A TIME SCALING APPROACH TO DEVELOPING AN *IN VITRO-IN VIVO* CORRELATION (IVIVC) MODEL USING A CONVOLUTION BASED TECHNIQUE

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A much sought after goal in pharmaceutical research is the ability to use laboratory data for predicting the performance of a drug product following administration to humans. For example, an *in vitro-in vivo* correlation (IVIVC) model uses *in vitro* dissolution data for a particular drug formulation to predict the *in vivo* plasma concentration-time profile of that drug formulation. These models prove very useful during drug formulation development, the setting of dissolution specifications and biowaiver applications following postapproval changes. It is common practice to fit an IVIVC model to deconvoluted data rather than to the raw plasma drug concentration-time data because the deconvoluted data are believed to reflect the dissolution of the drug *in vivo*. However, the deconvolution step and the associated methodology poses some statistical concerns. This has motivated the development of a convolution-based approach which uses the untransformed plasma drug concentration data and addresses the statistical issues. Recent studies confirm that this convolution-based approach is superior to the deconvolution method. For the present study, we considered the problem of finding an IVIVC model for a drug formulation for which the *in vitro* drug dissolution occurs over a much shorter time scale than the *in vivo* drug dissolution. Traditional methods of finding an IVIVC model for this particular drug had already proven unsuccessful. In order to successfully obtain a useful IVIVC model for a drug with such a disparity between the *in vivo* and *in vitro* time scales, we applied a modelling approach based on time scaling. Both the *in vitro* and the *in vivo* data are longitudinal in nature with appreciable between subject variation present in the *in vivo* data. A nonlinear mixed effects model was used to describe the data with a time-scale model linking the *in vitro* and *in vivo* components. The IVIVC model was successfully fitted to the data using the NONMEM package. The model utility was assessed by comparing model-predicted plasma drug concentration profiles with the actual *in vivo* plasma concentration-time profiles observed. This comparison met the FDA validation criteria demonstrating that the model was sufficiently accurate for regulatory purposes. It also demonstrates the versatility of the convolution-based methodology in obtaining an IVIVC.