$ (µM)
Use IVIVC to Estimate Dissolution Bounds
Can Multiple Level C be used to predict BE?

- Bioequivalence study between strengths to support interchangeability (much faster dissolution for 15 vs 30 mg and 20 vs 40 mg tablets)
- IVIVC used to inform POS and power study (maximum 9.5% difference predicted based on 20 min dissolution)

<table>
<thead>
<tr>
<th></th>
<th>AUC0-τ</th>
<th>AUC0-inf</th>
<th>Cmax</th>
<th>Cmax IVIVC prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>2x20 (n=59) vs 1x40 mg (n=60)</td>
<td>102.52% (99.09-106.07%)</td>
<td>102.33% (98.80-105.99%)</td>
<td>96.58% (90.96%-102.55%)</td>
<td>105.3%</td>
</tr>
<tr>
<td>2x15 (n=60) vs 1x30 mg (n=59)</td>
<td>99.71% (96.66%-102.85%)</td>
<td>99.66% (96.52%-102.91%)</td>
<td>108.74% (101.10%-116.95%)</td>
<td>109.5%</td>
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</table>
Question: IVIVC study focused on tablet hardness. How about other CQAs (eg. crystallinity)?

The dissolution curves can be linked to an absorption/PK model to predict impact on PK.
Assessment of Level C vs Level A for an IR product— a theoretical exercise (PQRI project)

Simplified dissolution + absorption model used
\[ \frac{D}{Dt} = -\text{Dissolution function}; \quad \frac{D}{Dt} = \text{ka} \times \text{Clumen} \]

Clinical PK profiles generated via convolution assuming an underlying IVIVC relationship (\( \text{DISvivo} = \text{DISvitro} \times (\text{Timescale} \times \text{Tvivo}) \))
Multiple Level C and Level A IVIVC

Individual PE<6%
Small differences in prediction of BE space between Multiple Level C and Level A
Conclusions

- Multiple Level C IVIVCs
  - may be more readily established than Level A models for complex PK and for IR formulations
  - have been successfully used to project bioequivalence outcomes
  - can be used to set clinically relevant specifications by estimating the bioequivalent dissolution space

- Especially for IR products, information gained from a Multiple Level C vs. a Level A model may not be that different
  - Especially for BCS II compounds, dissolution variability impact, if any, may be just on $C_{\text{max}}$ rather than AUC

- Additional modeling tools can be used to supplement the IVIVC model as needed (e.g. to assess impact of a CQA not included in the IVIVC study).
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