Bioequivalence Study Requirements

Manuscript Preparation Instructions for Authors: Bioequivalence Studies

(See also Tips for Authors)

ABSTRACT

- State the criteria used to assume regulatory bioequivalence in the Abstract's Methods.
- Provide actual data for the pharmacokinetic parameters evaluated (eg, 90% CI for AUC, C_{max}).
- Begin the Abstract's Conclusion(s) in the following manner: "This [single- or multiple-] dose study found that the test and reference products met the regulatory criteria for bioequivalence in these [fasting or fed] [healthy, male/female] [volunteers or patients with...]."

INTRODUCTION

- Indicate the rationale for the study (eg, obtain marketing authorization in...).
- Clearly state the objective of the study.

MATERIALS AND METHODS

- Provide the rationale for conducting a single-dose or multiple-dose, or a fasting or fed, study.
- Multiple-dose studies are required if there is a difference in the rate, but not the extent, of absorption; if there is large intersubject variability in pharmacokinetic parameters; if the blood concentration resulting from a single dose is too low for accurate determination; or if the drug product is an extended-release dosage form.
- Food-effect studies are needed for immediate-release drugs for which the prescribing information contains statements about the effect of food or if the drug cannot be taken on an empty stomach. Food-effect studies are also needed for most orally administered modified-release drugs *except* those for which the prescribing information recommends taking the drug on an empty stomach or does not mention the effect of food.

- Indicate the duration of sampling and the washout period as 3 and 5 times $t_{1/2}$, respectively, of the drug or active metabolite.
- Provide the rationale for selecting the parent or active metabolite for analysis.
- State and reference the criteria used to assume bioequivalence.
- Justify any deviation from the US Food and Drug Administration or the European Medicines Agency for conduct of bioequivalence studies (eg, discussion with agency).
- Provide a sample-size calculation to support the number of subjects included in the study.
- Describe analytical methods in enough detail to allow duplication. The analytical method used must be validated and its selectivity, precision, accuracy, recovery, and limit of detection reported.
- Consider correcting the pharmacokinetic parameters for mg/kg doses given.
- Detail the methods used to monitor adverse events. Subjective and objective methods to determine tolerability are recommended.
- Indicate the lot numbers and expiration date for all products.
- Provide references for the statistical approach selected (eg, average, population, or individual bioequivalence).

RESULTS

- Provided actual data in text and tables, along with statistical analysis. The primary end point analysis will be presented first.
- Evaluate subject, period, sequence, and treatment effects. Intersubject, intrasubject, and/or total variability should be reported.
- Report C_{min}, C_{av}, degree of fluctuations, and whether steady-state studies are employed.
- Document any statistically significant differences (or lack thereof) between the test drug and the reference drug.
- Report tolerability data in detail.

DISCUSSION

- Discuss the limitations of the study (eg, single dose, inclusion/exclusion criteria, food effect) and the limits of generalizability (eg, cannot predict performance in patients in clinical practice).
- Indicate whether the product is currently considered bioequivalent by a regulatory agency.

CONCLUSION(S)

- Format conclusion(s) in the same manner as requested in the Abstract: “This [single- or multiple-] dose study found that the test and reference products met the regulatory criteria for bioequivalence in these [fasting or fed] [healthy, male/female] [volunteers or patients with...].”