Assessment of Partial AUC Requirement for Bioequivalence Evaluation of Methylphenidate Hydrochloride Extended-Release Oral Suspension

Nan Zheng*, Lanyan (Lucy) Fang

Office of Generic Drugs, U.S. Food and Drug Administration

Objectives: Quillivant XR (methylphenidate hydrochloride [MPH] extended-release oral suspension) is a modified-release formulation designed for a rapid initial drug release followed by a sustained drug release throughout the day. This work evaluates whether partial AUC would offer additional assurance in bioequivalence evaluation of generic products that reference Quillivant XR.

Method: We conducted sensitivity analysis on the pharmacokinetics/pharmacodynamics (PK/PD) model developed by the reference product sponsor. We evaluated the sensitivity of PK (Cmax, AUC0-t, AUC0-3, AUC3-7, AUC7-12 and AUC3-24) and PD (Effmax, AUEC0-t, AUEC0-3, AUEC3-7, AUEC7-12 and AUEC3-24) endpoints in response to formulation changes. With the formulation-specific model parameters varied for the test formulation, we calculated the test-to-reference ratios of these PK and PD parameters in a typical study subject, and calculated the chances of passing when bioequivalence testing was based on Cmax, AUC0-t, AUC0-3, AUC3-7, AUC7-12 and AUC3-24, in simulated single-dose, 2-sequence, 2-treatment bioequivalence studies.

Results: A one-compartment model with linear elimination and a parallel, zero order and first order absorption as well as a direct effect Emax model was used to describe PK/PD profile after Quillivant XR administration. Dose level, fraction of total dose, lag time and absorption rate for the first order absorption, lag time and duration for the zero order absorption, were identified as the formulation-specific model parameters. PK endpoints are in general more sensitive than PD endpoints to changes in formulation-specific model parameters. For example, values of all PK endpoints increase proportionally with dose while PD endpoints exhibit less than dose proportional increase. AUC0-3 and AUC7-12 are more sensitive than AUC0-t to changes in most of formulation-specific model parameters.

Conclusions: Because rapid onset and sustained exposure up to 12 hours are important to achieve desirable therapeutic outcome for Quillivant XR and because partial AUCs are more sensitive to formulation-specific parameter changes than the conventional metrics of Cmax and AUC, we recommend using partial AUCs in bioequivalence evaluation of generic MPH extended-release oral suspension.

References: http://www.regulations.gov/#!documentDetail;D=FDA-2014-P-1269-0001