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General Commentary

Regulatory Considerations of Bioequivalence Studies for Oral Solid Dosage Forms in Japan

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ABSTRACT

Bioequivalence (BE) studies are used to infer the therapeutic equivalence of generic drug products to original drug products throughout the world. In BE studies, bioavailability (BA) should be compared between the original and generic drug products, with BA defined as the rate and extent of absorption of active pharmaceutical ingredients or active metabolites from a product into the systemic circulation. For most of BE studies conducted during generic drug development, BA comparisons are performed in single-dose studies. In Japan, the revised "Guideline for Bioequivalence Studies of Generic Products" was made available in 2012 by the Ministry of Health, Labour, and Welfare, and generic drug development is currently conducted based on this guideline. Similarly, the U.S. Food and Drug Administration and European Medicines Agency have published guidance and guideline on generic drug development. This article introduces the guideline on Japanese BE studies for oral solid dosage forms and the dissolution tests for the similarity and equivalence evaluation between the original and generic drug products. Additionally, we discuss some of the similarities and differences in guideline between Japan, the United States, and the European Union.

Introduction

The determination of bioequivalence (BE) is the most important aspect of establishing therapeutic equivalence but is also the most difficult aspect of generic drug product development. There is universal agreement that BE studies should use the most accurate, sensitive, and reproducible approaches available for each drug product being evaluated. The objective of BE studies is to infer the therapeutic equivalence of generic drug products to the original drug products. These studies must compare the bioavailability (BA) of generic drug products with the original product, with BA defined as the rate and extent of absorption of the active pharmaceutical ingredients (APIs) or active metabolites from a product into the systemic circulation. The rate and extent of absorption are expressed as the peak plasma concentration (C_{max}) and area under the drug plasma concentration versus time profile (area under the curve [AUC]). The quality and quantity of the generic drug product APIs are the same as in the original drug products; however, product properties, such as the composition of excipients and the manufacturing methods, are different between the products. To confirm the clinical equivalence of the different products, BE studies are required before the approval of generic drug products. After drug products that are orally administered disintegrate and dissolve, the drugs are mainly absorbed from the small intestine into the systemic circulation to exert their therapeutic effects. If the plasma drug concentration of a generic drug product is equivalent to that of the original drug product, the effective drug concentration at the site of action are considered to be equivalent, and therefore, both products are expected to be therapeutically equivalent.

Therefore, human BE studies with plasma drug concentrations are required as part of BE evaluations for generic drugs. BE studies that incorporate pharmacokinetic (PK) end points are primarily conducted as part of applications for the approval of generic drug products in Japan. If PK end points do not become the index of therapeutic effect, studies on the pharmacological effects that support therapeutic efficacy (pharmacodynamic studies) or therapeutic effectiveness (clinical studies) should be conducted. These approaches have been similarly adopted in the guidance from the

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U.S. Food and Drug Administration and guideline of the European Medicines Agency.[1,2] In the United States, there are product-specific BE guidance in addition to the general guidance on BE and that generic drug developers should also understand the BE requirements for a specific product.[3] In Japan, the revised "Guideline for Bioequivalence Studies of Generic Products" was made available in 2012 by the Ministry of Health, Labour, and Welfare.[4] Based on this guideline, the Office of Generic Drugs of the Pharmaceutical and Medical Devices Agency (PMDA) conducts its review of generic drugs.[5] In the present article, we introduce BE studies required for oral solid dosage forms that represent the highest number of generic product applications in Japan. We also discuss differences in the BE study requirements between Japan, the United States, and the European Union (EU).

BE Studies of Oral Solid Dosage Forms in Japan

BE studies for oral solid dosage forms (immediate-release [IR], delayed-release [DR], and extended-release [ER] drug products) are mainly conducted with a randomized, 2-period, 2-sequence, 2-treatment, single-dose crossover design study. Multiple-dose studies may be useful for highly variable drugs that require large sample sizes. The sufficient numbers of healthy adult volunteers are used as study subjects for assessing BE (usually $\geq$20 subjects). The drug products are usually administered to subjects with 100-200 mL (normally 150 mL) of water after fasting for >10 h. Generally, the studies are performed with the highest strength under a fasting state, unless the BA in the fasting state is very poor or a high incidence of severe adverse events is anticipated. Sampling should be performed at $\geq$7 time points, including the 0 time point, 1 point before the C_{max}, 2 points near the C_{max}, and 3 points during the elimination phase. Sampling should be continued until AUC_{0-t} is equal to >80% of the $AUC_{0-\infty}$. As a general rule, the parent compound should be measured because the concentration–time profile of the parent compound is more sensitive to detect differences between products than a metabolite. Major active metabolites may be measured instead of the parent compound, if it is rational (e.g., the parent compound levels are too low to allow reliable analytical measurement). Similarly, the prodrug is recommended for assessment because a difference in BA is generally easier to detect in prodrugs than in active metabolites. The enantiomers should be measured separately, and the enantiomer with the greatest contribution to the main pharmacological effect should be regarded as a substance to be measured. If no PK differences between the enantiomers have been reported for the API, it is acceptable to measure enantiomers together as the parent compound because a possibility that there is a difference in BE conclusion between the enantiomers is very low. Reference products are required to be the original drug products marketed in Japan. One lot that shows intermediate dissolution should be selected as the reference product from among the 3 lots of original drug products. Dissolution tests should be performed with $\geq$6 vessels for the 3 lots of original drug products and using the paddle method at 50 rpm. Preliminary studies, appropriate studies, and add-on subject studies are adopted for BE evaluations as shown in Figure 1. The aim of preliminary studies was to determine the appropriate evaluation protocol, including the number of subjects required to assess BE and the sampling intervals for appropriate studies. As long as a study meets the requirements stipulated in the regulatory guideline, it is acceptable to use the preliminary study data as BE study data for assessment. If the result of the preliminary study is non-BE, an appropriate study plan based on the preliminary study is established. If the result of an appropriate study is non-BE because of an insufficient number of subjects, an add-on subject study is accepted only once. The add-on subject study can be performed using not less than half the number of subjects evaluated in the appropriate study. It is acceptable to use data from a preliminary study as add-on subject data for the BE analysis. When the add-on subject study is performed and there are no fundamental differences between the 2 studies in formulation, design, assay, and subjects, data from the appropriate and add-on subject studies can be pooled and statistically analyzed. For single-dose studies, the AUC_{0-t} and C_{max} should be used as the parameters for BE evaluation. If the 90% confidence interval of the geometric mean ratios (GMRs) to be assessed between the generic and original drug products is within the acceptable range of 80%-125%, the products are considered to be bioequivalent. If the confidence interval is not within the range, the generic drug products are accepted as bioequivalent if the following 3 conditions are satisfied (second standard):

- The total sample size of the BE study is $\geq$20.
- The dissolution rates for the original and generic drug products are regarded as similar under all conditions presented in Tables 1 and 2.
- The GMR values to be assessed between the 2 products are in the range of 90%-111%.

In addition, this concept is acceptable in the appropriate study or the add-on subject study but not in the preliminary study. In the case of an add-on subject study, the total number of subjects in the appropriate study and add-on study must be $\geq$30.

In the assessment using the 90% confidence intervals, the probability (level of consumer risk) for a low-quality generic drug product that does not satisfy the BA requirements to pass a BE study does not exceed 5%. Risk to consumers must be kept <5%, even when assessment methods other than the 90% confidence interval

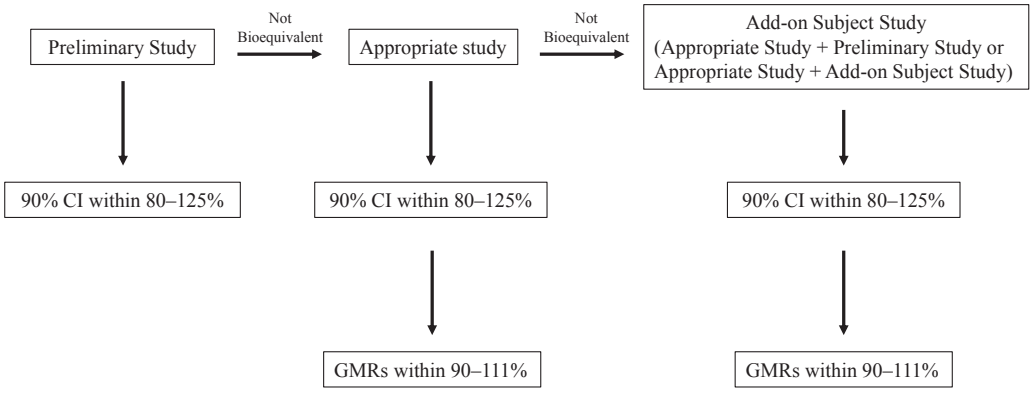

Figure 1. Bioequivalence study of oral solid dosage forms in Japan. CI, confidence interval.