Bioequivalence, Dissolution, Biosimilarity
From the “Chain Bridge” to other Bridges of the Pharmaceutical World
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In vitro in vivo correlations: an update

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Meaning of IVIVC

- IVIVC is a desideratum
  - desideratum is something we strongly wish but that facts insist in denying

- It would be very nice (and a lot cheaper) that we could predict pharmacokinetics (let alone clinical effect) on the basis of a physico-chemical parameter.
- Unfortunately life is much more complicated and a general set of concepts and facts supporting this objective have proved to be very elusive. For ca. 50 years we are still pursuing this goal.
- Therefore we have to live with some imperfect concepts and crude realities.
- That is why, to this date, IVIVC’s still remain a challenge and their use is somewhat limited.
- Recent developments (MR GL) tend to change this panorama
OUTLINE

• In Vitro / In Vivo Correlations (IVIVC)
  • What are they?
  • What do they mean?
  • What are they used for?
  • How do we use them?

• Successful IVIVC

• IVIVC correlations in modified release (MR) forms
  • Modelling methodology for developing an IVIVC

• Example

• Conclusions
In vitro/in vivo correlations (IV/IVC)
What are they?

- Functional relationships that allow prediction of in vivo PK behaviour from dissolution data
  - Level A - point to point relationship
  - Level B - moment analysis
  - Level C - one in vitro (eg, time to dissolve x%) and one in vivo parameter (eg, AUC, $C_{\text{max}}$).
  - Multi-level C - level C correlation is demonstrated for several dissolution time points

- Plenty of examples in the literature for A and C levels not so much for level B, but it is a costly way of proving BE
Functional relationships that allow prediction of in vivo PK behaviour from dissolution data

Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms
(EMA/CPMP/EWP/280/96 Corr1)

Appendix III: in vitro in vivo correlation

1. Introduction
   - An *in vitro in vivo correlation* (IVIVC) is a mathematical model describing the relationship between an *in vitro* property of a dosage form (mainly dissolution or drug release) and a relevant *in vivo* response (mainly drug plasma concentration or amount absorbed).
   - It is self-evident that such a relationship is only likely to exist when the formulation controls the rate of appearance of drug in plasma.
Dissolution, Intestinal absorption and pre-systemic elimination processes for an orally administered solid dosage form.
Appendix III: in vitro in vivo correlation

1. Introduction

When a modified release formulation is developed, it is highly recommended to establish an IVIVC:

a) to quantify in vivo release and formulation related effect on absorption,
b) to establish the in vivo relevance of in vitro dissolution tests and associated dissolution specifications,
c) to support biowaiver claims in later phases of clinical development or post-authorisation if there are changes in formulation.
In Vitro / In Vivo Correlations (IVIVC) What do they mean?

- There are situations where the concept is an IVIVC underlying regulatory actions leading to biowaivers.

- These are probably the most successful applications of the IVIVC concept
  - The Biopharmaceutics Classification System and BCS class I and III biowaivers in FDA and EMA guidelines
  - FDA SUPAC guidance and EU regulations on Variations
  - Various sections in the EU BE GL, e.g., Strength to be investigated
## BCS and IVIVC

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<th>Low Permeability</th>
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<tr>
<td><strong>I</strong></td>
<td><strong>III</strong></td>
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<tr>
<td>High Solubility</td>
<td>No IVIVC expected</td>
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<td>(if dissolution is faster than gastric emptying)</td>
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<table>
<thead>
<tr>
<th><strong>II</strong></th>
<th><strong>IV</strong></th>
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<tr>
<td>Low Solubility</td>
<td>IVIVC expected</td>
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<td>(dissolution rate controlled input)</td>
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## BCS and IVIVC

<table>
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<th>Low Permeability (LP)</th>
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<tr>
<td><strong>I</strong></td>
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<tr>
<td>High Solubility (HS)</td>
<td>No IVIVC expected</td>
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<tr>
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<td>naproxen carbamazepine</td>
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<td>metoprolol</td>
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<tr>
<td><strong>II</strong></td>
<td><strong>IV</strong></td>
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<td>Low Solubility (LS)</td>
<td>IVIVC expected</td>
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<tr>
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<td>hydrochlorotiazide</td>
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<tr>
<td>cimetidine</td>
<td>furosemide</td>
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<td>atenolol</td>
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Variations

Unless otherwise justified, a bioequivalence study is required, when the original product has been modified by the manufacturer in ways that could be considered to impact on the bioavailability with respect to:

- Change in composition or new strength
- Change in the manufacturing method (equipment and/or process)

Any justification presented should be based upon general considerations, or on whether an acceptable in vivo/in vitro correlation has been established.
WHEN CAN IN VITRO/IN VIVO CORRELATIONS BE THE BASIS FOR ACCEPTING DISSOLUTION TESTS DATA AS A SURROGATE FOR BIOAVAILABILITY TESTING?

- Batch to batch bioequivalence assurance (Quality Control)
  - Change in the site of manufacture
  - Change in manufacturing equipment and/or process
  - Change in the source of excipients
  - Minor qualitative change in excipients: Colours, preservatives, sweeteners, flavours
  - Minor quantitative change in excipients
  - Scale-up of batch size
  - Additional strengths of the same formulation
### Need for a Biostudy or an IVIVC when considering a variation for a modified release formulation (FDA)

<table>
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<tr>
<th>Type of variation</th>
<th>Level I</th>
<th>Level II</th>
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<tr>
<td>Non-release controlling components</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Release controlling components</td>
<td>No</td>
<td>No/Yes*</td>
<td>Yes</td>
</tr>
<tr>
<td>Site</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Scale up/down</td>
<td>No</td>
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<td>NA</td>
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<tr>
<td>Manufacturing equipment</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Manufacturing process</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* NTI: No; Non NTI: Yes
“By establishing a meaningful correlation between *in vitro* release characteristics and *in vivo* bioavailability parameters, the *in vitro* dissolution test can serve as a surrogate marker for *in vivo* behaviour and thereby confirm consistent performance of batches for routine production”
In Vitro / In Vivo Correlations (IVIVC)

What are they used for?

- For formulation design –
  - Know the Drug

- For dissolution method development –
  - Know the Absorption Process

- To reduce cost burden associated with BE trials –
  - Fail Less

- To reduce regulatory burden –
  - Do Less
CORRELATION LEVELS

Historical background

- Proposal:
  - Pharmacopeial Forum, 1988

- Discussion:
  - 2nd Workshop on in vitro and in vivo testing and correlation for oral Controlled/Modified Release Forms (Pharm. Res. 7(9): 975-982, 1990)

- USP – Open Hearing, 1992, Toronto, Canada

- Publication: - USP XXIII, 1995

- FDA 1997
Level A:
- Represents a point-to-point relationship established by comparing the in vitro dissolution curve to the input function obtained from deconvolution (meaning Wagner-Nelson, Loo-Riegelman, or model-independent mathematical deconvolution) of the plasma concentration/time curve.
  - “(T)he simplest way to demonstrate a correlation is to plot fraction absorbed versus fraction released in vitro...[There] is a point-to-point or Level A correlation when the relationship is linear with a slope of 1”
  - However, even non linear relationships can be considered level A correlations
CORRELATION LEVELS

Historical background

Level B:

- Correlation based on statistical moments: the mean dissolution time (MDT _vitro_) is compared to either the mean residence time (MRT) or the mean in vivo dissolution time (MDT _vivo_).

- \[ \text{MRT}_{\text{oral}} = \text{MIT} + \text{MRT}_{\text{iv}} \]

Level C:

- Point-to-point relationship between one dissolution parameter (\( t_{50\%}, t_{90\%}, \) etc.) and one pharmacokinetic parameter related to extent and/or rate of absorption (AUC, Cmax, tmax, Cmax/AUC, truncated AUC, etc).

Multiple Level C

- Level C relationships at several time points of dissolution curve

Obs: Correlations at the Levels B and C require in vivo testing of three or more formulations having different release rates.
CORRELATION LEVELS
Historical background

Level C:

✓ USP 30: Since this type of correlation is not predictive of actual in vivo performance, it is generally only useful as a guide in formulation development

1957
penicillin V
Average Conc.

1961
Aspirin
Amount excreted

1976
Prednisone
Time to reach half Cmax
PSEUDOEPHEDRIN:
TYPICAL STUDY FOR A "LEVEL A" IN VITRO / IN VIVO CORRELATION

Need to correct for lag time
CHLORPHENYRAMINE:
four extended release formulations

New Regulatory developments

- Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1)
  - PK MR GL

- Guideline on quality of oral modified release products (EMA/492713/2012)
  - Quality MR GL
A step by step methodology to establish a level A IVIVC

1. develop formulations with different release rates, such as slow, medium, fast, or a single release rate if dissolution is condition independent;

2. obtain in vitro dissolution profiles and in vivo plasma concentration profiles for these formulations;

3. estimate the in vivo absorption or dissolution time course using an appropriate deconvolution technique for each formulation and subject (e.g., Wagner-Nelson, numerical deconvolution).

4. establish the IVIVC model, i.e., the mathematical relationship that converts in vitro dissolution data into plasma concentrations;

5. actually convert dissolution data into plasma levels;

6. calculate the prediction error
A step by step methodology to establish a level A IVIVC

1. develop formulations with different release rates, such as slow, medium, fast, or a single release rate if dissolution is condition independent;
2. obtain in vitro dissolution profiles and in vivo plasma concentration profiles for these formulations;

PK MR GL

2. Study Design Considerations in vivo

- Generally, **two or more formulations** exhibiting the same release mechanism with sufficiently different dissolution profiles
- and an appropriate **reference formulation** (for the purpose of deconvolution) (RFD) with fast drug release (e.g., oral solution or immediate release formulation) are administered in a crossover study in healthy volunteers
- For oral MR products, the **in vivo release-time** profile is normally obtained by **deconvolution** and truly reflects drug release in vivo only when the RFD is an oral solution.
A step by step methodology to establish a level A IVIVC

1. develop formulations with different release rates, such as slow, medium, fast, or a single release rate if dissolution is condition independent;

2. obtain in vitro dissolution profiles and in vivo plasma concentration profiles for these formulations;

- Quality MR GL
- 2. Developing an IVIVC in vitro
  - 2.1. Level A
    - Initial testing of the formulations in a variety of different dissolution tests/conditions at the time of product release allows identification of the dissolution test that provides the most suitable discrimination.
    - The in vitro dissolution testing time points for the formulations used in the IVIVC study should be of sufficient frequency to fully characterise the dissolution profile, including the plateau (e.g., three consecutive points differing by less than 5%).
A step by step methodology to establish a level A IVIVC

3. estimate the in vivo absorption or dissolution time course using an appropriate deconvolution technique for each formulation and subject (e.g., Wagner-Nelson, numerical deconvolution).

- PK MR GL
  - Two general categories of mathematical approaches to IVIVC modelling are one- and two-stage methods. The two-stage method is deconvolution-based.
  - Non-compartmental methods of deconvolution are preferred over compartmental methods such as Wagner-Nelson or Loo-Riegelman.

\[ C(t) = r(t) \ast C_\delta = \int_0^t C_\delta(t - \tau) r(\tau) d\tau \]
Deconvolution-based IVIVC methods (two-stage)

Traditional options

Model-dependent:
- Wagner-Nelson
  \[ F_T = \frac{C_T + K_E \int_0^T C dt}{K_E \int_0^\infty C dt} \]
- Loo-Riegelman
  \[ F_T = \frac{C_T + k_{10} \int_0^T C dt + k_{12} e^{-k_{11}T} \int_0^T C e^{k_{11}u} du}{K_{10} \int_0^\infty C dt} \]

Model-independent:
- Numerical deconvolution
  \[ c(t) = \int_0^t c(t - u) r_{abs}(u) du \]
4. establish the IVIVC model, i.e., the mathematical relationship that converts in vitro dissolution data into plasma concentrations;

- PK MR GL
  - Two general categories of mathematical approaches to IVIVC modelling are one- and two-stage methods.
  - One stage approaches include
    - convolution-based
    - differential equation-based methods
    - use of physiologically-based pharmacokinetic (PBPK) models
  - For drugs with solubility and/or permeability limitations, particularly where permeability changes throughout the gastrointestinal tract, PBPK modelling approaches to IVIVC may bring value
Convolution-based IVIVC methods

one-stage modeling procedure

- directly relate the time course of the in-vivo measured plasma concentration to the time profile of the in-vitro dissolution.

Traditional options
Convolution integral

\[ C_t = \int_0^t C_{\delta IR}(t - u) \cdot r_{\text{diss-vitro}}(u) \cdot du \]

\[ \frac{dC}{dt} = r(t) - kC \]
5. actually convert dissolution data into plasma levels;

- PK MR GL
  - A **linear relationship** between in vivo absorption and in vitro release, **although desirable, is not necessary** and there are many physiological and physicochemical factors that make this less likely.
A step by step methodology to establish a level A IVIVC

5. actually convert dissolution data into plasma levels;

- PK MR GL

- In principle, any relationship that is applicable to all IVIVC formulations is acceptable including
  - sigmoidal,
  - Hill,
  - incorporation of time-scaling and time-shifting parameters and
  - approaches to account for incomplete absorption (e.g. absorption cut-off time, for oral formulations) with justification based on an understanding of the formulation, physicochemical, pharmacokinetic and physiological factors controlling drug release in vitro and vivo.

\[ r(t) = s_r \cdot r_{diss}(t_0 + s_1 \cdot t) \]
Plasma levels prediction (need IV data for drug disposition)

\[ C = \left( \frac{FD}{V} \right) \left( \frac{k_a}{k_a - k_e} \right) \left( e^{-k_e t} - e^{-k_e t} \right) \]

use compartmental equation or convolution (preferred)
6. calculate the prediction error

The objective of IVIVC evaluation is to estimate the magnitude of the error in predicting the in vivo bioavailability results from in vitro dissolution data.

\[
\% \text{ prediction error (PE)} = \frac{\text{observed parameter} - \text{estimated parameter}}{\text{observed parameter}}
\]

PK MR GL

- Internal predictability is assessed using the IVIVC model to predict the concentration-time profile from the respective dissolution data for each formulation.
- The summary parameters (Cmax, etc) are calculated from the predicted concentration-time curve and compared to the respective summary parameters for the observed data.
- The absolute value of the prediction error for all summary parameters should be less than 15% for each formulation and the average prediction error for all formulations included in IVIVC development should be less than 10% for each summary parameter.
Predictability

- **Internal Predictability**
  - ✓ (data set used to develop the IVIVC):
    - Enough if IVIVC established with 3 or more formulations with different release rates

- **External Predictability**
  - ✓ (data set not used to develop the IVIVC):

- **External Predictability needed when**
  - Only 2 formulations with different release rates
  - or
  - Internal prediction inconclusive (PE = 10 – 20%)
  - or
  - NTI
Example

- BCS class IV drug
- $F = 23\%$, $T_{\text{max}} = 2h$, OATP substrate
- $V_d = 17L$, bi-phasic distribution
- 10% metabolism; 86% dose excreted in faeces; 13% dose excreted in urine
- Terminal $t_{1/2} = 6-9h$
- $\text{AUC and } C_{\text{max}} \text{ linear}$
Model Building

- PK published studies after administration of 20 mg IV and oral solution of 80 mg
- Data collected in plasma and Urine
- Simultaneous modelling of the plasma and urine data for the IV and oral solution data
- ADAPT II, Least Squares estimation
Adjustment Results

<table>
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<tr>
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<th>IV 20 mg</th>
<th>Oral Solution 80 mg</th>
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<tbody>
<tr>
<td><strong>Plasma</strong></td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td><strong>Urine</strong></td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
</tbody>
</table>

- Plasma: Adjustments for IV 20 mg show a higher R² of 0.998 compared to Oral Solution 80 mg at 0.949.
- Urine: Both forms show similar trends with R² values close to 1 (0.999 and 0.993 for their respective forms).
Oral simulation
Various “in-house” BE trials were collected in two different dosages.

dissolution assays on pH1.2, pH4.5 and pH 6.8 without surfactants, on 900-1000ml, 37º C and 50 rpm (100 rpm on Apparatus-I)

Formulations were capsules and tablets

Dissolution was adjusted and included in the PBPK model.
Modelling dissolution

- Non “sink-conditions” at pH 1.2 and only marginally at pH 4.5
- Dissolution according to Noyes-Brunner (first-order)

\[
d\frac{M_{\text{solid}}}{dt} = -Z \left( \frac{M_{\text{solid}}}{M_{\text{ini}}} \right)^{2/3} \left[ C_s - \left( \frac{M_{\text{soluble}}}{V} \right) \right] \cdot M_{\text{solid}}
\]

\[
d\frac{M_{\text{soluble}}}{dt} = Z \left( \frac{M_{\text{solid}}}{M_{\text{ini}}} \right)^{2/3} \left[ C_s - \left( \frac{M_{\text{soluble}}}{V} \right) \right] \cdot M_{\text{solid}}
\]

- Cs fixed as 0.091 mg/ml at pH 1.2, 1.952 mg/ml at pH 4.5 and 43.53 mg/ml at pH 6.8
Results
## Results

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<th>Pred</th>
<th>Observed</th>
<th>90% CI</th>
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<td>T/R</td>
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<tr>
<td>1</td>
<td>101.92</td>
<td>101.73</td>
<td>87.36</td>
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<td>2</td>
<td>97.26</td>
<td>97.02</td>
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<tr>
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<td>93.32</td>
<td>100.17</td>
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<td>4</td>
<td>116.06</td>
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<td>106.62</td>
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<tr>
<td>5</td>
<td>106.83</td>
<td>105.19</td>
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<td>114.88</td>
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<td>5</td>
<td>104.34</td>
<td>105.30</td>
<td>99.52</td>
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Successful use of BCS for biowaivers in:

- SUPAC IR (FDA) and Variations (EMA)
- Biowaivers for different strengths
- BCS class I and class III biowaivers
  - Traditional levels B and C – less and less used except for SUPAC IR

Level A IVIVC for MR formulations

- New EMA GL but methodology has been around for many years (since the 90’s or earlier)
Summary of Current use of IVIVC

- Level A IVIVC methodology
  - Deconvolution:
    - Wagner/Nelson, Loo/Riegelman, noncompartmental
  - Convolution:
    - One stage limited use
    - Two-stage for predictability
    - More intensive use of differential equations and PBPK encouraged by the GL
Summary of Current use of IVIVC

- New MR GL stresses
  - the use of one-stage convolution and noncompartmental deconvolution for two-stage
  - More emphasis on M&S following recent trend in regulatory science