Pharmacokinetic Modeling, Simulation, and Scaling to Support a European Submission

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Abstract

Objective: Gain regulatory approval in EMEA using US dose data and population PL modeling.

Background: A successful drug application in one country or jurisdiction is often followed by applications to agencies in other countries or regions. For example, a successful US application could be followed by a submission in Europe (to the EMEA) or Japan (PMDA). Often, compounds will have different development rules or dosing recommendations for each region. In some cases it may be acceptable to use pharmacokinetic and pharmacodynamics (PK/PD) models of clinical trial data for a dose level acceptable to one agency to interpolate or extrapolate expected outcomes at dose levels preferred by other agencies. [1] A case study is presented showing how modeling and simulation was used to support a submission to the EMEA using data from a trial conducted at a dose level preferred by the North American regulators. While data are disguised, the lessons from this example should be useful to companies facing similar situations.

Methods: Population pharmacokinetic (popPK) models were created to simulate dose-concentration relationships in adults, neonate pediatric patients, and non-neonate pediatric patient pediatric subjects. The popPK models were used to create predictions of the fraction of subjects remaining above a threshold effective concentration over a 60-day interval between doses. A complication faced by the modeling exercise was that actual potency can be significantly different from label-claim potency; thus the actual distribution for both trial and production lot potencies were used in the simulations. In addition, because the product persists in therapeutic concentrations over months, the growth of neonate pediatric patients had to be included in the neonate pediatric patient model. In fact, the data supported weight, and no other variable, as a covariate (sex, age, and race were also considered). The weight of non-neonate pediatric patient subjects exceeded the predictive range of the neonate pediatric patient model, and so predictions for these patients required scaling of the adult model using allometric techniques.

Results: One-compartment popPK models with linear clearance and absorption fit the data well for both neonate pediatric and adult patients given doses based on North American recommendations for the product. Using these models, we predicted that the compound titer in a high percentage of adult and non-neonate patients given a dose consistent with European dosing recommendation guidelines would also meet or exceed the minimum effective concentration threshold 60 days post-dose. Because actual potency varies and is greater than the label-claim potency, the analysis was performed under several potency scenarios and the conclusions were robust for all patient types. In neonates, for example, 99% of subjects receiving a weight-based dose (5mg/kg, illustrative) would be expected to meet or exceed threshold under all potency assumptions. In adults, 93% of subjects receiving fixed 100 mg (illustrative) doses would be expected to meet or exceed the threshold, assuming that doses had the same potency distribution as actual production lots. Scaling the model to non-neonate pediatric patient patients (10-50kg) and using a 1mg/kg dose, 89% of subjects would be expected to meet the threshold with production lot potencies.

Reference:

[1] Volumes 1-4 and 9-10 of The Rules Governing Medicinal Products in the European Union, available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm .

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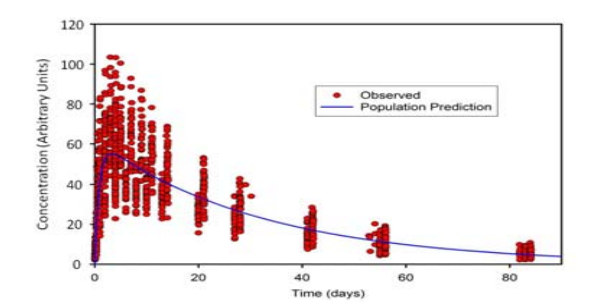
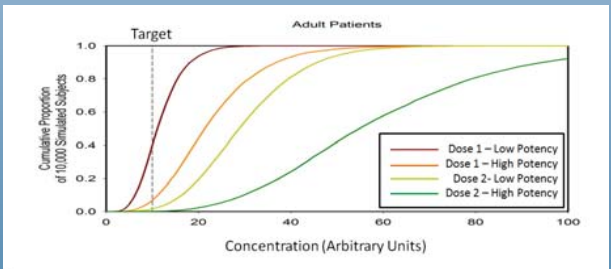
Population PK fit of compartmental model (Adults)



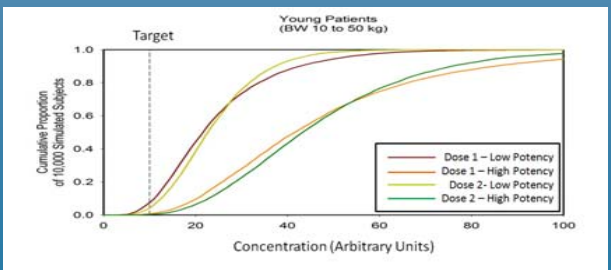
Summary of Fitting Adult Data

- Data from adult-patient two studies modeled using NONMEM (v 6, Icon Plc, Md, USA).
- Studies each had approximately 35 subjects.
- All subjects receiving therapy were included in modeling analysis and parameter estimation.
- Data fit a single-compartment model with first-order absorption from an intramuscular (I.M.) dosing depot and first-order clearance.
- Systemic clearance and volume of distribution were computed as functions of body weight (proportional to BW0.75 and BW1.0, respectively).
- Between-subject variability in the absorption rate constant (ka), clearance (CL) and volume of distribution (V) was estimated using a full-block variance-covariance matrix.
- Residual error was estimated using a proportional error model.

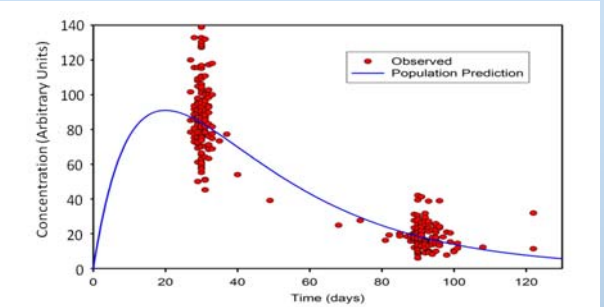
Fraction of Adult subjects by dose & trough concentration



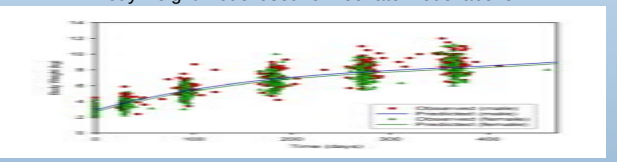
Fraction of non-neonate pediatric (10-50kg) subjects by dose & trough concentration



Population PK fit of compartmental model (neonates)



Body weight model used for neonate model above



Summary of Fitting Neonate Data

- Data from single study modeled using NONMEM
- Studies each had approximately 250 subjects, of whom about 100 were culled due to presence of a endogenous substance confounding the assay.
- A one-compartment model with linear clearance and absorption fit these data well.
- Sparse data precluded estimating absorption rate constant; used the adult rate constant
- Body weight fit a cubic equation in time since birth., allowing predictions of volume and clearance as a function of time, permitting predictive simulations.
- Nonlinear, mixed-effects modeling showed sex had a significant effect on the y-intercept for the model of age (viz. time) on predicted body weight..

Summary of Fitting Adult Data and Scaled non-neonate pediatric data

- Result of10,000)simulated subjects
- Key idea was using distribution of potencies for these simulations.
- Allometric scaling and population age and weight distribution data used to scale adult model to predict non-neonate outcome.
- Scaling method tested using similar, analogous therapies.

Conclusions: In this case, neonate- and adult-patient data from trials using North American doses was modeled and used to simulate EMEA doses under various potency scenarios. In addition, a model of weight change as a function of age, combined with a popPK model and allometric scaling, allowed predictions in neonate pediatric patients, whose weight changes significantly over the 60-day dosing interval. The models facilitated an analysis of sensitivity of treatment outcome to both model variations and to different doses, potencies, and dose protocols. This modeling and simulation supported a regulatory submission without having to perform additional clinical trials. Our client has stated that they feel that the modeling work was received favorably by the EMEA, and has facilitated efficient discussions.