
Guidance for Industry

Bioequivalence

Recommendations for

Specific Products

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**June 2010
OGD**

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*Office of Communication
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 51, Room 2201
Silver Spring, MD 20993-0002
(Tel) 301-796-3400*

Internet: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

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Guidance for Industry¹

Bioequivalence Recommendations for Specific Products

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

I. INTRODUCTION

This guidance describes FDA's process for making available to the public FDA guidance on how to design bioequivalence (BE) studies for specific drug products to support abbreviated new drug applications (ANDAs). Under this process, applicants planning to carry out such studies in support of their ANDAs will be able to access BE study guidance on the FDA Web site,² rather than having to request this information from the Agency and wait for the Agency to respond, as has been the case in the past. The FDA believes that making this information available on the Internet will streamline the guidance process, making it more efficient than the previous process. This process also will provide a meaningful opportunity for the public to consider and comment on BE study recommendations for specific drug products.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. What Are BE Studies?

To receive approval for an ANDA, an applicant generally must demonstrate, among other things, that its product has the same active ingredient, dosage form, strength, route of administration and conditions of use as the listed drug, and that the proposed drug product is bioequivalent to the

¹ This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

² We update guidance documents periodically. To make sure you have the most recent version of a product-specific bioequivalence (BE) study guidance, check the FDA Drugs guidance page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, Individual Product Bioequivalence Recommendations.

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reference listed drug (21 U.S.C. 355(j)(2)(A); 21 CFR 314.94(a)). If a drug acts through absorption into the bloodstream, bioequivalent drug products are those that show no significant difference in the rate and extent of absorption of the therapeutic ingredient (21 U.S.C. 355(j)(8)(B); 21 CFR 320.1(e)). For a drug that is not intended to be absorbed into the bloodstream, FDA may establish alternative methods to show bioequivalence that may be expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect (21 U.S.C. 355(j)(8)(C); 21 CFR 320.24). BE studies are undertaken in support of ANDA submissions with the goal of demonstrating BE between a proposed generic drug product and its reference listed drug. The regulations governing BE are provided at 21 CFR part 320.

B. How Did the Agency Make This Information Available in the Past?

Previously, the Office of Generic Drugs (OGD) provided guidance on how to design BE studies for specific products only when asked for assistance by individual applicants. We had determined that making recommendations to applicants about how to design BE studies would help the generic drug industry, the innovator drug industry, contract research organizations, academia, and others understand the Agency's expectations with regard to demonstrating bioequivalence. In most cases, the requested information was not available anywhere else, and, in some cases, OGD performed its own research before responding to an applicant's request for product-specific information. In many cases, OGD responded to individual requests for information on BE studies in letter format after specific recommendations were prepared within the Center for Drug Evaluation and Research (CDER). This meant that information about BE studies was only being provided to those specifically requesting such information. In addition, the staff developing the recommendations and responding to requests for information have been the same individuals who are responsible for reviewing the BE data in ANDAs. With the increase in the number of ANDA submissions and in the requests for BE information during the last few years, the process of providing BE recommendations has become extremely time-consuming for the Agency.

In October 2000, to help address this growing problem, FDA issued the guidance *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*,³ which describes general recommendations for demonstrating bioequivalence. These general recommendations were helpful, but many individuals have continued to seek assistance from the Agency in designing their product-specific BE studies, as certain drug products may raise BE issues not squarely addressed in more general guidance. As a result, after exploring various mechanisms that would allow us to conserve our resources while responding to the needs of industry and other interested persons, OGD has developed a new approach to making guidance available on product-specific BE studies. As before, the Agency intends to develop BE recommendations based on its understanding of the characteristics of the listed drug, information derived from published literature, Agency research, and consultations within different offices in CDER as needed based upon the novelty or complexity of the BE considerations. Once developed, the Agency intends to make BE recommendations for specific drug products available through the process described here.

³ The October 2000 guidance was finalized in March 2003 and is available on the FDA Drugs guidance page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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FDA is not required to publish draft or final product-specific BE recommendations before it approves an ANDA for the drug product. If the Agency determines that, as required by the statute and regulations (21 U.S.C. 355(j)(2); 21 CFR 314.94), an ANDA contains sufficient evidence that the proposed generic drug product is bioequivalent to its reference listed drug and the application meets the other requirements for approval, FDA will approve the ANDA. In assessing whether an ANDA contains adequate evidence of BE, the Agency considers available relevant information, which may include information submitted by the public to dockets for citizen petitions and product-specific BE recommendations.

III. PROCEDURES FOR MAKING RECOMMENDATIONS AVAILABLE

To streamline the process for making guidance available to the public on how to design product-specific BE studies, the Agency intends to use the following process:

- Product-specific BE recommendations will be developed and posted on the Internet on the FDA Drugs guidance page (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, Individual Product Bioequivalence Recommendations) in draft to facilitate public comment. Users can also search for a specific product BE recommendation using the search tool on the guidance page.
- Product-specific BE recommendations may contain differing amounts of detail and background information regarding the specific basis for the recommendations, depending upon the novelty and complexity of the scientific considerations.
- Newly posted draft and final BE recommendations will be announced in the New/Revised/Withdrawn list, which is posted on the FDA Drugs guidance page.
- The Agency will issue a notice in the *Federal Register* (FR) announcing the availability on the FDA Web site of new and revised product-specific draft and final BE recommendations. The notice will identify a comment period for the draft recommendations.
- Comments on product-specific draft BE recommendations will be considered in developing final BE recommendations.
- The BE recommendations will be revised as appropriate to ensure that the most up-to-date BE information is available to the public.

On occasion, the appropriate methodology for establishing bioequivalence for a specific drug product will be the subject of a citizen petition or other correspondence, and of a product-specific BE recommendation. This situation is particularly likely when the drug product raises novel or complex bioequivalence issues, as may be posed by certain topical and non-systemically absorbed products. When the same BE issue is under consideration in different contexts, the Agency will take into account the status of related matters in determining how to best address the scientific issues. This may involve, for example, coordinating the consideration of a pending citizen petition with the development and publication of a product-specific BE recommendation,

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or identifying in the notice of availability for the draft BE recommendation the docket number of a related citizen petition.