A Retrospective Analysis of Pharmacokinetic Variability Between Fasting and Fasting-Sprinkle Bioequivalence Studies of Generic Modified-Release Drug Products: A Case Study on Esomeprazole Magnesium

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Background

For generic drug approval of modified-release (MR) products sprinkled on soft food (e.g., applesauce), a fasting-sprinkle bioequivalence (FSBE) study may be recommended in addition to fasting BE (FBE) study. As more MR products with sprinkle (SP) option are approved, we need to understand what the key factors are to determine whether an FSBE study should be conducted. One of these factors is the pharmacokinetic (PK) variability under a fasting-sprinkle condition. To assess this, an estimated within-subject variability (E-WSV) was determined in both studies submitted to FDA.

Methods

- A search using multiple FDA databases (including labeling and drug application databases) was used to identify MR products labeled for sprinkle administration.
- For each approved abbreviated new drug application (ANDA), a non-compartmental analysis (NCA) and BE analysis of PK metrics (AUC_t, $AUC_{0\text{-}inf}$, and C_{max}) using Phoenix WinNonlin 8.3 (Certara, Princeton, NJ, USA) were performed. This was followed by a calculation of the E-WSV in both FBE and FSBE studies using the equation below:

$$\text{E-}WSV = SQRT\,(EXP(Residual\,Variance) - 1) * 100$$

- To evaluate the effect of the following factors on the E-WSV difference between FBE and FSBE studies:

1. *The type and amount of release controlling excipients in each ANDA, and its respective reference listed drug (RLD)*. The formulations were considered "similar" or "different" based on the (w/w %) difference between the release controlling excipients for each ANDA and the RLD.
2. *The study design for each ANDA and its respective RLD*.

Results

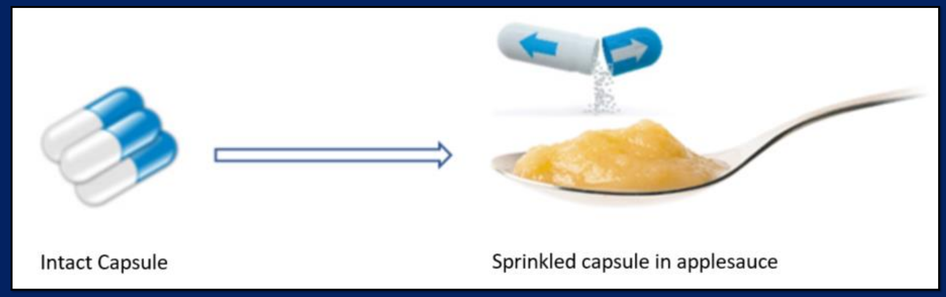
- Thirty-seven MR RLD identified with sprinkle administration; 20 of them have approved ANDAs and represented 18 active pharmaceutical ingredients (Figure 2).

Case Study of Esomeprazole Magnesium (EM)

- EM is a proton pump inhibitor used to treat certain stomach and esophagus problems.
- EM is marketed as delayed-release capsule containing esomeprazole magnesium in the form of enteric-coated granules.
- In FSBE study, all ANDAs used applesauce as soft-food vehicle.
- The average E-WSV for all approved ANDAs was less than 30% in both FBE and FSBE studies, and the difference between both studies was minimal (Figure 1).
- EM RLD and all respective ANDAs used the same control releasing excipient. The difference (w/w %) of control releasing excipient between the RLD and all respective ANDAs was similar except for four ANDAs.
- For the four ANDAs, the E-WSV was different when the difference in the number of subject completers was >5 between FBE and FSBE studies (Figure 3).
- The average Tmax was not statistically significant between the test and reference products for FBE and FSBE studies (Figure 4).
- This data suggest the soft food may not have an impact on the PK variability in fasting-sprinkle condition compared to standard fasting condition.

FDA U.S. FOOD & DRUG ADMINISTRATION

Some drug products can be sprinkled on soft food for flexible dosing and patient compliance.



In fasting and fasting-sprinkle bioequivalence studies, lack of significant difference in estimated within subject variability for PK metrics suggests that rate and extent of exposure are similar when esomeprazole magnesium administered as an intact capsule or sprinkled in soft food.

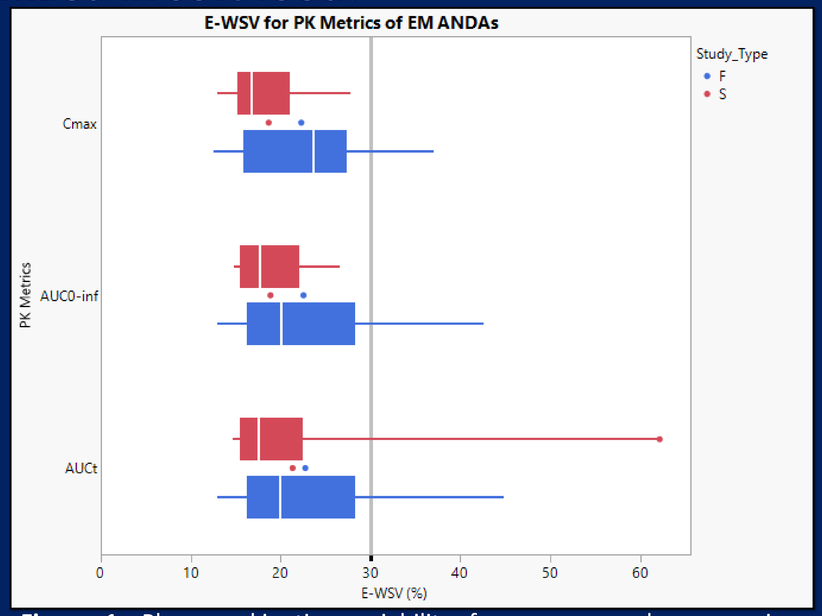


Figure 1: Pharmacokinetics variability for esomeprazole magnesium across 19 generic drug products for fasting and fasting-sprinkle bioequivalence studies.

Get more information

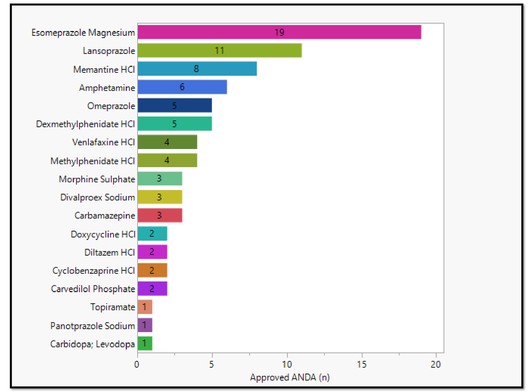


Figure 2: Number of Approved ANDAs per MR RLD approved for sprinkle administration.

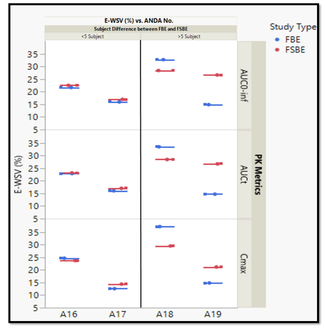


Figure 3 : E-WSV and the number of subjects for the four ANDAs of EM in FBE and FSBE studies.

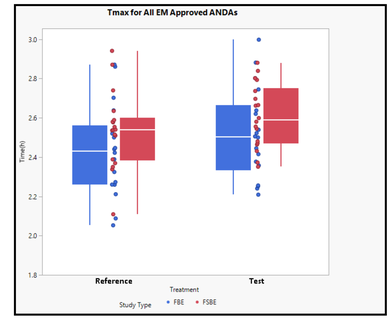


Figure 4: Tmax (h) for the test and reference products for all approved ANDAs

Conclusions

- In this EM case study, the average E-WSV was less than 30%.
- Among 19 approved ANDAs of EM, only 2 ANDAs had a high E-WSV in FBE (>30%) compared to low E-WSV in FSBE (<30%).
- The difference in the E-WSV was most likely observed with an imbalanced number of subjects rather than with formulation variation between the test and reference arms.
- Results of this study may be used to provide assessment criteria for the expected PK profiles for FBE and FSBE studies and help regulatory decision making for determining the need of FSBE study for future ANDA submissions.

Disclaimer and Acknowledgement

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