Comparison of conventional In Vitro In Vivo Correlation methodology with nonlinear mixed effects modelling

Clare Gaynor [1] , Adrian Dunne [1] and John Davis [2]

(1) UCD School of Mathematical Sciences, University College Dublin, Ireland
Scoil na nEolaíochtaí Matamaitice UCD, An Coláiste Ollscoile, Baile Átha Cliath, Éire

(2) Clinical Pharmacology, Pfizer Global Research and Development, Sandwich, England

INTRODUCTION:

The rate and extent to which a tablet or capsule dissolves can easily be examined in a laboratory, the information gathered in such *In Vitro* dissolution studies can be used, by means of a mathematical or statistical model, to predict the *In Vivo* performance of a product e.g. plasma concentration of drug. This model has a number of applications including reducing the number of human studies necessary during drug development, setting specification limits for batch approval during routine manufacturing and acting as a substitute for the human studies required for regulatory approval. As a result, the accuracy and reliability of the predictions made by these *In Vitro – In Vivo* Correlation (IVIVC) models is of the utmost importance and substantial effort and resources go in to their development.

Methods of establishing IVIVC models for Extended Release formulations fall into two main categories: those based on convolution and those based on deconvolution. Some fundamental flaws in the conventional deconvolution based approach have been highlighted (1) and are outlined in Table 1. It is clear that, in principle, the use of this method may not be advisable. The convolution based technique (2) does not suffer from the same inherent problems and should, in theory, produce superior results. The objective of this study is to investigate the two methods' dissimilarities and to quantify the extent of the difference in their performance.

TABLE 1: SOME LIMITATIONS OF THE CONVENTIONAL DECONVOLUTION BASED METHOD

Issues with conventional method	Effect
Data for individual subjects or tablets is averaged	Ability to distinguish between subjects/tablets is lost. Curve of averages is different to individual curves. An individual subject is the 'system' being modelled.
Arbitrary choice of independent and dependent variable in a regression step	Two possible models giving different predictions.
Errors in independent variable	Biased predictions
Correlation between observations made on the same dosage unit or subject is ignored	Estimates are less efficient.
Fractions dissolved or absorbed are not constrained	Can predict fractions outside [0,1]
Data for sampling times not common to *In Vitro* and *In Vivo* studies are discarded	Reduced efficiency due to loss of information
Method includes a deconvolution step [3]	Deconvolution is an inherently unreliable process which can introduce errors [5].

METHOD:

A simulation study to compare the conventional deconvolution based methods of establishing an IVIVC to an alternative non-linear mixed effects modelling approach was undertaken. In practise, the Extended Release (ER) dosage units of interest are dissolved In Vitro and the fractions which have dissolved are recorded at a series of time points. ER dosage units from the same batch are then administered to a number of human subjects and their plasma drug concentrations are measured over time - these data contain information on dissolution, absorption, distribution, and elimination of the drug. A reference dose, which dissolves instantly, is administered to each of the same group of subjects and the resulting plasma drug concentrations are repeatedly measured for a predetermined period. These three kinds of data: *In Vitro*, *In Vivo* and reference, are used to establish the *In Vitro - In Vivo* Correlation model. The current project involves simulating such an IVIVC study for which the true model and parameter values are known.

The data were simulated as follows: let $F_{1i}(t)$ be the true fraction of drug dissolved from the i^{th} tablet at time t *In Vitro*, then the observed fraction dissolved is given by

$$Y_{1i}(t) = \phi_i F_{1i}(t) + \varepsilon_{1i}(t) \qquad \varepsilon_{1i}(t) \sim N(0, \sigma_1^2)$$

with $\text{logit}(F_{1i}(t)) = \text{logit}(F_1(t)) + u_i \qquad u_i \sim N(0, \omega_1^2)$

and $F_1(t) = 1\text{-}exp(-\lambda_1 t^{\alpha})$

where the tablet-to-tablet variation is given by ω_1^2, the intra-tablet variation by σ_1^2, λ_1 and α determine the rate of dissolution of the drug and ϕ_1 accounts for any difference between true dose and label claim. The *In Vivo* plasma concentration measured from the k^{th} subject following administration of the i^{th} tablet is described as

$$Y_{2ik}(t) = Dose\ \phi_2 \int c_{\delta k}(t-\tau)\, F_{2ik}'(\tau)\, d\tau + \varepsilon_{2ik}(t) \qquad \varepsilon_{2ik}(t) \sim N(0, \sigma_2^2)$$

where $F_{2ik}'(\tau)$ is the *In Vivo* dissolution rate and ϕ_2 allows for a difference in bioavailability between the reference dose and the ER dose. The response of the k^{th} subject to a unit dose follows a standard one compartment pharmacokinetic model with first order absorption given by

$$Y_{3k}(t) = c_{\delta k}(t) + \varepsilon_{3k}(t) \qquad \varepsilon_{3k}(t) \sim N(0, \sigma_3^2)$$

$$c_{\delta k}(t) = (\lambda_3/(\lambda_3-\lambda_2))\,(e^{-\lambda 2\,(t)} - e^{-\lambda 3\,(t)})$$

with λ_2 and λ_3 representing the rate constants of elimination and absorption of the drug respectively. The relationship between *In Vitro* and *In Vivo* dissolution is given by

$$\text{logit}(F_{2ik}(t)) = \text{logit}(F_{1i}(t)) + \theta_1 + u_i + s_{ik} + \theta_2 t$$

$$u_i \sim N(0, \omega_1^2)$$

$$s_{ik} \sim N(0, \omega_2^2)$$

where ω_2^2 gives the subject-to-subject variation. With the exception of θ_1 and θ_2, which were set to zero, values for all parameters were based on estimates obtained when this model was fit to a real dataset.

The simulated data (1000 sets) were analysed using both the convolution and deconvolution methods. The convolution method used was based on that of O'Hara et al (2) and implemented the NONMEM software developed by Beal and Sheiner (6). The deconvolution method used was Constrained Deconvolution (CoDe) as described by Hovorka et al (3). The IVIVC models established were used to predict *In Vivo* plasma concentrations. Software to implement both techniques and compare the results was written in FORTRAN.

The US Food and Drug Administration (FDA) recommend assessment of the prediction error for both the area under a plasma concentration curve (AUC) and for the peak plasma concentration (Cmax) when developing an IVIVC (4). In particular they require that average absolute percent prediction error (%|PE|) be 15% or less for Cmax and AUC. Predictions made using each method were used to compute the Cmax and AUC for each subject and compared to the known true values to calculate %PE. The values obtained were averaged and the results were examined in terms of bias (average %PE), efficiency (standard deviation of %PE) and whether or not they would meet the FDA criteria for establishing an IVIVC.

RESULTS:

The figures below show histograms of percentage prediction error for each of one thousand simulated batches of drug product as follows:

Fig 1) % PE in AUC produced by deconvolution method;
Fig 2) % PE in AUC produced by convolution method;
Fig 3) % PE in Cmax produced by deconvolution method;
Fig 4) % PE in Cmax produced by convolution method.

FIGURE 1:
DECONVOLUTION METHOD AUC

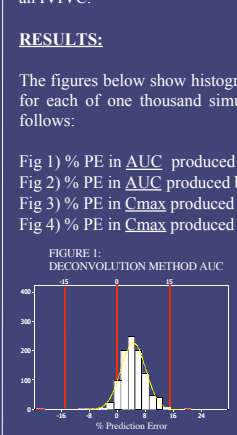

FIGURE 2:
CONVOLUTION METHOD AUC

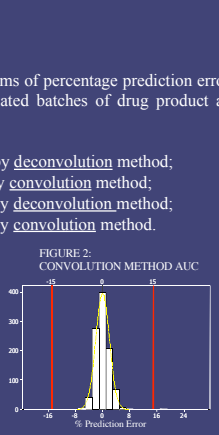

FIGURE 3:
DECONVOLUTION METHOD Cmax

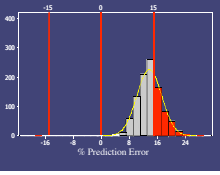

FIGURE 4:
CONVOLUTION METHOD Cmax

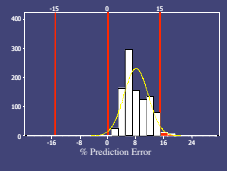

Table 2 shows the mean and standard deviation of the %PE obtained using both methods along with the percentage of simulations which failed the FDA validation. When comparing the two methods, the alternative convolution based approach produces results which are consistently more efficient with lower bias. The results of this study demonstrate that, where an IVIVC relationship exists, the conventional deconvolution based method fails the FDA validation much more frequently than the alternative technique.

It is evident, as would be expected, that both methods produce better predictions of the AUC than the Cmax although the alternative method retains its advantage in terms of bias and efficiency as apparent in Figs 1 and 2. These results corroborate the statistical theory, demonstrating and quantifying the superiority of the alternative nonlinear mixed effects modelling approach.

TABLE 2: SUMMARY OF RESULTS

METHOD	PROPERTY	MEAN	SD	% FAILURE
DECONVOLUTION	AUC	4.557	3.524	32%
	Cmax	13.604	3.540	
CONVOLUTION	AUC	0.0302	2.029	2%
	Cmax	8.057	3.458	

DISCUSSION AND CONCLUSIONS:

The development of *In Vitro – In Vivo* Correlation models is an important step in drug development and, as with all aspects of this process, precision is vital. The method most frequently employed at present, i.e. the conventional deconvolution based method, is statistically flawed and performs inadequately, especially by comparison to the alternative non linear mixed effects modelling technique. The fact that the conventional approach frequently fails to establish an IVIVC when it really does exist (i.e. fails the FDA test when it ought to pass) should be of great concern to those currently implementing this method. It is clear from the results of this study that the commonly used approach is substandard and that the alternative convolution based method produces reliable, accurate results of a far higher caliber.

REFERENCES:

1) Dunne A., Gaynor C. and Davis J. (2005) Deconvolution Based Approach for Level A In Vivo-In Vitro Correlation Modelling: Statistical Considerations. *Clinical Research and Regulatory Affairs*, **22**, 1-14.
2) O'Hara T., Hayes S., Davis J., Devane J., Smart T. and Dunne A. (2001) In Vivo-In Vitro Correlation (IVIVC) Modeling Incorporating a Convolution Step. *Journal of Pharmacokinetics and Pharmacodynamics*, **28**, 277-298.
3) Hovorka, R., Chappell, M.J., Godfrey, K.R., Madden, F.N., Rouse, M.K. and Soons, P.A. (1998) CODE: A Deconvolution Program Implementing a Regularization Method of Deconvolution Constrained to Non-Negative Values. Description and Pilot Evaluation. Biopharmaceutics and Drug Disposition 19: 39-53.
4) Food and Drug Administration (1997) Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In vitro/In vivo Correlations.
5) Wing G.M. (1991) *A Primer on Integral Equations of the First Kind – The Problem of Deconvolution and Unfolding.* Society for Industrial and Applied Mathematics, Philadelphia.
6) S.L. Beal and L. B. Sheiner. *NONMEM User's Guides, NONMEM Project Group,* University of California, San Francisco, 1992.