Dose-Response Modeling for Combination Drug Products

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Objectives: Drugs are sometimes formulated in combination products with the goal of improving efficacy or reducing dose. Modeling the dose response relationship offers potential benefits in planning studies and in interpreting study results. The dose response relationship may be modeled empirically or mechanistically. Example datasets are used to compare several modeling methods.

Methods: The scope of this work covers fixed-dose combinations of two drugs, where both are effective alone, where efficacy is measured by one continuous end-point, and where there is no PK interaction. Empirical response-surface methods [1, 2], mechanistic models [3], and empirical synergy models [4] (i.e., Loewe additivity and Bliss independence) are compared. Modeling methods are illustrated using data from published studies (combinations of simvastatin/ezetimibe and atorvastatin/gemcabene) [5, 6] or simulated data.

Results: Improvement in efficacy or potential for dose-reduction can be concluded when the expected gain surface (also called the “excess over single-agent”) is favorable. Descriptive response surface methods or mechanistic modeling can lead to inferences about the expected gain surface. Response surface methods can provide a description of the 3-D surface and allow for interpolation and prediction of optimal dose combinations. Mechanistic modeling will have the added benefit of allowing for estimation of parameters that may have biological meaning for combinations of related drugs in a class. However, validating a mechanistic model in comparison with rival models may require time course data and supporting information about the mechanisms of action of each drug alone. Empirical synergy methods may provide results that are contradictory to the results of response surface modeling.

Conclusions: Assessment of dose-response for combination drug products is best done with a good prior understanding of the dose-response patterns and mechanisms of action of the component drugs. Response surface methods and mechanistic modeling methods can be used to describe the dose-response surface and to make inferences about improvement in efficacy or potential for dose reduction. Lack of empirical synergy does not imply lack of improvement in efficacy or lack of potential for dose reduction.

References: