Guidance for Industry

Statistical Approaches to Establishing Bioequivalence

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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GUIDANCE FOR INDUSTRY[1]

Statistical Approaches to Establishing Bioequivalence

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I. INTRODUCTION

This guidance provides recommendations to sponsors and applicants who intend, either before or after approval, to use equivalence criteria in analyzing in vivo or in vitro bioequivalence (BE) studies for investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs) and supplements to these applications. This guidance discusses three approaches for BE comparisons: average, population, and individual. The guidance focuses on how to use each approach once a specific approach has been chosen. This guidance replaces a prior FDA guidance entitled *Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design*, which was issued in July 1992.

II. BACKGROUND

A. General

Requirements for submitting bioavailability (BA) and BE data in NDAs, ANDAs, and supplements, the definitions of BA and BE, and the types of in vivo studies that are appropriate to measure BA and establish BE are set forth in 21 CFR part 320. This guidance provides recommendations on how to meet provisions of part 320 for all drug products.

Defined as *relative BA*, BE involves comparison between a test (T) and reference (R) drug product, where T and R can vary, depending on the comparison to be performed (e.g., to-be-marketed dosage form versus clinical trial material, generic drug versus reference listed drug,

[1] This guidance has been prepared by the Population and Individual Bioequivalence Working Group of the Biopharmaceutics Coordinating Committee in the Office of Pharmaceutical Science, Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

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drug product changed after approval versus drug product before the change). Although BA and BE are closely related, BE comparisons normally rely on (1) a criterion, (2) a confidence interval for the criterion, and (3) a predetermined BE limit. BE comparisons could also be used in certain pharmaceutical product line extensions, such as additional strengths, new dosage forms (e.g., changes from immediate release to extended release), and new routes of administration. In these settings, the approaches described in this guidance can be used to determine BE. The general approaches discussed in this guidance may also be useful when assessing pharmaceutical equivalence or performing equivalence comparisons in clinical pharmacology studies and other areas.

B. Statistical

In the July 1992 guidance on *Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design* (the 1992 guidance), CDER recommended that a standard in vivo BE study design be based on the administration of either single or multiple doses of the T and R products to healthy subjects on separate occasions, with random assignment to the two possible sequences of drug product administration. The 1992 guidance further recommended that statistical analysis for pharmacokinetic measures, such as area under the curve (AUC) and peak concentration (Cmax), be based on the *two one-sided tests procedure* to determine whether the average values for the pharmacokinetic measures determined after administration of the T and R products were comparable. This approach is termed *average bioequivalence* and involves the calculation of a 90% confidence interval for the ratio of the averages (population geometric means) of the measures for the T and R products. To establish BE, the calculated confidence interval should fall within a BE limit, usually 80-125% for the ratio of the product averages.[2] In addition to this general approach, the 1992 guidance provided specific recommendations for (1) logarithmic transformation of pharmacokinetic data, (2) methods to evaluate sequence effects, and (3) methods to evaluate outlier data.

Although average BE is recommended for a comparison of BA measures in most BE studies, this guidance describes two new approaches, termed *population* and *individual bioequivalence*. These new approaches may be useful, in some instances, for analyzing in vitro and in vivo BE studies.[3] The average BE approach focuses only on the comparison of population averages of a BE measure of interest and not on the variances of the measure for the

[2] For a broad range of drugs, a BE limit of 80 to 125% for the ratio of the product averages has been adopted for use of an average BE criterion. Generally, the BE limit of 80 to 125% is based on a clinical judgment that a test product with BA measures outside this range should be denied market access.

[3] For additional recommendations on in vivo studies, see the FDA guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products* ***C*** *General Considerations*. Additional recommendations on in vitro studies will be provided in an FDA guidance for industry on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*, when finalized.

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