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Challenge with New FDA Requirement for Partial AUCs for Bioequivalence Assessment of Modified-Release Products

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Methods

Retroactive analyses from successful studies conducted for both Methylphenidate ER tablets and Zolpidem ER tablets in which the pAUCs were applied. All studies applied are single dose, 3-way crossover trial to assess the BE in healthy subjects. The Test/Reference (T/R) ratio of geometric means and the 90% CI approach were used to investigate BE. For studies analyzed, the 80% CI of the T/R ratio of geometric means of AUC(0-24) were within 80 to 125% or 90 to 125%. The same criteria applied for specific pAUCs.

Results and Discussion

Methylphenidate:

Our investigation used that 50% of AUC_{1-7}, AUC_{2-7}, and AUC_{7} were below 20%, which were comparable to those obtained from AUC_{0-24}. However, in some cases, the T/R ratios of pAUCs (g 3, 3.7, and 7.1-D) were significantly different between the test and reference products, while the T/R ratios of AUC were close to 100% and the 90% CI (AUC) were entirely within 80 to 125%. Meanwhile, the 90% CI of these pAUCs were within or outside the acceptable range of 80-125% in 94.9%.

The difference in the pharmacokinetic profile of the methylphenidate products can result in different therapeutic effects or parallel time duration through the day. The Figures 1 and 2 showed the difference of the early time of the PK profiles between the test and reference products.

Zolpidem:

Our results indicated that the intra-subject coefficient variability (ISCV) of AUC_{0-7} was similar to what obtained from the AUC, and the T/R ratio and 90% confidence intervals for AUC_{0-7} were also within 80 to 125%.

The results for AUC_{0-7} showed that the intra-subject coefficient variability (ISCV) of AUC_{0-7} were much higher (range from 50 to 200%) than those obtained from AUC. Such high ISCV might introduce difficulty to demonstrate BE using a sample size estimated originally on AUC, AUC_{0-24}, and AUC_{0-7}. In addition, the T/R ratios of AUC_{0-7} were not optimum showing significant differences between the test and reference products, while the T/R ratios for AUC were close to 100%. Meanwhile, the 90% CI of AUC_{0-7} were within 80 to 125%.

The difference in early AUC_{0-7} can lead to either lack of the efficacy and the scale AUCs.

The Figures 3 and Table 1 illustrated the difference of the early AUC_{0-7} for both test and reference products.

Conclusion

The additional pAUC metric of BE assessment for drug with both ER and IR components may ensure the therapeutic equivalence between the products.

The results of our retrospective data analysis at pAUC showed that the ISCV can be significantly higher and the T/R ratio significantly different when using multiple pAUCs for specific compounds such as Zolpidem and Methylphenidate. Consequently, the impact on the sample sizes could be significant and the general development of the product with pAUC requirement may be more challenging.

Reference

1. FDA Draft Guidance on Methylphenidate Hydrochloride Extended-Release Tablets, November 2014
2. FDA Draft Guidance on Zolpidem Extended-Release Tablets, October 2011
3. FDA Draft Guidance on Dexmethylphenidate Hydrochloride Extended-Release Capsules, March 2015