How to predict a daily concentration for exposure-response analyses when no population PK model is available?

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Introduction
Analysis of the relationship between exposure and efficacy or safety endpoints is routinely required as part of drug development. To better characterize the E-R relationship it is important to consider the patient exposure at any time, to account for the dosing changes and interruptions or changes in dosing regimen at the time of an event. However it is frequent in oncology, and particularly for pediatric indication, that only sparse sampling is collected at specific time point and no final population PK model is available. This poster describes an approach that allows the prediction of PK concentrations at any time in situation where no population PK model can be used but pharmacokinetic properties of the drug, such as linear PK, allow for the use of superposition principle and basic PK equations.

Methods
Prediction of steady state concentrations:
Standard approach:
Dose proportionality of steady state concentrations is usually used to fit the following log-log linear mixed effect model and predicted steady state Cmim concentrations can then be computed for any dose administration within the dose proportionality range.

\[
\log(C_{\text{mim}}(dose)) = \mu + \beta_1 s_{\text{unit}} + \ldots + \beta_k s_{\text{unit}} + \varepsilon_i + (y + u_i) \log(dose_{\text{dosing-1)}) + \epsilon_{id}
\]

Where:
- \(\mu\) represents the population mean
- \(\beta_1, \ldots, \beta_k\) represents the coefficient for covariates or factors \(x_j\), \(j=1\ldots k\).
- \(s_{\text{unit}}\) and \(u_i\) represent the random effects on the intercept and slope of subject \(i\), \(i=1\ldots n\), and assumed to be normally distributed \(s_i \sim N(0, \sigma_s^2)\) and \(u_i \sim N(0, \sigma_u^2)\).
- \(\varepsilon_i\) represents the coefficient for total daily dose given 1 day prior to Cmim at steady-state of subject \(i\).
- \(\epsilon_{id}\) is the residual error, assumed to be normally distributed, \(\epsilon_{id} \sim N(0, \sigma_e^2)\)

New approach:
For an oral dose administration, the plasma concentration after multiple dose follow the below standard PK equation:

\[
P_{\text{max}} = \frac{F \cdot D \cdot k_a \cdot \left(1 - e^{-\frac{t}{\tau}}\right)}{V_d \cdot (k_e - k_d) \cdot \left(1 - e^{-\frac{t}{\tau}}\right)}
\]

Observed steady state concentrations can be fitted using the following non-linear mixed effect model:

\[
\log(C_{\text{max}}(dose)) = \log\left(\frac{F \cdot D \cdot k_a \cdot \left(1 - e^{-\frac{t}{\tau}}\right)}{V_d \cdot (k_e - k_d) \cdot \left(1 - e^{-\frac{t}{\tau}}\right)}\right) + \epsilon_{id}
\]

Where
- \(F, D, k_a, k_e, k_d, V_d, t, \tau\) are usually available from first CP trials (e.g. ADME, BA trials)
- \(V_d, k_d, k_a, k_e\) are estimated, including random effect \(v_i \sim N(0, \sigma_v^2)\) and \(h_i \sim N(0, \sigma_h^2)\)
- \(t\) is the elapsed time (not limited to Cmim)
- \(\epsilon\) error, assumed to be normal \(\epsilon_i \sim N(0, \sigma_e^2)\)

Superposition principle
The concentration over time of a multiple dose treatment schedule can be calculated as the sum of the concentrations which would be observed from the individual doses were they given alone.

Prediction of non steady state concentrations
If the concentration is not expected to be at steady state according to the dosing history (based on the number of doses needed to reach steady state), the concentration will not be predicted using the non linear model. The non steady state predicted concentration will be computed as the sum of remaining concentrations from:
- a. The last predicted steady state concentration (as an IV bolus):
- b. Each of the individual doses administered since the last predicted steady state concentration

Results
In 2016, FDA requested an integrated pooled dose- and exposure-response analyses for efficacy and safety endpoints using pediatric clinical trial data (ages 2 to 16 years).
Safety measures were laboratory parameters e.g. different levels of ALT/TBL at any visit. PK exposure were collected at a single visit or at a few visits only (pre-dose and/or C2h concentrations).

Key challenges:
- Obtain drug exposure matching with safety measure at any given time point under steady-state and non-steady state conditions
- No up-to-date population PK model available
- Sparse samples and large variability in children’s PK expected
- Data inconsistencies between dosing history and exposure detected

PK properties of the drug:
- PK is linear and drug exposure is dose proportional
- Time-independent PK
- Absolute bioavailability 70% (aBA study)
- Steady-state reached after 4 equal consecutive daily doses

Steady state predictions using linear and non linear model

Non steady state predictions

Conclusions
Fitting non-linear models utilizing standard PK equations and the superposition principle allows for predictions of Cmin/Cmax at non-steady state situations. However, the approach can only be used for linear PK drugs and knowledge of several PK parameters such as fraction of absorption F etc are required. Both linear and non-linear models underpredict at higher concentrations and overpredict at lower concentrations. Deviations from assumptions may explain the under/over predictions, e.g. constant dosing window of 24 hours, dosing and sampling history assumed to be correct, model assumptions, C2h used as surrogate for Cmax. However base on the dosing history, there is no influence of implausible PK observations at non steady-state on model predictions. And underpredictions are conservative for exposure-safety analyses. The method allows exposure-response analyses of sparse PK data even in the absence of a popPK model.