Title: Linking Modeling & Simulation, Decision Analysis, and the Technology of Drug Formulation

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Objectives:

- Link modeling and simulation (M&S) and decision analysis (DA) in order to analyze a critical decision:

  “Can sufficient additional patient benefit by provided by an alternative formulation to warrant further development?”

- Specific tasks included:
  - Generating a pharmacokinetic (PK) model to predict concentration given dose, time, and formulation,
  - Generating exposure-response (E-R) models for the major clinical endpoints,
  - Constructing a Clinical Utility Index (CUI) to measure trade-offs among endpoints,
  - Conducting simulations and sensitivity analyses to address the primary decision.

Background: Dopahexidine is a mature drug indicated for a chronic neuromuscular condition. RePharmaCo, the maker of Dopahexidine, is investigating the value of a new formulation as a way to differentiate the product and offer additional patients benefit. Both efficacy and incidence of adverse events are related to drug level. Due to its quick elimination, relatively large doses have to be given multiple times per day. Although substantial historical data is available, it does not necessarily include ideal PK/PD information.

Methods:

Literature data was used to develop a PK model, as well as E-R models for (SES), hypotension, drowsiness, and dyskinesia. Simulations of the models were conducted to determine which parameters effected the most meaningful changes in clinical utility. An overview of the process is shown in the figure below:
Standard compartmental models were for the PK model, with data from IR and MR regimens. Various linear and saturable models were investigated for each clinical endpoint’s exposure-response model. The CUI was constructed according to Pharsight’s standard CUI process: (1) Identify critical treatment attributes and relative weights, (2) Identify metrics and relevant response levels for each attribute, (3) Assign preference values for each response level, and (4) Conduct sensitivity checks. As the modeling work was completed, results were published in Drug Model Explorer (DMX) and explored with the project team.

**Results:**

Based on data from 6 studies, a 1-compartmental model was adequate to describe the concentration data. SES change from baseline was modeled with a sigmoidal Emax curve versus concentration. Incidence of drowsiness/somnolence and incidence of dyskinesia were each modeled as a function of Cmax in logistic regression models. For systolic blood pressure, a simple linear model versus concentration described the data well.

The CUI was initially completed with the project and subsequently in a small survey of prescribing physicians. Rankings of attributes changed somewhat, but attribute weights were similar overall. Efficacy was ranked first in both cases, with remaining attributes relatively equally valued amongst themselves.

Sensitivity analyses revealed that substantial increases in CUI could be realized with increased duration of efficacy (via lower absorption rate).

**Conclusions:**

The main efficacy and tolerability characteristics were gathered from a variety of public sources, enabling the construction of PK/PD models describing the main endpoints. A CUI was elicited to integrate this information into a single metric of clinical benefit.

Outcomes were simulated for a variety of drug absorption scenarios, and the results were explored with the project team. The process enabled the identification of specific, actionable recommendations for a reformulated drug likely to have superior benefit to the current formulation. Supported by these insights, project development was continued.