Integrating Dose Estimation into a Decision Making Framework for Model-Based Drug Development

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Objective: To describe a method for integrating dose-response modeling and clinical dose estimation into formal go/no-go decision criteria.

Methods: Lalonde et al. proposed a statistical-based decision criteria to formalize evidence-based decision criteria in drug development.¹ The approach uses a priori definitions of success or futility. Performance is characterized with a Target Value (TV) and a Lower Reference Value (LRV).

Sufficient efficacy is critical for eventual success, but the decision to advance development phase is also dependent on adequate knowledge of appropriate dose. To address this issue, we incorporate dose estimation through dose-response modeling into the go/no-go decision process. We apply the philosophy of MCPMod in Bretz² and incorporate a set of response models, followed by Buckland’s method³ to estimate a target clinical dose. Bootstrapping provides inferences, which are then compared to a priori reference values in the decision process.

Results: To demonstrate the methodology, we analyzed data post hoc from a phase 2 study (N=159) of naloxegol for opioid-induced constipation (OIC). Patients were classified as responders or non-responders, and logistic regression models were developed for the link-level dose-response models of linear, log-linear, emax, and quadratic. The Buckland³ approach was applied to a dose providing 80% of maximum response over the studied range. The figure shows the results, with relevant confidence levels indicated by the rectangular box. In this case, the efficacy performance meets both TV and LRV, and the comparatively narrow width of the box indicates sufficient knowledge of dose for phase 3, which confirmed efficacy.⁴

Figure: (A) Decision Tree (B) Estimated dose (red *) with study response rates (black *) and estimated dose response

Conclusions: Both efficacy and dose-knowledge may be included in model-based drug development and joint decision criteria, resulting in improved decision making.

References:
1. Lalonde et al, CLINICAL PHARMACOLOGY & THERAPEUTICS, 82, 21-32, 2007
2. Bretz et al, BIOMETRICS 61, 738-748, 2005