CERTARA

Phoenix Allometric Scaling Tool Accelerates Predicting First-In-Man Dosing

Global, Tier 1 pharmaceutical company engages Phoenix Technology Services to develop a new solution that streamlines designing early clinical studies based on pre-clinical data

Background

Humans have a distinct biochemistry, anatomy, and physiology compared to other animals. Predictions of a drug's PK profile in humans based on animal PK data must account for these differences. Allometric scaling is used to predict differences in PK parameters based only on size.

Challenge

Allometric scaling is commonly used to predict human pharmacokinetic (PK) parameters based on animal data. While allometric scaling has been used in drug development for many years, it is a complicated and laborious process. The client, a global Tier 1 pharmaceutical company, wanted to streamline designing first-in-man (FIM) clinical studies based on pre-clinical data.

Solution

Getting the dose right for FIM trials is critical. Allometric scaling calculations are performed frequently in pre-clinical groups as they study various drugs in different model organisms. To help accelerate the pace of drug development for the client, Certara's Phoenix Technology Services developed an application that automates FIM allometric scaling using pre-clinical PK data.

Assumptions of the model

Like any model, the tool uses several assumptions. For example, the system is assumed to exhibit linear kinetics. Different species have unique pharmacokinetic profiles. Thus, the volume of distribution, clearance from plasma, transfer rate from/to plasma and to/from peripheral compartments (for 2-compartment models) were assumed to differ between species.

The input into the tool is either oral or IV PK data from rats, dogs, or monkeys. First, the algorithm determines the average values for the PK parameters and finds the best model (one- or two-compartment with or without a time lag) to fit the pre-clinical data. These parameters are then

Challenge

The client, a global pharmaceutical company, had been using allometric scaling to predict human pharmacokinetic (PK) parameters based on animal data. They wanted a tool that simplified and accelerated this complicated and laborious process.

Solution

Phoenix Technology Services developed an application that automates first-in-man (FIM) allometric scaling using pre-clinical PK data.

Benefit

The user-friendly tool can be operated by any scientist involved in pre-clinical DMPK projects. This enabled the client to save time and money when transitioning drug programs from pre-clinical to clinical development.

subjected to a pre-defined allometric scaling equation that extrapolates from each animal species to humans. Each animal species has its own pre-defined allometric scaling equation. All other model parameters (K_a, bioavailability, etc) are assumed to be shared across the different species including humans.

Modeling strategy

A population PK modeling approach is used to fit the model to the combined species input data. The advantage of a population PK modeling approach is that it enables both rich and sparse individual data to be combined. The end product of the model is both average and individual PK parameters for each species. The average animal PK model parameters are then used to extrapolate to humans using a pre-defined allometric scaling equation.

Optimal dosing regimen

Based on user-defined threshold values for either the drug concentration-time area under the curve (AUC), maximum concentration (C_{max}) or minimum concentration (C_{min}), the program automatically estimates the dose needed to reach each of these threshold values. Finally, the user defines their desired dosing interval, and the program calculates the optimal dosing scenario to achieve steady state IV or oral dosing. The output of the program is a Phoenix project which includes capabilities for performing data manipulations, non-compartmental analysis (NCA), descriptive statistics, and generating accompanying graphics.

Application Architecture

The allometric scaling plugin is connected to Phoenix via an API. These can access data stored externally. The plugin application maps input data to Phoenix objects, executes and compares models, and acquires results from executed objects to set up the fixed and random effects for the next executable non-linear mixed effects (NLME) model.

Application Output

The automation procedure delivers as output a Phoenix project with all the model templates as well as the entire workflow. The user can then edit those, run any of the models, and decide what to do next to achieve optimal dosing using the manual mode rather than the automated one. He can still take advantage of all the templates that are generated during the automation procedure (models, NCA, descriptive statistics, graphics, etc).

Benefit

This unique application saves time and money by automating allometric scaling using Phoenix. It can also be easily customized. The same automation concept can be expanded to include individual Bayesian based model predictions, population PK/PD models, and combined PK/PD with categorical response models.

Impact

This automation procedure opens the door for new opportunities in the pharmacometrics community. Once the algorithm that automatically calculates initial estimates for model parameters has been determined, it can be implemented in an application that is linked to Phoenix. This user-friendly application can be operated by any scientist involved in pre-clinical DMPK projects.

About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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