
Guidance for Industry

Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
March 2003
BP**

Revision 1

Guidance for Industry

Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations

*Additional copies are available from:
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
<http://www.fda.gov/cder/guidance/index.htm>*

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
March 2003
BP**

Revision 1

TABLE OF CONTENTS

BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR ORALLY ADMINISTERED DRUG PRODUCTS — GENERAL CONSIDERATIONS	1
I. INTRODUCTION	1
II. BACKGROUND	2
A. General.....	2
B. Bioavailability.....	3
C. Bioequivalence.....	4
III. METHODS TO DOCUMENT BA AND BE	6
A. Pharmacokinetic Studies	6
B. Pharmacodynamic Studies	9
C. Comparative Clinical Studies	9
D. In Vitro Studies	10
IV. COMPARISON OF BA MEASURES IN BE STUDIES	11
V. DOCUMENTATION OF BA AND BE	11
A. Solutions.....	12
B. Suspensions.....	12
C. Immediate-Release Products: Capsules and Tablets.....	12
D. Modified-Release Products	14
E. Miscellaneous Dosage Forms	17
VI. SPECIAL TOPICS	17
A. Food-Effect Studies.....	17
B. Moieties to Be Measured	17
C. Long Half-Life Drugs	19
D. First Point Cmax.....	19
E. Orally Administered Drugs Intended for Local Action.....	20
F. Narrow Therapeutic Range Drugs	20
ATTACHMENT: GENERAL PHARMACOKINETIC STUDY DESIGN	21
AND DATA HANDLING	21

Guidance for Industry¹

BA and BE Studies for Orally Administered Drug Products — General Considerations

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. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance is intended to provide recommendations to sponsors and/or applicants planning to include bioavailability (BA) and bioequivalence (BE) information for orally administered drug products in investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and their supplements. This guidance contains advice on how to meet the BA and BE requirements set forth in part 320 (21 CFR part 320) as they apply to dosage forms intended for oral administration.² The guidance is also generally applicable to nonorally administered drug products where reliance on systemic exposure measures is suitable to document BA and BE (e.g., transdermal delivery systems and certain rectal and nasal drug products). We believe that the guidance will be useful for applicants planning to conduct BA and BE studies during the IND period for an NDA, BE studies intended for submission in an ANDA, and BE studies conducted in the postapproval period for certain changes in both NDAs and ANDAs.³

This guidance revises the October 2000 guidance. We have revised our recommendations regarding (1) study design and dissolution methods development, (2) comparisons of BA measures, (3) the definition of proportionality, and (4) waivers for bioequivalence studies. The guidance also makes other revisions for clarification. We believe that these revisions provide clear guidance to sponsors conducting BA and BE studies for orally administered drug products.

² These dosage forms include tablets, capsules, solutions, suspensions, conventional/immediate release, and modified (extended, delayed) release drug products.

³ Other Agency guidances are available that consider specific scale-up and postapproval changes (SUPAC) for different types of drug products to help satisfy regulatory requirements in part 320 and § 314.70 (21 CFR 314.70).

Contains Nonbinding Recommendations

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. General

Studies to measure BA and/or establish BE of a product are important elements in support of INDs, NDAs, ANDAs, and their supplements. As part of INDs and NDAs for orally administered drug products, BA studies focus on determining the process by which a drug is released from the oral dosage form and moves to the site of action. BA data provide an estimate of the fraction of the drug absorbed, as well as its subsequent distribution and elimination. BA can be generally documented by a systemic exposure profile obtained by measuring drug and/or metabolite concentration in the systemic circulation over time. The systemic exposure profile determined during clinical trials in the IND period can serve as a benchmark for subsequent BE studies.

Studies to establish BE between two products are important for certain changes before approval for a pioneer product in NDA and ANDA submissions and in the presence of certain postapproval changes in NDAs and ANDAs. In BE studies, an applicant compares the systemic exposure profile of a test drug product to that of a reference drug product (RLD). For two orally administered drug products to be bioequivalent, the active drug ingredient or active moiety in the test product must exhibit the same rate and extent of absorption as the reference drug product (see 21 CFR 320.1(e) and 320.23(b)).

Both BA and BE studies are required by regulations, depending on the type of application being submitted. Under § 314.94, BE information is required to ensure therapeutic equivalence between a pharmaceutically equivalent test drug product and a reference listed drug. Regulatory requirements for documentation of BA and BE are provided in part 320, which contains two subparts. Subpart A covers general provisions, while subpart B contains 18 sections delineating the following general BA/BE requirements:

- Requirements for submission of BA and BE data (§ 320.21)
- Criteria for waiver of an in vivo BA or BE study (§ 320.22)
- Basis for demonstrating in vivo BA or BE (§ 320.23)
- Types of evidence to establish BA or BE (§ 320.24)
- Guidelines for conduct of in vivo BA studies (§ 320.25)
- Guidelines on design of single-dose BA studies (§ 320.26)
- Guidelines on design of multiple-dose in vivo BA studies (§ 320.27)
- Correlations of BA with an acute pharmacological effect or clinical evidence (§ 320.28)

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.