Use of a Model Based Approach for Evaluation of partial Area Under the Curve for Bioequivalence Assessment of Methylphenidate Transdermal products

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Objectives: To evaluate the value of additional bioequivalence (BE) metrics for Methylphenidate (MPH) transdermal products using a model based approach.

Methods: Methylphenidate is a central nervous system stimulant used in the treatment of attention-deficit hyperactivity disorder in children. A population pharmacokinetic (PK) model was developed for MPH transdermal products using internally available datasets from Abbreviated New Drug Applications (ANDAs). This population PK model was linked to the previously published pharmacodynamic (PD) model [1] to study the impact of formulation changes on PK and PD (SKAMP-Composite score). Several clinically plausible PK profiles corresponding to potential formulation changes of MPH patch were simulated and were subsequently explored to study the impact on predicted PD response. One thousand cross-over BE studies were simulated for two hypothetical test formulations (change in lag time for release/absorption and change in rate of absorption) to detect the power of various BE metrics (such as AUC, Cmax and partial AUCs) in detecting clinically meaningful PK differences associated with formulation changes.

Results: PK of MPH following patch application was best described by a one-compartment model with zero-order input and first-order elimination. PK model linked to the PD model that describes time-dependent placebo effects and a direct effects Emax model for drug induced response. For practical purpose, clinically meaningful PK differences associated with formulation changes are defined as PK changes that resulted in greater than 20% difference in the predicted PD response, at clinically relevant time windows. Clinical trial simulations showed that partial AUC 2-9h was the most sensitive metric that could detect clinically relevant and meaningful PK differences with formulations changes.

Conclusions: A strong PKPD correlation has been well documented in literature for all MPH products. Since PD is highly correlated with MPH concentrations, PK profile similarity is recommended in evaluation of ANDAs of MPH patch. This work supports recommendation of pAUC 2-9h as an additional evaluation metric to ensure BE and therapeutic equivalence among formulations of MPH patch products.

References: