Guidance for Industry

Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact the CDER Office of Clinical Pharmacology at 301-796-5008 or OCP@fda.hhs.gov.

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

March 2014
Biopharmaceutics

Guidance for Industry

Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs—General Considerations

Additional copies are available from:

Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Silver Spring, MD 20993
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov

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

March 2014
Biopharmaceutics

TABLE OF CONTENTS

Guidance for Industry[1]

Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations to sponsors and/or applicants planning to include bioavailability (BA) and bioequivalence (BE) information for drug products in investigational new drug applications (INDs), new drug applications (NDAs), and NDA supplements (referred to as the NDA BA and BE Draft Guidance).[2] This guidance contains advice on how to meet the BA and BE requirements set forth in 21 CFR part 320 as they apply to dosage forms intended for oral administration.[3] The guidance may also be applicable to non-orally administered drug products when reliance on systemic exposure measures is suitable to document BA and BE (e.g., transdermal delivery systems and certain rectal and nasal drug products). The guidance should be helpful for applicants conducting BA and BE studies during the IND period for an NDA and also for applicants conducting BE studies during the postapproval period for certain changes to

[1] This guidance was developed by the Office of Clinical Pharmacology, Office of Translational Sciences, and the Office of New Drugs Quality Assessment, Office of Pharmaceutical Science, in the Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA).

[2] BA and BE information for drug products in abbreviated new drug applications (ANDAs) and ANDA supplements are not the subject of this guidance. FDA has issued a separate draft guidance on this topic entitled *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (December 2013) (ANDA BE Draft Guidance). The ANDA BE Draft Guidance, when finalized, will represent FDA's current thinking on this topic. Many guidances are referenced throughout this document. The guidance referred to in this footnote, as well as others referenced throughout the remainder of the document, can be found on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page.

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

drug products that are the subject of an NDA.[4] This guidance document is not intended to provide recommendations on studies conducted in support of demonstrating comparability or biosimilarity for biological products licensed under section 351 of the Public Health Service Act.[5]

When finalized, this guidance will revise and replace the parts of FDA's March 2003 guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (the March 2003 BA and BE Guidance) relating to BA and BE studies for INDs, NDAs, and NDA supplements.[6] Since the March 2003 BA and BE Guidance was issued, FDA has determined that providing information on BA and BE studies in separate guidances according to application type will be beneficial to sponsors and applicants. Thus, FDA is issuing this NDA BA and BE Draft Guidance and, as previously noted, has issued the ANDA BE Draft Guidance for ANDA and ANDA supplements.[7]

We recognize that this guidance cannot address every issue pertaining to the assessment of BA or BE studies for INDs and NDAs, so we suggest sponsors and applicants contact the appropriate review division for guidance on specific questions not addressed by this guidance.

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 guidance documents means that something is suggested or recommended, but not required.

II. BACKGROUND

[4] *Bioequivalence* is a statutory term reflected in the Federal Food, Drug, and Cosmetic Act (FD&C Act) in section 505(j) (21 U.S.C. 355(j)), which requires ANDA applicants to demonstrate, among other things, that the proposed generic product is bioequivalent to its reference listed drug. Section 505(j)(2)(A)(iv) of the FD&C Act; see also section 505(j)(8) of the FD&C Act. There is no similar statutory requirement for an NDA applicant either under section 505(b)(1) or (b)(2) of the FD&C Act to demonstrate bioequivalence of its proposed product to another product. As a scientific matter, however, the same or a similar showing of the bioavailability of two products in the NDA context may be needed for the purposes of evaluating the safety or effectiveness of a product. For ease of the reader, we refer to such evaluations of the relative bioavailability for two or more products as an evaluation of bioequivalence in this guidance.

[5] For information on these types of studies, see FDA's Drugs guidance Web page. See footnote #2 for information on accessing this Web page.

[6] Revisions to the March 2003 BA and BE Guidance include (1) expansion of the section on modified-release products, (2) addition of a section on concomitant administration of drug products and combination drug products, (3) addition of a section on alcoholic beverage effects on modified-release dosage forms, (4) addition of an endogenous substance section, (5) addition of a section on drug products with high intrasubject variability, and (6) removal of references to BE studies conducted for ANDAs. The guidance also makes other revisions for clarification.

[7] See footnote #2.

DOCKET ALARM

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.