**IVIVC definition**

- **Definition**

A predictive mathematical treatment describing the relationship between an *in vitro* property of a dosage form (usually the *rate* or *extent* of drug release) and a relevant *in vivo* response (e.g. drug concentration in plasma or amount of drug absorbed).

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Typical industrial applications of IVIVC

**Primary Objective : Obtain Biowaiver**  
- i.e. use dissolution test as a surrogate for pharmacokinetic data

- Used as surrogate to bioequivalency studies which might typically be required with scaling up or minor post-approval changes (SUPAC), which may include
  - Site of manufacture
  - Formulation composition
  - Dose strength
- To waive bioequivalence requirements for lower strengths of a dosage form
- To reduce development time and optimize the formulation
- Setting dissolution specifications
- Recommended by regulatory authorities for most modified release dosage forms
Basic steps towards establishing IVIVC

- **In vitro**
  - Dissolution: drug release as a function of time
  - Ensure same mechanism of release of drug from dosage form
  - Calculation of percent of drug release as function of time: Weibull

- **In vivo**
  - Linear pharmacokinetics & knowledge of BCS category
  - Pharmacologic properties of the drug (Therapeutic Index)

- **Unit impulse function**
  - Oral solution
  - Immediate release tablet/capsule
  - Population PK analysis
  - IV
Basic steps towards establishing IVIVC

- **Convolution**
  The convolution method is a simulation method used to predict the blood/plasma concentration using percent absorbed data. Solving \( c(t) \) given \( f(t) \) and \( c_\delta(t) \)

- **Deconvolution**
  Deconvolution is the process to obtain input function (percent absorbed) using known plasma concentrations. Solving \( f(t) \) given \( c(t) \) and \( c_\delta(t) \)

*Deconvolution is the reverse process of convolution*

\[
c(t) = \int_0^t f(\tau) \cdot c_\delta(t - \tau) \cdot d\tau
\]
Approaches undertaken to establish IVIVC

- Retrospective analysis of existing PK/dissolution data
  - Historical dosage development and PK data
  - Often full cross-over comparison of formulations is not available
- Prospective planning & developing clinical study designs for establishing IVIVC
  - Formulation scientists develop and provide:
    - Formulations with different release rates, such as slow, medium and fast
    - IV or oral solution or IR dosage form for unit impulse
  - Analytical scientists: obtain in vitro dissolution profiles
  - Clinical: in vivo plasma concentration profiles for these formulations
  - Money and Time
Illustrative example: Compound A

Problem statement: a single Level A IVIVC was accepted by regulatory agency for Compound A at dose $X$, can we request biowaiver for lower strengths?

Weibull Equation

$$W_{\text{max}} = W_t \cdot \left(1 - e^{-\frac{(t-\gamma)}{\tau_d} \beta}\right)$$

- $W_t$: the fraction of drug dissolved/absorbed at time $t$
- $W_{\text{max}}$: the maximum cumulative fraction dissolved/absorbed
- $\gamma$: the location parameter (the lag time before the onset of dissolution)
- $\tau_d$: the time parameter (provides information about the overall rate of the process)
- $\beta$: the shape parameter
**Illustrative example: Compound A**

**IVIVC - Mathematical Relationship**

\[ \text{fraction of drug absorbed} = A \times \text{(fraction drug dissolved)} \]

**Retrospective Analysis**

**Matrix SR tablets**

**BCS 1 compound**

\[ \%PE_{C_{max}} = \left( \frac{C_{max}(obs) - C_{max}(pred)}{C_{max}(obs)} \right) \times 100\% \]

\[ \%PE_{AUC_{max}} = \left( \frac{AUC_{max}(obs) - AUC_{max}(pred)}{AUC_{max}(obs)} \right) \times 100\% \]

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Parameter</th>
<th>Absolute %PE</th>
<th>Ratio</th>
</tr>
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<tbody>
<tr>
<td><strong>Internal Validation</strong></td>
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<td></td>
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<tr>
<td>1*X (target release)</td>
<td>AUCINF</td>
<td>6.7</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>Cmax (ng/ml)</td>
<td>2.3</td>
<td>1.02</td>
</tr>
<tr>
<td>1*X (fast release)</td>
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<td>1.6</td>
<td>0.98</td>
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<tr>
<td></td>
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<td>Avg Internal</td>
<td>AUCINF</td>
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<td></td>
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<tr>
<td><strong>External Validation</strong></td>
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<tr>
<td>0.5*X dose (study 1)</td>
<td>AUCINF</td>
<td>6.6</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>Cmax (ng/ml)</td>
<td>5.7</td>
<td>0.94</td>
</tr>
<tr>
<td>0.25*X dose (study 1)</td>
<td>AUCINF</td>
<td>7.6</td>
<td>1.08</td>
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<tr>
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<td>Cmax (ng/ml)</td>
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<td>0.5*X dose (study 2)</td>
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<td>0.94</td>
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<td>0.94</td>
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<td>0.91</td>
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<td>0.97</td>
</tr>
<tr>
<td>1*X dose</td>
<td>AUCINF</td>
<td>1.5</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>Cmax (ng/ml)</td>
<td>5.3</td>
<td>1.05</td>
</tr>
</tbody>
</table>

Conclusion: the Level A IVIVC confirmed that the dissolution method developed for Compound A is sufficient to predict in vivo results for all dose strengths from 0.25*X to 1*X mg. The correlation was used to justify dissolution specifications.
Illustrative example: Compound B

Problem statement: A single Level A IVIVC was accepted by regulatory agency for Compound B at dose X, can we extend the current IVIVC to higher strengths? Can we use the IVIVC to request biowaiver for the site changes?

- **Compound B**
  - Compound marketed at unit dose strengths of $0.5X$ mg and $1X$ mg
  - The $3X$ dose strength is currently registered and used as multiple units of $X$ dose strength
  - New $3X$ single dose is currently in development
  - Similar dissolution profiles and characteristics in vitro over the dose range of $X$ dose to $3X$ dose
  - Same formulation composition for Compound B over the dose range of $X$ dose to $3X$ dose
  - Both $C_{max}$ and AUC increased in a linearly dose-proportional manner over the dose range studied over the dose range of $X$ dose to $3X$ dose

Retrospective Analysis

- Matrix SR tablets
- BCS 1 compound

\[3 \times X = 3X\]
Illustrative example: Compound B

Problem statement: a single Level A IVIVC was accepted by regulatory agency for Compound B at dose X, can we extend the current IVIVC to higher strengths? Can we use the IVIVC to request biowaiver for the site changes?

Retrospective Analysis
- Matrix SR tablets
- BCS 1 compound

• Compound B extended release
  - Level A IVIVC was developed using a single release rate
  - Dissolution method is independent of disso conditions (pH, agitation and media)

\[
\text{fraction of absorbed} = A \times (\text{fraction dissolved}) + B
\]

\[3 \times X = 3X\]

Conclusion: In vitro-in vivo correlation (IVIVC) model predicted AUC and C_max of Compound B at strengths up to and including 3X dose strengths, therefore biowaiver for higher dose strength is justifiable.
Illustrative example: Compound C

Problem statement: design clinical study to establish IVIVC based on existing development data for extended release tablets. Which is the preferred method to be used for deconvolution? Do we need to include IR arm in the IVIVC clinical study?

**Compound C**

- Typical (ideal?)
  - Three or four formulations developed with differing dissolution profiles
  - Study in healthy volunteers
  - Three or four way crossover in 12 to 24 subjects
  - 2 or 3 formulations used to develop IVIVC, one arm of study for conducting external validation
- Can we use Wagner-Nelson equation to perform deconvolution analysis?
- Can we use population based mean IR PK data to generate unit impulse response and perform numerical deconvolution?
Determining the fraction of dose absorbed

- **Model dependent methods**
  - Wagner Nelson Equation (one compartment model)
    \[
    F_t = \frac{C_t + k_{el} \cdot AUC_t^i}{k_{el} \cdot AUC_0^\infty}
    \]
  - Loo-Riegelman Method (multiple compartment models)
    \[
    F_t = \frac{c_t + K_{10}AUC_0^i + (X_p)_t / V_c}{K_{10}AUC_0^\infty} \quad X_p: \text{ the amount of drug in the peripheral compartment}
    \]
    \[
    K_{10}: \text{ the apparent first order elimination rate}
    \]

- **Model independent methods**
  - Deconvolution
    \[
    c(t) = \int_{0}^{t} f(\tau) \cdot c_\delta(t - \tau) \cdot d\tau
    \]
    \[
    \begin{align*}
    \text{Response} & \quad \text{Impulse} & \quad \text{Unit impulse response} \\
    \text{IV bolus} & \quad \text{Oral solution} & \quad \text{IR dosage form}
    \end{align*}
    \]
Compound C: deconvolution method

Wagner Nelson Method
Percent drug absorbed at any time

\[ \% \text{absorbed} = \frac{C + k_e[AUC]^t}{k_e[AUC]^\infty} \cdot 100 \]

Numerical deconvolution from individual IR data

\[ c(t) = \int_0^t f(\tau) \cdot c(\delta(t - \tau)) \cdot d\tau \]

- Some subjects demonstrated flip-flop mechanism
- Some subjects do not fit with one compartment model
- % PE not acceptable

- No model related restrictions on analyses
- Excellent % PE
Compound C (two release rates)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
<th>Develop IVIVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Fast dissolution</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Immediate Release</td>
<td></td>
</tr>
</tbody>
</table>

Prospective Analysis

Matrix tablets

BCS 1 compound

Deconvolution from individual IR data

- IVIVR developed using previous clinical Data
- Two release rates
- Small PE errors (<15%) between predicted and observed values for AUC and C max
- Caveats:
  - Different release mechanism

\[ F_{abs} = A^* Diss(B^*T_{vivo}) \]

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<th>Formulation</th>
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<th>% PE</th>
<th>Ratio</th>
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<td>AUClast</td>
<td>4.6</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td>2.3</td>
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</tr>
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<td>B</td>
<td>AUClast</td>
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<tr>
<td></td>
<td>Cmax</td>
<td>8.6</td>
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Compound C (two release rates)

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<td>C</td>
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</tbody>
</table>

Deconvolution from **mean IR data from previous studies**

- Small PE errors (<15%) between predicted and observed values for AUC and \( C_{max} \)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Parameter</th>
<th>Abs % PE</th>
<th>Ratio</th>
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<tbody>
<tr>
<td>A</td>
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<tr>
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**Conclusion:** analysis showed that sufficient predictability could be achieved using historical reference IR data available from a number of clinical studies. The data reviewed demonstrated the consistent PK performance of the IR dosage forms. A numerical deconvolution using mean IR data is the preferred method. Therefore IR arm is not required for IVIVC study – reduce cost of study without compromising on quality.
Outcomes of IVIVC for illustrative examples

• Compound A
  - Successfully obtained biowaiver

• Compound B
  - Biowaiver justification under review with regulatory agency

• Compound C
  - No IR arm will be needed in the IVIVC clinical study use population based PK model for unit impulse
  - IVIVC design and protocol being prepared for pre-submission discussion with regulatory agency
Challenges for establishing/developing IVIVC - Industrial perspective

- Majority of focus is for modified release dosage forms
  - Obtaining multiple release rates while maintaining same release mechanism is not trivial for some compounds
  - GMP manufacturing, analytical testing, meeting dissolution criteria, etc. requires significant resources
  - Clinical studies with different release profiles preferably in cross-over design
  - Time and cost

- What about IVIVC for immediate release dosage form especially for BCS 2
  - Potential approach/how to develop?
  - Different particle size to achieve different dissolution rates
  - Develop oral solution formulation (unit impulse) that does not precipitate/crystallize during GI transit?

- Typically regulatory guidance require IVIVC to be conducted in fasted state, is it necessary for a compound with a label requirement to take it with food?

- Should there be standardized approaches to evaluating dose dumping based on MR technology used (matrix, osmotic, multi-particulates, etc.)?
Questions?

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