Development, Evaluation and Applications of In Vivo In Vitro Correlations

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Food and Drug Administration
Outline

- Definitions
- General Considerations
- Development of IVIVC
  - Methodology
- Validation of IVIVC
  - Internal vs external predictability
  - Criteria
- Applications of IVIVC
  - Waivers
  - Dissolution specifications
- Conclusion
Level A Correlation

- Is a point to point relationship between in vitro dissolution and the in vivo input rate
- Usually is linear but non linear relationships can exist and are acceptable by the FDA
Level B Correlation

- The mean in vitro dissolution time is compared to either the mean residence time or the mean in vivo dissolution time.
- It utilizes the principle of statistical moment analysis.
- Not a point to point correlation.
- Different profiles can give the same parameters values.
Level C Correlations

- Establish a single point relationship between a dissolution parameter, e.g. % dissolved in 4 hours and a pharmacokinetic parameter such as AUC and CMAX

- Useful in formulation selection and development but not for regulatory purposes
Multiple Level C

- A multiple Level C correlation relates one or several pharmacokinetic parameters to the amount dissolved at several time points of the dissolution profile.
Multiple Level C Correlation

<table>
<thead>
<tr>
<th>Formulation</th>
<th>CMAX</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>J</td>
<td>260</td>
<td>2623</td>
</tr>
<tr>
<td>J</td>
<td>192</td>
<td>2547</td>
</tr>
<tr>
<td>K</td>
<td>192</td>
<td>2249</td>
</tr>
<tr>
<td>L</td>
<td>163</td>
<td>2365</td>
</tr>
<tr>
<td>M</td>
<td>125</td>
<td>1980</td>
</tr>
<tr>
<td>N</td>
<td>211</td>
<td>2462</td>
</tr>
<tr>
<td>O</td>
<td>151</td>
<td>2057</td>
</tr>
<tr>
<td>P</td>
<td>118</td>
<td>2034</td>
</tr>
</tbody>
</table>
Level D Correlations

- Rank order correlations are qualitative and are not considered useful for regulatory purposes.
General Considerations
In Vivo

- Human data are required
- Number of subjects should be sufficient to characterize the bio performance of the drug product
- Data sets I have analyzed included from 6 to 36 subjects
General Considerations
In Vivo

• No restrictions on study designs
  – Crossover design preferred
  – Parallel design
  – Cross study comparisons

• Inclusion of a reference treatment such as:
  – Oral solution
  – IV solution
  – Immediate release product
General Considerations

In Vivo

- Studies usually are conducted in the fasted state
- When a drug is not tolerated in the fasted state, studies may be conducted in the fed state
General Considerations In Vitro

- Any in vitro dissolution method can be utilized
- The system once defined should be the same for all formulations tested
- The preferred dissolution apparatus is USP apparatus I or II used at compendially recognized speeds
- An aqueous medium either water or buffered solutions not exceeding pH 6.8 is recommended
General Considerations
In Vitro

- For poorly soluble drugs, addition of a surfactant may be appropriate
- In general non aqueous and hydroalcoholic systems are discouraged
- Dissolution profiles should be obtained from at least 12 units
- The coefficient of variation (% CV) for mean dissolution of a single batch should be less than 10 %
Dissolution Profiles

- % Dissolved vs. Time (hours)

- Y-axis: % Dissolved
- X-axis: Time (hours)

Lines represent different dissolution profiles over time.
Plasma Profiles

Cp(ng/ml) vs Time (hours)
Fraction of Drug Absorbed

Graph showing the fraction of drug absorbed over time (hours) in different conditions.
Plasma Profiles

Deconvolution

Cp (ng/ml)

Time (hours)

% Drug absorbed

Time (hours)
Deconvolution

- Deconvolution of plasma profiles to obtain the fraction of drug absorbed for each corresponding formulation
- Deconvolution techniques such as:
  - Wagner Nelson Method for 1 compartment model
  - Loo-Riegelman Method for 2 compartment model
  - Numerical Deconvolution methods
    - PC Decon Program
Level A Correlation

Slow Formulation

Medium Formulation

Fast Formulation

All Formulations
Additional Considerations

- 2 or more formulations with different release rates
- Dissolution independent of dissolution conditions, IVIVC developed with one formulation is acceptable
Additional Considerations

- Highest or lowest release formulations can be dropped out
Additional Considerations

- The in vitro dissolution methodology should adequately discriminate between formulations.
- Dissolution conditions should be the same for all the formulations tested in the bio study.
- The dissolution conditions should be fixed before further evaluation of the correlation is undertaken.
Scaling Factors

Fabs (t) = Fdiss(t + lag)
Scaling Factors

\[ \text{Fabs} = a \times \text{Fdiss} \]
\[ a = 0.5 \]
EVALUATION OF PREDICTABILITY OF IVIVC
Plasma profiles

OBSERVED          PREDICTED

Calculate absolute % PE on Cmax & AUC: 
(lobs - predl / obs) * 100
Evaluation Procedures

• **Internal predictability:** Based on data used to define the IVIVC model

• **External predictability:** Based on additional test data sets
Important considerations

- Amount of data used for IVIVC development
- Some combination of 3 or more formulations with adequately different release rates is recommended
Therapeutic index of drug

- Narrow therapeutic index drug
  - Internal and external predictability

- Non-narrow therapeutic index drug
  - Internal predictability
  - External predictability recommended but not necessary if internal pred. criteria are met
Internal Predictability Criteria

- % PE_{abs} (Cmax and AUC)
  - Average of 10% or less with none greater than 15% is acceptable
  - If criteria are not met, proceed to evaluation of external predictability
External Predictability Criteria

- % PEabs (Cmax and AUC)
  - ≥ 10 % or less is acceptable
  - ≥ 10-20% is inconclusive
  - ≥ Greater than 20% is unacceptable
Predictions

Dissolution $\rightarrow$ Absorption $\rightarrow$ Plasma profile

IVIVC model    PK parameters
Cumulative diss

Dissolution rate

Predicted plasma profiles

Absorption rate
Evaluation of Predictability

**INTERNAL**

**MEDIUM FORMULATION**

![Graph of MEDIUM FORMULATION](image)

**FAST FORMULATION**

![Graph of FAST FORMULATION](image)

**SLOW FORMULATION**

![Graph of SLOW FORMULATION](image)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>%PECmax</th>
<th>%PEAUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDIUM</td>
<td>5.14</td>
<td>3.77</td>
</tr>
<tr>
<td>FAST</td>
<td>7.08</td>
<td>12.91</td>
</tr>
<tr>
<td>SLOW</td>
<td>8.33</td>
<td>10.43</td>
</tr>
<tr>
<td>Avg.</td>
<td>6.85</td>
<td>9.04</td>
</tr>
</tbody>
</table>
Evaluation of Predictability
EXTERNAL

Predicted plasma concentrations from in vitro
EXTERNAL PREDICTABILITY

%PECmax
0.11

%PEAUC
9.7
Applications of IVIVC
Ideally, one would like to be able to predict the *in vivo* performance of the product from its *in vitro* dissolution.

“As a surrogate for bioavailability”
Types of Waivers

- Waivers for Bioavailability Studies:
  - Manufacturing site changes
  - Equipment changes
  - Method of manufacture
  - Source of raw materials
  - Formulation changes
Criteria for Granting Biowaivers with an IVIVC

% Dissolved vs Time (Hours)

- Reference
- Test

Graph showing the dissolution profile over time for reference and test samples.
Results (Continued):

![Graph showing plasma concentration over time for different treatments]

- **Plasma conc. (nmol/L)**
- **Time after dose (h)**

- Markered
- Modified
<table>
<thead>
<tr>
<th></th>
<th>Modified Formulation</th>
<th>Original Formulation</th>
<th>90 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>6129</td>
<td>6073</td>
<td>98-108</td>
</tr>
<tr>
<td>CMAX</td>
<td>316</td>
<td>327</td>
<td>93-103</td>
</tr>
<tr>
<td>CMIN</td>
<td>160.7</td>
<td>165</td>
<td></td>
</tr>
<tr>
<td>TMAX</td>
<td>10.1</td>
<td>6.14</td>
<td></td>
</tr>
<tr>
<td>Flss</td>
<td>.67</td>
<td>.73</td>
<td></td>
</tr>
</tbody>
</table>
Level C Correlation

- Data obtained from 36 healthy volunteers

- Eight formulations consisting of different ratios of slow and fast releasing beads

- 4 way incomplete block crossover design
  multiple dose study
### Relationship between % dissolved at various times and certain PK parameters of interest

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Linear Correlation Equation</th>
<th>R values</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3022.7+(14.32*D6)</td>
<td>0.782</td>
<td>0.0110</td>
</tr>
<tr>
<td></td>
<td>3041.1+(12.18*D9)</td>
<td>0.704</td>
<td>0.0154</td>
</tr>
<tr>
<td></td>
<td>3038.47+(11.79*D12)</td>
<td>0.679</td>
<td>0.0171</td>
</tr>
<tr>
<td><strong>CMAX</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>101.8+(4.01*D6)</td>
<td>0.970</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>102.3+(3.5*D9)</td>
<td>0.965</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>99.26+(3.43*D12)</td>
<td>0.967</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Dissolution Specifications
With No IVIVC

- Minimum of 3 points required

- Last time point should be the time where 80% of claimed labeled amount is dissolved

- Specifications set to pass at stage 2 level of testing of the USP acceptance criteria
Dissolution Specifications

% Dissolved vs Time (Hours)

- Lower Limit
- Target Formulation
- Upper Limit
Dissolution Specifications

- Ideally, all lots within the lower and upper limit of the specifications are bioequivalent.

- Minimally, these lots should be bioequivalent to the clinical trials lots or an appropriate reference standard.
Dissolution Specifications

- Variability should no longer be a primary consideration

- Specifications wider than 20% are acceptable only when evidence is submitted that lots with mean dissolution profiles that are allowed by the upper and lower limits are bioequivalent
Dissolution Specifications

- Impart meaning to the *in vitro* dissolution profile

- Justify the specifications and acceptance criteria
Dissolution Specifications with IVIVC

- IVIVC should be used to set the specification

- External validation is not required to use the IVIVC for setting specifications

- Wider specifications based on what the correlation predicts
Dissolution Specifications
with an IVIVC

% Dissolved

0 10 20 30 40 50 60 70 80 90 100

Time (Hours)

0 3 6 9 12 16

CP

0 20 40 60 80 100 120 140 160

Time (hours)

Lower Limit

Upper Limit

Lower Limit

Upper Limit
Dissolution Specifications with a Level C Correlation

• One time point correlation:

  – Use that point to establish the specification in a way that you have a maximum difference of 20 % in the mean predicted CMAX or AUC

  – The other points should be no more than 20 % wide with the clinical/bio profile considered to be the target profile to achieve
Dissolution Specifications with a Level C Correlation

- Multiple Level C Correlation:
  - establish specifications at each time point in a way to have a maximum difference of 20% in the mean predicted CMAX or AUC whichever is tighter
Release Rate Specifications

- If the release characteristics of the formulation can be described by a zero order for some period of time and the dissolution profile appears to fit a linear function over that time then

  - A release rate specification to describe the dissolution characteristics could be established
Zero Order Release Rate
Release Rate Specification
Release Rate Specification

![Graph showing release rate specification with time on the x-axis and % diss as well as Cp on the y-axis.](image)
Level A Correlation not Involving Deconvolution

- Correlation was obtained from in vivo data obtained from 6 different studies

- Media Consisted of PH 1.5 for the first 1.5 hours then PH 6.8 buffer for the remainder of the 24 hours
**Input Function**

- **WEIBULL FUNCTION:**

\[ F_t = \text{Dose}(1 - \exp(-(\frac{t-t_l}{t_d})^{\beta})) \]

where \( \text{Dose} \) = labelled dose.
\( t \) and \( t_l \) = time and lag time for dissolution.
\( t_d \) = time required for 63.2% of the drug to dissolve.
\( \beta \) = unitless number ranging from 0 to 1.
Plasma Profile Observed And Predicted from Dissolution
Dissolution Limits

- Observed Range of Dissolution
- Current Dissolution Limits
- Bioequivalent Dissolution Limits

Percent Released vs. Hours graph.
# Level A Correlation

## Table 1

<table>
<thead>
<tr>
<th>Dosage Strength</th>
<th>Average In-Vitro Slope (1/10% / hr)</th>
<th>Average In-Vivo Slope (1/10% / hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95 mg, Batch E-11685 (#84, 85, 87)</td>
<td>6.15 (0.26)</td>
<td>6.17 (0.43)</td>
</tr>
<tr>
<td>95 mg, Batch E-12175 (#92, 94)</td>
<td>6.48</td>
<td>6.62 (0.43)</td>
</tr>
<tr>
<td>190 mg, Batch E-11687 (#86, 87, 88, 91)</td>
<td>5.35 (0.14)</td>
<td>5.28 (0.27)</td>
</tr>
<tr>
<td>190 mg, Batch E-11067 (#63)</td>
<td>5.89</td>
<td>5.91 (0.50)</td>
</tr>
<tr>
<td>285 mg, Batch E-12387 (#92)</td>
<td>6.22 (0.11)</td>
<td>6.55 (1.0)</td>
</tr>
<tr>
<td>380 mg, Batch E-12385</td>
<td>6.1 (0.07)</td>
<td>6.12 (0.87)</td>
</tr>
</tbody>
</table>
Predicted Plasma Profiles
For the Upper and Lower Specification