**Specifying Models with Time-Dependent Pharmacokinetic Parameters in NONMEM**

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**Introduction**

Time-dependent parameters are sometimes required to describe the pharmacokinetics of a drug. Such models can be implemented in NONMEM in a number of different ways [1]. Two of them use the PREDPP library and were considered in this work:

- using an analytical solution
- using a numerical solution to the differential equations

The differences between these methods were investigated using an example of time-varying absorption previously presented [2,3].

**Methods**

**Model**

A one-compartment pharmacokinetic model with a time-dependent first order oral absorption was applied. The time dependency of the absorption rate constant was described using a sigmoidal Emax model:

$$ KA(t) = K_{A,asym} \frac{t^\gamma}{t^\gamma + T_{0.5}^\gamma} $$

where $K_{A,asym}$ is the asymptotic value of $K_A$, $T_{0.5}$ is the time at which $K_A$ reaches 50% of its final values, and $\gamma$ is a shape factor that modulates the onset of $K_{A,asym}$.

The model was parameterized using apparent clearance and volume. No inter- nor intra-subject variability was introduced in the model to facilitate relevant comparisons to be made.

**Dataset**

Two datasets were simulated, one using the analytical solution and the other using the numerical solution to the differential equations. Each dataset contained 3 individuals, receiving the same dose level of 100mg but having a different sampling scheme (from very rich to sparse) as illustrated in Table 1.

**Results**

The IPRED values up to Tmax simulated with the two control streams are given in Table 2 and Table 3.

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<th>Sampling Time (h)</th>
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</table>

**Implementation**

Simulations were performed in NONMEM (v7) [1] using two different control streams. The first control stream used the analytical solution in ADVAN2, whilst the second control stream used a numerical solution through ADVAN6. The NONMEM control streams are shown in Figure 1 and Figure 2, respectively.

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**Conclusion**

It is clear from Figure 3 and Figure 4 that the control stream using the analytical solution from ADVAN2 does not use the model as described in Equation 1, and even uses a different model for each subject when the sampling scheme differs between individuals. The model obtained in this case is a step function approximation of the desired model.

On the other hand, the numerical differential equation solver in NONMEM uses the desired model but is more computer intensive.

If the analytical solution is used, the introduction of a sufficient number of time points is required to have an acceptable approximation of the model.

**References**

