Age Is a Statistically Significant Predictor of the Within Subject Variability in Dabigatran Pharmacokinetics

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Objective: To quantify the magnitude and to identify predictors of the observed within subject variability (WSV) of dabigatran in bioequivalence (BE) studies.

Methods: The WSV in pharmacokinetic parameters from a total of 17 Abbreviated New Drug Applications (ANDAs) with a total of 815 healthy volunteers submitted to the Center for Drug Evaluation and Research (CDER) were analyzed using meta-analysis. Age, body weight, height, body mass index, sex, race, the number of subjects per ANDA and region were evaluated as possible predictors of the observed magnitude of WSV of dabigatran using meta-regression.

Results: The WSV of the maximum concentration (C_{max}) and the area under the time concentration curve (AUC) expressed as coefficient of variation were 40% (95%CI: 35, 44%) and 38% (95%CI: 34, 42%), respectively, based on a total of 815 healthy subjects. Among 17 studies, WSV ranged from 28% to 61% for C_{max}, and from 30% to 58% for AUC. Age was a statistically significant predictor of WSV for both C_{max} (p = 0.007) and AUC (p = 0.018). Other tested demographic factors were found to be insignificant predictors of the WSV of C_{max} and AUC for dabigatran.

Conclusions: Large heterogeneity was observed across studies. Age was found to be a statistically significant predictor of observed WSV magnitude. Sponsors may expect larger WSV with an increase in the mean age of the recruited subjects. Of note, significant WSV of PK parameters of dabigatran remains even after adjusting the impact of age.