FY 2020 Generic Drug Regulatory Science Initiatives Public Workshop

Breakout 3: In Vitro Bioequivalence Methods

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IVPT Data Analysis: Raw Data

1. **Missing Data:**

'Skin sections (diffusion cells) that are discontinued from the study based upon criteria specified in the study protocol may be replaced with new skin sections....' (Acyclovir, FDA draft guidance 2016).

   - The purpose of replacing missing data as per the guidance is to ensure balanced data, but does this introduce bias?
   - Are there mathematical methods to account for missing data instead of replacement, i.e., a weighted average?

IVPT Data Analysis: Raw Data

2. Zero Values:

Logarithmic transformation of zero values are non existent (-∞) and as such, a profile with zeros will result in that data being excluded from the inferential statistical analyses.

- Initial research suggests that imputing ½ LOQ generally appears to over estimate s_{WR} and that treating BLOQ values as missing generally appears to under estimate s_{WR} leading to an increase type-I error.
- Imputation with the LOQ seemed to behave well, however, more research is needed.
- Other, more sophisticated methods of imputation would be interesting to research.

IVPT Data Analysis: Outliers

1. There are multiple methods of outlier detection.
   - Which is most suited for IVPT?
2. The recommended statistical methodology to evaluate BE for IVPT includes a mixed criterion that uses s_{WR} as a cutoff point.
   - Falsely declaring a value to be outlying may lead to the removal of pertinent data, which may in turn affect BE conclusions.
   - BUT not excluding data that is legitimately outlying may lead to over estimating s_{WR} and perhaps concluding that BE criteria is met using the RSABE method when in fact the product may not be highly variable.
   - Conducting sensitivity analyses to examine the influence of the removal of outlying value(s) may be warranted.

IVPT Data Analysis: ABE Modelling

- When $s_{WR} \leq 0.294$, ABE analyses are in order. To declare T and R bioequivalent, the (1-2α)*100% confidence interval :

$$exp(\bar{I} \pm t_{(n-1),\alpha} * \sqrt{S_I^2/n})$$

must be contained within the limits $[1/m, m]$. (Acyclovir FDA draft guidance)

- Initial research suggests that the statistical method of analyses from the Acyclovir FDA draft guidance may be more powerful in concluding BE but also suggests an increase in type I error compared to using ANOVA suited for replicate data.
- Further research would be warranted in this area.