Once-a-Day Extended-Release Dosage Form of Divalproex Sodium III: Development and Validation of a Level A In Vitro–In Vivo Correlation (IVIVC)

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Received 1 February 2005; accepted 31 March 2005

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.20387

ABSTRACT: Defining a quantitative and reliable relationship between in vitro drug release and in vivo absorption is highly desired for rational development, optimization, and evaluation of controlled-release dosage forms and manufacturing process. During the development of a once-daily extended-release (ER) tablet of divalproex sodium, a predictive in vitro drug release method was designed and statistically evaluated using three formulations with varying release rates. In order to establish an internally and externally validated Level A IVIVC, a total of five different ER formulations of divalproex sodium were used to evaluate a linear IVIVC model based on the in vitro test method. For internal validation, a single-dose four-way crossover study (N = 16) was performed using fast-, medium-, and slow-releasing ER formulations and a 12-h IV infusion of valproic acid as reference. To validate the IVIVC externally, a second three-way crossover study (N = 36) was performed using slightly-fast-, medium-, and slightly-slow-releasing ER formulations. The in vivo absorption–time profile was inferred by deconvolution of the observed plasma concentration–time profiles against the unit disposition function (UDF). A linear IVIVC model was established in which the in vivo absorption was expressed as a function of in vitro drug release. Plasma profiles of ER formulations were estimated via convolution of in vitro release profiles with the UDF. Successful internal and external validations of the model were demonstrated by individual and average absolute percent prediction errors of ≤9% for both Cmax and AUC∞. In conclusion, a Level A IVIVC describing the entire time-course of plasma concentrations was developed and validated, both internally and externally, for ER formulations of divalproex sodium.

Keywords: controlled-release; dissolution; matrix formulation; in vitro/in vivo correlations (IVIVC); pharmacokinetics; modified-release

INTRODUCTION

The challenges and values of developing in vitro/in vivo correlations (IVIVC) have undergone extensive debates and discussions since the 1980s.1–6 With controlled- or extended-release (ER) products, patients are often exposed to specific plasma levels over an extended period of time (e.g. up to 24 h); bio-relevant in vitro methods are desired to assure the consistent in vivo performance. Over the past decade, there has been increased confidence and success in using in vitro dissolution to evaluate and predict in vivo performance of modified release drug product based on IVIVC, particularly since the publication of a guidance on IVIVC by the FDA in 1997.7 The guidance provides a comprehensive perspective and framework on development, validations and applications of IVIVC.
Establishing IVIVC is highly dependent on the ability of in vitro tests to correlate with oral absorption and quantitatively predict in vivo performance. The state-of-the-art is such that there is no universal in vitro model that can mimic highly complex gastrointestinal environment and predict in vivo performance. Thus, IVIVC development is often carried out on a case-by-case basis. Once properly established and validated, IVIVC can be utilized to guide formulation and process development in the early stages of product development, to facilitate scale-up and post-approval changes, to set meaningful dissolution specifications, and to use dissolution as a surrogate for bioequivalency studies.

The commercially available ER tablet of divalproex sodium (Depakote ER®, Abbott Laboratories, IL, USA) was developed using controlled-release matrix technology. It provides nearly 24 h of apparent zero-order in vivo absorption of divalproex sodium that allows once daily administration. In our previous work on the ER matrix system of divalproex sodium, a predictive in vitro method was designed and evaluated using a linear model that accounts for inter and intra-subject variability in the in vivo absorption. The differences in the release rate were correlated quantitatively with the in vivo differences in performance of three different formulations. In order to establish an internally and externally validated Level A IVIVC in the present study, five different divalproex-ER formulations were designed by varying the percent of the release-controlling polymer, hydroxy propyl methyl cellulose (HPMC), for obtaining faster and slower release rates. Two in vivo studies were performed to investigate these ER formulations in healthy volunteers. The first study was used to develop and internally validate the IVIVC model. The second study was carried out to externally validate the IVIVC model.

METHODS

Materials and Equipment

The following materials and equipment were used in the study: Divalproex sodium (Pharmaceutical Products Division, Abbott Laboratories, North Chicago, IL), Methocel K15MP CR (Dow Chemical Co., Midland, MI), Depacon® (Abbott Laboratories), Collette high shear mixers (model Gral-75, Gral-600), Stokes tablet machine (model B-2), Fette tablet machine (model 2090), Vanderkamp dissolution tester (model 600) and Abbott TDx® Analyzer.

Test Formulations

Three ER hydrophilic matrix tablets of divalproex sodium, designated as medium-, fast- and slow-releasing tablets (Table 1), used in this study have been discussed previously. Two additional formulations, that were slightly-slow- and slightly-fast-releasing relative to the medium-releasing tablets, were designed for external validation of the IVIVC. Tablets were prepared using the same methods previously described at 15 kg scale. Two separate lots of medium-releasing tablets were manufactured at 120 kg

Table 1. ER Formulations of Divalproex Sodium Used in the Development and Validations of IVIVC

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Fast²</th>
<th>Slightly Fast²</th>
<th>Medium⁽²⁾</th>
<th>Slightly Slow²</th>
<th>Slow²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet strengths (mg)</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>Biostudy</td>
<td>Study 1</td>
<td>Study 2</td>
<td>Study 1</td>
<td>Study 2</td>
<td>Study 1</td>
</tr>
<tr>
<td>Bioequivalency</td>
<td>no</td>
<td>yes</td>
<td>Reference</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Ingredients</td>
<td>Divalproex sodium 53.8%</td>
<td>Divalproex sodium 53.8%</td>
<td>Divalproex sodium 53.8%</td>
<td>Divalproex sodium 53.8%</td>
<td>Divalproex sodium 53.8%</td>
</tr>
<tr>
<td></td>
<td>Methocel K15M 20%</td>
<td>Methocel K15M 27%</td>
<td>Methocel K15M 30%</td>
<td>Methocel K15M 33%</td>
<td>Methocel K15M 40%</td>
</tr>
<tr>
<td></td>
<td>Fillers/lubricant 26.2%</td>
<td>Fillers/lubricant 19.2%</td>
<td>Fillers/lubricant 16.2%</td>
<td>Fillers/lubricant 13.2%</td>
<td>Fillers/lubricant 8.0%</td>
</tr>
<tr>
<td></td>
<td>Tablet weight 1.00 g</td>
<td>Tablet weight 1.00 g</td>
<td>Tablet weight 1.00 g</td>
<td>Tablet weight 1.00 g</td>
<td>Tablet weight 1.02 g</td>
</tr>
</tbody>
</table>

²Internal validation (study 1); formulations F, B, and G from Ref. 9 were designated as fast-, medium-, and slow-releasing tablets, respectively.

²External validation (study 2).

²Two registration lots.
granulation scale and used in two separate validation studies.

**In Vitro Drug Release**

*In vitro* release rates from the divalproex-ER formulations were determined using a predictive test method. The test uses USP Apparatus II operating at 100 rpm in 500 mL of 0.1N HCl for 45 min followed by 900 mL of 0.05 M phosphate buffer containing 75 mM SLS, pH 5.5, 37 ± 0.5°C for up to 24 h. Samples were taken at predetermined time intervals, filtered through a 35 μm polyethylene filter, and assayed for valproate by TDx® fluorescence polarization immunoassays after dilution with dissolution medium.

**In Vivo Studies**

**Internal Validation (Study 1)**

To develop and internally validate the IVIVC model, a single-dose four-way crossover study was performed in 16 healthy volunteers (10 males and 6 females) using fast-, medium-, and slow-releasing ER formulations and a 12-h infusion of intravenous (IV) valproic acid (VPA) (Depacon®) as reference. Subjects were randomly assigned in equal numbers to four sequences of formulations such that they would receive all four formulations upon completion of the study. Doses in the consecutive periods were separated by one week. The four treatments were 500 mg doses of: (1) fast-releasing ER; (2) medium-releasing ER; (3) slow-releasing ER, and (4) 12-h IV-VPA infusion.

**External Validation (Study 2)**

To validate the IVIVC externally, a second single-dose three-way crossover study was performed in 36 healthy volunteers (30 males and 6 females) using slightly-fast-, medium-, and slightly-slow-releasing ER formulations. Subjects were randomly assigned in equal numbers to three sequences of formulations such that they would receive all three formulations upon completion of the study. Doses in the consecutive periods were separated by one week. The three treatments were 500 mg doses of: (1) slightly-fast-releasing ER, (2) medium-releasing ER, and (3) slightly-slow-releasing ER.

For both studies, blood samples (5-mL) were collected into heparinized collection tubes prior to dosing (0-h) and at 1, 2, 3, 4, 5, 6, 7, 5, 9, 10.5, 12, 15, 18, 24, 36, 48, and 72 h after dosing in each period. Plasma samples were assayed for valproate content using a validated gas chromatography with flame ionization detection method. The lower limit of quantitation was 0.5 mg/L.

**Development and Validations of IVIVC Model**

**Deconvolution**

The percent absorbed versus time profiles obtained for the fast-, medium-, and slow-release ER formulations were calculated from the plasma concentration–time data by deconvolution using the Wagner–Nelson method (Eq. 1).

\[
\% \text{ In Vivo} = \text{Percent absorbed} = \frac{(C_t/k) + AUC_t}{AUC_\infty}
\]

The terminal elimination rate constant \((k)\) obtained after IV–VPA administration was used for the calculation of the percent absorbed. \(AUC_t\) and \(AUC_\infty\) represent the area under the curve from time zero to time “t” and infinity, respectively.

**IVIVC Model**

To establish the *in vivo–in vitro* correlation, the percent absorbed (\% *in vivo*) for the *i*th measurement of the *j*th subject was modeled as a function of the mean percent dissolved (\% *in vitro*) using the following linear model.

\[
\% \text{ In Vivo}_{i,j} = \alpha_{(j)} + \beta * \% \text{ In Vitro}_{i,j} + \epsilon_{(i,j)}
\]

The analysis was carried out using the following assumptions and definitions:

(1) \(\alpha\) and \(\beta\) are the intercept and slope, respectively, of the correlation line.
(2) Only *in vivo* data obtained at times corresponding to those for which there were *in vitro* measurements were used.
(3) The intercept was assumed to vary among subjects. This variability was modeled using an additive error model with a normal probability distribution. Initially, the slope was likewise assumed to vary among subjects, but the estimate of the variance of the slope from the fitting of the data was essentially zero. Therefore, the slope was assumed to be the same for all subjects.
(4) Intrasubject variability, represented by \(\epsilon\), was assumed to have a normal probability distribution with mean 0 and variance \(\sigma^2\).
All observations from a subject were assumed to be independent of observations from other subjects. All intrasubject errors were assumed to be mutually independent and also independent of the random component of the intercept.

A full model with separate intercepts and slopes for each formulation, as well as a reduced model with the same intercept and slope for all three formulations, were fitted to the data using the NONMEM software. Under the null hypothesis that the in vivo—in vitro relationship is the same for all three formulations, the difference in the minimum value of the objective function (MVOF) of the full and reduced models have an approximate chi-square distribution with four degrees of freedom. A reduction of more than 9.5 in the MVOF when the additional four parameters are included in the model is considered to be statistically significant at the 0.05 level.

**Convolution**

To generate the predicted VPA concentration—time profiles, % in vivo versus time profile was calculated from the in vitro data based on IVIVC model and then convolved with the Unit Disposition Function (UDF). The following closed form equation (Eq. 3) was used to perform the convolution using Microsoft Excel 2000.

\[
C_p(t) = \sum_{i=1}^{n} \sum_{j=1}^{m} \left[ \frac{R_j C_i}{\lambda_i} \left( e^{-\lambda_i(t-\tau_{j2})} - e^{-\lambda_i(t-\tau_{j1})} \right) \right]
\]

where \( C_p(t) \) is the plasma concentration at time “t” for a subject who has “i” number of exponentials for the UDF (i = 1 in this case) and;

- \( R_j \) = jth input rate
- \( \tau_{j1} \) = Start time of the jth input rate
- \( \tau_{j2} \) = Stop time of the jth input rate
- \( C_i \) = IV intercept for the ith exponential
- \( \lambda_i \) = rate constant for the ith exponential

\[
(t - \tau)^+ = t - \tau \quad \text{for} \quad t > \tau \\
= 0 \quad \text{for} \quad t \leq \tau
\]

**Internal Validation of IVIVC Model (Study 1)**

Using the IVIVC equation (Eq. 2) and the % in vitro values (Figure 1), % in vivo values were calculated for fast-, medium-, and slow-releasing ER formulations. Subsequently, the piece-wise continuous zero-order absorption rate was determined from the slope of the IVIVC model predicted % in vivo versus time profile. A slope was calculated for each pair of consecutive (on time scale) % in vivo values; time values served as the start and stop times for the piece-wise constant zero-order absorption rate.

The UDF parameters (IV intercept and first-order elimination rate constant for an unit dose) were estimated by fitting a one-compartment model to the IV-VPA plasma concentration—time data using WinNonlin (Pharsight Corporation, Mountain View, CA). The IV intercept, \( C_1 \), for the UDF was calculated as the reciprocal of the volume of distribution for a one-compartment model. The IVIVC model predicted % in vivo vs. time profile was convolved with the UDF to generate the predicted plasma VPA concentration—time profile.

**External Validation of IVIVC Model (Study 2)**

Using the IVIVC equation (Eq. 2) and the % in vitro values (Figure 1), % in vivo values were calculated for slightly-fast-, medium-, and slightly-slow-releasing ER formulations. Subsequently, the piece-wise continuous zero-order absorption rate was determined from the slope of the % in vivo vs. time profile as described for the internal validation. Convolution of IVIVC model predicted % in vivo vs. time profile with the UDF was used to generate the predicted VPA concentration—time profiles as described for the internal validation.

![Figure 1. Mean in vitro release of five ER formulations of divalproex sodium used in development and validations of IVIVC.](image-url)
IVIVC Model Evaluations

For both internal and external validations, the absolute % prediction error, was calculated as:

\[
\% \text{PEabs} = \left| \frac{\text{Predicted} - \text{Observed}}{\text{Observed}} \right| \times 100
\]

(4)

The \(C_{\text{max}}\) and \(\text{AUC}_{\infty}\) values predicted by the convolution of the IVIVC model predicted \% in vivo (Eq. 2) with the UDF was compared with the observed values using % PEabs.

RESULTS

The results of the in vitro release from the five ER formulations are shown in Figure 1.

For the internal validation study (study 1), all 16 enrolled subjects (10 males, 6 females) completed the study. The mean ± SD (range) age, weight, and height were 33.9 ± 11.3 (18–50) years, 73.0 ± 9.3 (54.9–88.9) kg, and 173.4 ± 9.9 (160.0–190.5) cm, respectively. The mean (SD) VPA pharmacokinetic parameters are presented in Table 2 and the plasma VPA concentration–time profiles are shown in Figure 2.

For the external validation study (study 2), 36 healthy subjects (30 males, 6 females) were enrolled into the study, and 34 subjects (29 males, 5 females) completed the study. Two subjects missed one or more periods during the study. The mean ± SD (range) age, weight, and height of the 34 subjects completing the study were 32 ± 10 (19–51) years, 75.5 ± 8.1 (57.6–88.0) kg, and 176.7 ± 8.0 (160–190.5) cm, respectively. The mean (SD) VPA pharmacokinetic parameters are presented in Table 2 and the plasma VPA concentration–time profiles are shown in Figure 2.

Table 2. Mean (SD) VPA Pharmacokinetic Parameters for Internal and External Validation Studies

<table>
<thead>
<tr>
<th>Formulations</th>
<th>(C_{\text{max}}) (mg/L)</th>
<th>(T_{\text{max}}) (h)</th>
<th>(\text{AUC}_{\infty}) (mg · h/L)</th>
<th>(\lambda_z) (1/h)</th>
<th>CL/F (L/h)</th>
<th>V/F (L)</th>
<th>(t_{1/2}) (h)</th>
<th>Abs F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1: internal validation study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast</td>
<td>39.3 (8.8)</td>
<td>9 (3)</td>
<td>1148 (311)</td>
<td>0.046 (0.009)</td>
<td>0.47 (0.14)</td>
<td>10.1 (1.6)</td>
<td>15.7 (3.4)</td>
<td>1.01 (0.10)</td>
</tr>
<tr>
<td>Medium</td>
<td>29.7 (7.9)</td>
<td>16 (5)</td>
<td>1056 (347)</td>
<td>0.047 (0.009)</td>
<td>0.56 (0.33)</td>
<td>11.9 (6.2)</td>
<td>15.5 (3.1)</td>
<td>0.92 (0.19)</td>
</tr>
<tr>
<td>Slow</td>
<td>31.1 (9.4)</td>
<td>21 (6)</td>
<td>1040 (367)</td>
<td>0.047 (0.009)</td>
<td>0.56 (0.29)</td>
<td>11.9 (5.5)</td>
<td>15.2 (3.1)</td>
<td>0.90 (0.18)</td>
</tr>
<tr>
<td>IV-VPA</td>
<td>41.8 (8.5)</td>
<td>13 (1)</td>
<td>1141 (308)</td>
<td>0.046 (0.008)</td>
<td>0.47 (0.13)</td>
<td>10.2 (1.8)</td>
<td>15.7 (3.2)</td>
<td>—</td>
</tr>
<tr>
<td>Study 2: external validation study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slightly-fast</td>
<td>31.0 (6.9)</td>
<td>14 (5)</td>
<td>935 (293)</td>
<td>0.050 (0.009)</td>
<td>0.60 (0.28)</td>
<td>11.8 (3.9)</td>
<td>14.4 (3.6)</td>
<td>—</td>
</tr>
<tr>
<td>Medium</td>
<td>33.1 (7.1)</td>
<td>15 (4)</td>
<td>942 (319)</td>
<td>0.049 (0.010)</td>
<td>0.59 (0.22)</td>
<td>11.7 (2.5)</td>
<td>14.6 (3.8)</td>
<td>—</td>
</tr>
<tr>
<td>Slightly-slow</td>
<td>31.2 (10.3)</td>
<td>16 (6)</td>
<td>930 (338)</td>
<td>0.050 (0.010)</td>
<td>0.63 (0.33)</td>
<td>12.3 (4.6)</td>
<td>14.1 (3.6)</td>
<td>—</td>
</tr>
</tbody>
</table>

\(C_{\text{max}}\), maximum observed plasma VPA concentration; \(T_{\text{max}}\), time to \(C_{\text{max}}\); \(\text{AUC}_{\infty}\), area under the curve from time zero to infinity; \(\lambda_z\), terminal elimination rate constant; CL/F, apparent oral clearance; V/F, apparent volume of distribution; \(t_{1/2}\), terminal elimination half-life; and Abs F, absolute bioavailability.

Figure 2. Mean plasma VPA concentration–time profiles of five ER formulations of divalproex sodium tested in internal and external validation studies.
The estimates of intercepts and slopes for each formulation of the full model, as well as the reduced model with the same intercept and slope for all three ER formulations tested in Study 1 are provided in Table 3. Based on the difference in MVOF between the full and reduced model (5 units), it is concluded that the three regression lines are not statistically significantly \((p = 0.284)\) different at the significance level of 0.05, and that a single regression line (Figure 3 and Table 3) adequately fits the combined data from the three ER tablet formulations.

The VPA concentration–time profiles predicted by the IVIVC model for both the internal and external validation studies are shown in Figure 4 and the %PEabs values are provided in Table 4.

**DISCUSSION**

The analysis of the percent absorbed data of the individual subjects by NONMEM with a mixed effects model supports the conclusion that the relationship between \textit{in vivo} percent absorbed and \textit{in vitro} percent dissolved is the same for all three ER formulations (same regression line for all three) in Study 1. For the average subject, the relationship was estimated as:

\[
\text{Percent absorbed (}\%\text{ in vivo}) = 8.73 + 0.900 \\
\times \text{Percent dissolved (}\%\text{ in vitro})
\]

\(\text{(5)}\)

Complete \textit{in vivo} release of the drug occurred within approximately 12, 18, and 24 h for the fast-, medium-, and slow-releasing ER formulations used for IVIVC model development and internal validation (Study 1), respectively. The absolute bioavailability of the fast-, medium-, and slow-releasing ER formulations was about 90% or higher with average \(T_{\text{max}}\) values of 9, 16, and 21 h (Table 2), respectively. The VPA concentration–time profiles predicted by the IVIVC model adequately described the observed VPA concentration–time course as shown in Figure 4 and quantitated using % PEabs (Table 4). The IVIVC model attains a Level A correlation based on the internal validation since the average % PEabs is less than 10% with no formulation having a % PEabs greater than 9% for either \(C_{\text{max}}\) or AUC\(_{\infty}\).

The slightly-fast-, medium-, and slightly-slow-releasing ER formulations used for the external validation (Study 2) had average \(T_{\text{max}}\) values of 14, 15, and 16 h (Table 2), respectively. The VPA concentration–time profiles predicted by the IVIVC model adequately described the observed VPA concentration–time course as shown in Figure 4 and quantitated using % PEabs (Table 4). The IVIVC model attains a Level A correlation.

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**Table 3.** Estimates of Intercepts and Slopes for Reduced and Full Regression Models

<table>
<thead>
<tr>
<th></th>
<th>Estimate of Central Value</th>
<th>SE</th>
<th>MVOF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reduced model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>0.900</td>
<td>0.020</td>
<td>1849.9</td>
</tr>
<tr>
<td>Intercept</td>
<td>8.73</td>
<td>2.46</td>
<td></td>
</tr>
<tr>
<td><strong>Full model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope/intercept—fast</td>
<td>0.908/10.8</td>
<td>0.048/3.09</td>
<td></td>
</tr>
<tr>
<td>Slope/intercept—medium</td>
<td>0.875/8.61</td>
<td>0.022/3.09</td>
<td></td>
</tr>
<tr>
<td>Slope/intercept—slow</td>
<td>0.912/7.74</td>
<td>0.029/3.22</td>
<td>1844.9</td>
</tr>
</tbody>
</table>

SE, standard error; MVOF, minimum value of NONMEM objective function.
Table 4. IVIVC Model Predictions

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Parameters of IVIVC Predicted Curves</th>
<th>Mean Observed Parameters</th>
<th>% PEabs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{max}$</td>
<td>$AUC_{\infty}$</td>
<td>$C_{max}$</td>
</tr>
<tr>
<td>Study 1: internal validation study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast</td>
<td>35.95</td>
<td>1066</td>
<td>39.30</td>
</tr>
<tr>
<td>Medium</td>
<td>31.91</td>
<td>1060</td>
<td>29.74</td>
</tr>
<tr>
<td>Slow</td>
<td>28.31</td>
<td>1077</td>
<td>31.13</td>
</tr>
<tr>
<td>Mean % PEabs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 2: external validation study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slightly-fast</td>
<td>32.47</td>
<td>962</td>
<td>30.98</td>
</tr>
<tr>
<td>Medium</td>
<td>30.32</td>
<td>960</td>
<td>33.08</td>
</tr>
<tr>
<td>Slightly-slow</td>
<td>30.79</td>
<td>943</td>
<td>31.15</td>
</tr>
<tr>
<td>Mean % PEabs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4. Observed versus predicted plasma VPA concentration–time profiles of ER formulations of divalproex sodium based on the IVIVC model. Symbols represent mean, and error bars represent standard deviation of observed plasma VPA concentrations. The continuous lines represent the IVIVC model predicted plasma VPA concentration–time profiles.
based on the external validation since the average \% \text{PE}_{\text{abs}} is less than 10\% with no formulation having a \% \text{PE}_{\text{abs}} greater than 8\% for either \text{C}_{\text{max}} or \text{AUC}_{\infty}.^7

In conclusion, a Level A IVIVC describing the entire time-course of plasma concentrations was developed and validated, both internally and externally, for ER formulations of divalproex sodium. This IVIVC has been applied to setting bio-relevant dissolution specifications, guiding new product development, supporting SUPAC change, waiving bioequivalence study and, more importantly, ensuring commercial product quality over the years.

REFERENCES