Modeling and Simulation in Early Drug Development

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OBJECTIVE

The use of mathematical models to describe and predict pharmacokinetic (PK) and pharmacodynamic (PD) pharmacological responses to pharmaceutical agents and medical devices is a relatively new and exciting area of research and constitutes the foundation of model-based drug development. Modeling is the quantitative summarization of the data, prior knowledge and assumptions to learn more about the drug. Models are built using drug concentration data, clinical endpoints, biomarker data, and other available PD information. Simulation is taking the model and the model parameters and then varying the inputs. Modeling and simulation (M&S) involves knowledge of pharmacologic systems, statistical analysis, scientific creativity, and the pharmacological imagination to ask "what if".

During early clinical development, clinical studies are short and are rich with systemic drug levels, clinical chemistry information, and intense subject observations. These rich data sets provide an excellent basis for development of models that describe pharmacologic responses. These models can then be used to simulate PK profiles and to predict pharmacological responses in order to optimize and accelerate drug development. These models can also be used in conjunction with the sparse data obtained in later stages of development programs. In either case the role of M&S in drug development can be a supportive or it can be a key tool.

Here we present 3 case studies as examples of how M&S has helped in the drug development process. Case Study 1 presents the use of a mixed-effects model to describe the PK and predict different dosage regimens of a combination product, when a non-compartmental analysis (NCA) was not appropriate. In Case Study 2, the model developed in Case Study 1 is taken a step further to show how a non-linear mixed effects model can be used to reconcile inconclusive results from inferential statistical analysis performed in 2 thorough QT (TQT) studies. Case Study 3 presents how the PK model developed in Case Study 1 was used for the analysis of sparse data obtained from late stage studies (*maximum a posteriori* [MAP]-Bayesian analysis) and how the fitted PK exposure parameters were utilized as covariates in the analysis of efficacy data.

METHODS

Identify Problem: What question needs to be answered? What problem needs to be solved? Identify the problem allows for a clearer approach to reviewing the data and defining an initial model.

Review Data: It is important to review the available concentration, PK, PD, biomarker, and demographic data, in order to define the intended use of the model. Is the data clean, accurate and unbiased? Does the raw data contain the appropriate information to support a PK and/or PK/PD model? A solid understanding of the raw data will help in defining the need and direction of the model.

Define Model: Answer the questions: What is the intended use of the model? Will the model be used for descriptive or predictive purposes; where descriptive models are applied to the population at hand and predictive models built with one population and applied to other populations, which did not provide input in the model building? Will the model describe the data or a system; an empirical model versus a mechanistic model? Defining an initial model gives a solid foundation in the every evolving model development process.

Develop Model: What is the structural model? How will the population parameters and their error models be defined? What overall residual error models will be considered? Will covariates be utilized? If so, how will they be incorporated to the model (additively, proportionally, multiplicatively, or as a saturable covariate? Developing a model is an iterative process, where the data dictates the path to be followed.

Evaluate Model: How will models be evaluated and compared? Does the model reasonably predict the observed data? What goodness-of-fit methods will be employed, graphical or metric-like criteria? How will the model be validated, with internal data or external data?

Once a model is built, it can be used in different ways:

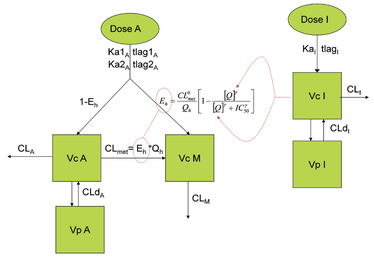
- To predict the exposure resulting from different dosing regimens for future clinical use, as shown in Case Study 1
- Be revised by adding new information coming from additional studies
- Be linked to a PD model, as shown in Case Study 2
- To analyze sparse data from late phase studies using MAP-Bayesian analysis in which the values of the model parameters (fixed and random) are being used as constraints to fit the sparse data, as shown in Case Study 3

RESULTS OVERVIEW

Case Study 1:

The recent approval of a combination drug (AI; A+I) where M&S was employed is a good example of the successful use of M&S in the support of drug development. The first assumption for using NCA is that a drug has linear and time-independent PK. When this assumption is not fulfilled, predictions based on NCA models are erroneous. In this combination compound, Drug I inhibits the metabolism of the active drug (A) to its metabolite (M) to increase Drug A's bioavailability and half-life, resulting in non-linear PK. Thus, the use of NCA was not appropriate and M&S was utilized to describe the PK. A population mixed-effects model (Figure 1) was built using data from 3 studies in order to predict plasma concentrations with various dose combinations of the 2 drugs and various dosing regimens.

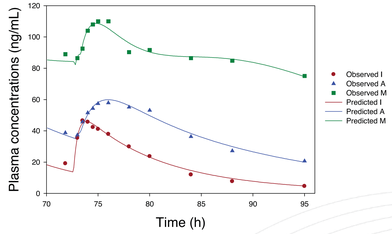
Figure 1: Outline of the Non-linear Pk Model



Ka_x = first-order absorption rate constant of Drug X; $tlag_x$ = absorption lag time of Drug X;
Eh = hepatic extraction ratio (constrained between 0 and 1); Qh = hepatic blood flow;
CL_X = systemic clearance of Drug X; CLd_X = distributional clearance of Drug X;
VcX = volume of central compartment for Drug X;
Vp X = volume of peripheral compartment for Drug X;
CL^0_{met} = metabolic clearance of Drug A to M in the absence of Drug I;
CL_{met} = metabolic clearance of Drug A to M;
IC_{50} = inhibitor concentration at half the maximum inhibition effect; γ = Hill coefficient

The PK of all 3 analytes (A, M and I) in plasma following single and multiple doses of the combination drug were well described by the population PK model developed with this meta-analysis (Figure 2). The model was also able to successfully predict the plasma PK of these 3 analytes from studies not utilized in the model development.

Figure 2: Example of an Individual Fit For the Active Compound (A), Its Metabolite (M) and the Inhibitor (I)

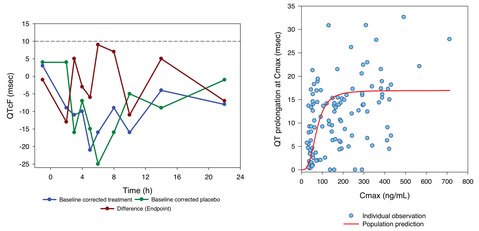


Case Study 2:

M&S can help reconcile inconclusive results obtained with the standard inferential statistical analysis performed on TQT data (referred to as central tendency analysis, noninferiority testing, or intersection-union testing). TQT studies are more often becoming part of Phase I development programs. During the development process of Drug AI presented in the first case study, 2 TQT studies were performed, due to a change in drug regimen during Phase III. Based on the central tendency analysis performed for each study, doses 2 to 3 times lower than the original Phase I dose resulted in the same mild QT prolongation observed with the original dose. In order to reconcile these results, non-linear mixed-effects PK/PD modeling, using the PK model previously developed, was utilized to allow for pooling of the 2 TQT studies, which had different endpoints (QTcF and QTcI) and different baseline correction methods (average and timematched), and successfully modeled the QT observations.

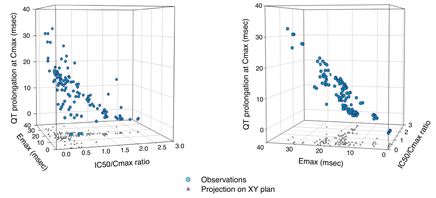
While the inferential statistical analysis performed on the TQT data had a null hypothesis that the one-sided 95% confidence interval (CI) for the difference between the baseline corrected placebo and the treatment would be greater than 10 milliseconds (msec) for at least one time point (Figure 3A), the non-linear mixed-effects approach looked at the relationship between the PD response (in this case QT measurements) and the AI drug concentrations, the sensitivity of individuals towards the drug, the available covariates (eg. age, sex, etc.), the diurnal variation within an individual, the inter-subject variability, etc. The final structural PD model included fitted individual correction for heart rate, a baseline model and diurnal variations.

Figure 3: Illustration of Inferential Statistics Approach (A) Versus Non-linear Mixed-Effects Modeling (B)



Furthermore, using the non-linear mixed-effects approach, the data can be viewed from a different perspective than using just probabilistic statistics. Figure 4 represents a couple of the mixed-effects model derived parameters (E_{max} and IC_{50}) found in the model versus the individual data presented in Figure 3B. When portrayed in this perspective, the different sources of variability in the observed data are able to be seen in more detail and allow for a better understanding of the drug effect.

Figure 4: Representation of the Multidimensional Aspect of Non-linear Mixed-effects Modeling: QT Prolongation at C_{max} Versus the Model Predicted Parameters E_{max} and the IC_{50}/C_{max} Ratio



E_{max} = maximum QT prolongation
IC_{50} = the plasma concentration required to reach half the E_{max} value

In this particular analysis, the PK and PD were linked through a sigmoidal model and the plasma concentrations of I were sufficient to explain the drug-induced QT prolongation.

Case Study 3:

In a clinical study where patients were randomly assigned to 3 treatment arms, 10 mg Drug X, 15 mg Drug X and placebo, 2 efficacy response markers were assessed after 4 weeks and 8 weeks on treatment. Only 13% of the patients consented to provide blood samples for PK assessment. However, sparse PK samplings from about 20 other studies for this compound provided enough data to develop an adequate population model to simulate complete PK profiles. With simulated PK profiles, exposure parameters (C_{max} and AUC) for all patients were completed and incorporated into the statistical model fitting to examine the relationship of efficacy response to PK exposure. Without simulated PK parameters, association of PK exposure with efficacy response would not have been significant. Treatment comparisons only showed positive response in the 10 mg arm compared to placebo. When simulated PK parameters were included in the statistical model fitting, the association between exposure parameters and efficacy response was significant, suggesting increasing efficacy with increasing PK exposure. Treatment comparisons not only showed favorable response for active arms, it also showed favorable response of 15 mg treatment arm over 10 mg treatment arm.

CONCLUSION

The 3 case studies illustrated why traditional inferential statistics or standard non-compartmental analysis are not always adequate to fully explore, explain and identify the true nature of observed variability. M&S provides options to further investigate.

Although M&S can be beneficial, great attention must be placed on the limitations and confidence levels of simulations. Effective use of M&S within confidence bounds can create value for sponsors and patients in drug development.

Modeling and simulation is a powerful tool in drug development when used appropriately. Expertise in both pharmacological sciences and statistics is required to deliver high quality results that effectively provide directions to advance research.

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