DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00D–1513]

Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance for industry entitled ''Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations.'' This guidance provides recommendations to sponsors and applicants intending to submit bioavailability (BA) and/or bioequivalence (BE) information on investigational new drug applications (IND's), new drug applications (NDA's), abbreviated new drug applications (ANDA's), and their supplements, to the Center for Drug Evaluation and Research (CDER). This guidance provides general information on how to comply with the BA and BE requirements for orally administered dosage forms under the bioavailability and bioequivalence requirements regulations. It is one of a set of planned core guidances designed to reduce or eliminate the need for FDA drug-specific guidances.

DATES: Submit written comments on agency guidances at any time.

ADDRESSES: Copies of this guidance for industry are available on the Internet at http://www.fda.gov/cder/guidance/index.htm. Submit written requests for single copies of ''Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations'' to the Drug Information Branch (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your requests. Submit written comments on the guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Mei-Ling Chen, Center for Drug Evaluation and Research (HFD–350), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5688.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled ''Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations.'' This guidance provides recommendations to sponsors and applicants intending to provide BA and BE information in IND's, NDA's, ANDA's, and their supplements that complies with the BA and BE requirements in part 320 (21 CFR part 320) as it applies to dosage forms intended for oral administration.

In September 1999, FDA announced the availability of a draft guidance entitled ''BA and BE Studies for Orally Administered Drug Products—General Considerations'' (64 FR 48409, September 3, 1999). When the draft guidance was published, FDA requested comments on the use of the new criteria. A total of 16 public comments were received. Most of these comments were supportive of the recommendations in the draft guidance, but FDA received a number of comments that expressed concern about the use of the individual BE criterion.

The public comments fell into four general categories as follows: (1) Comments on the justification for an individual BE criterion (absence of documentation of public health risk, absence of evidence that subject-by-formulation interaction is clinically relevant); (2) comments on the burden of conducting replicate study designs (recruitment costs, institutional review board approval, capacity constraints, study delays, increased monitoring for adverse drug reactions, subject dropouts, increased drug exposure, and increased volume of blood collected); (3) comments on statistical issues (aggregate versus disaggregate criterion, discontinuity, and mean/variance trade-off); and (4) miscellaneous comments (experimental aspects of 2-year period recommended in the notice, absence of community consensus, barriers to international harmonization and globalization).

II. Discussion

Many aspects of this guidance represent departures from past practices used to document BE. The general intent of many of these changes is to reduce the regulatory burden while maintaining sound scientific principles consistent with public health objectives. Examples of ways these changes might reduce the regulatory burden include: (1) Enabling biowaivers (i.e., waivers of in vivo BE studies) for lower strengths of modified-release dosage forms; (2) eliminating multiple dose BE studies for modified-release dosage forms; (3) enabling biowavers for higher strengths of immediate-release dosage forms; and (4) reducing emphasis on measuring metabolites in BE studies.

FDA acknowledges the public concerns about the use of the individual criterion for BE studies. These concerns were also considered in a meeting of the Advisory Committee for Pharmaceutical Science on September 23, 1999 (September 23 meeting). The committee concluded that replicate study designs should be recommended for modified release drug products and should be strongly encouraged for other drug products, subject to certain exceptions.

In finalizing the guidance, FDA has followed the advisory committee's recommendations. FDA believes that replicate study designs offer significant advantages compared to nonreplicate designs. Replicate study designs: (1) Allow comparison of within-subject variances for the test and reference products; (2) indicate whether a test product exhibits higher or lower within-subject variability in the BA measures when compared to the reference product; (3) suggest whether a subject-by-formulation interaction may be present; (4) provide more information about factors underlying formulation performance; and (5) reduce the number of subjects needed in the BE study.

In accordance with the advisory committee's recommendation, FDA recommends in the guidance the use of an average BE criterion for both replicate and nonreplicate studies. A further committee conclusion in the September 23 meeting was that an individual BE criterion can be used to allow market access of drug products in compelling circumstances. For this reason, the guidance states that sponsors have the option to choose an individual criterion for highly variable drugs. The use of an individual criterion with reference-scaling in this circumstance can permit a further reduction in the number of subjects in BE studies. Reduction in the number of subjects in BE studies of highly variable drugs is in keeping with the basic regulatory principle that no unnecessary human research should be done (§ 320.25(a)(1)).

By continuing to recommend the use of the average BE criterion in most circumstances, the agency has addressed many of the public comments expressing concern about the use of the individual BE criterion. To avoid a large test and reference difference, constraint on the allowable difference has been recommended in this guidance. Use of the individual BE criterion for highly

variable drugs is expected to occur rarely. In these instances, FDA believes that all relevant statistical issues have been sufficiently resolved and that no important public health risk will arise if the criterion is used to allow market access.

This guidance replaces the following guidances: (1) ''Guidelines for the Evaluation of Controlled Release Drug Products'' (April 1984); (2) ''Oral Extended (Controlled) Release Dosage Form: In Vivo Bioequivalence and In Vitro Dissolution Testing'' (September 1993); (3) ''Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design'' (July 1992); (4) the preliminary draft guidance on ''In Vivo Bioequivalence Studies Based on Population and Individual Bioequivalence Approaches'' (October 1997), and (5) the draft guidance on ''BA and BE Studies for Orally Administered Drug Products—General Considerations.'' This guidance supersedes any prior guidance, or any relevant part of a prior guidance issued to assist sponsors in meeting the requirements in part 320.

This level 1 guidance is being issued consistent with FDA's good guidance practices (65 FR 56468, September 19, 2000). This guidance document represents the agency's current thinking on BA and BE studies for orally administered drug products. 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 an approach satisfies the requirements of the applicable statutes and regulations.

Interested persons may submit written comments on the guidance to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The guidance and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: October 19, 2000.

Margaret M. Dotzel,

Associate Commissioner for Policy.

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DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

[Docket No. FR–4561–N–67]

Notice of Submission of Proposed Information Collection to OMB; Uniform Physical Standards and Physical Inspection Requirements for Certain HUD Housing, Administrative Process for Assessment of Insured and Assisted Properties

AGENCY: Office of the Chief Information Officer, HUD.

ACTION: Notice.

SUMMARY: The proposed information collection requirement described below has been submitted to the Office of Management and Budget (OMB) for review, as required by the Paperwork Reduction Act. The Department is soliciting public comments on the subject proposal.

DATES: *Comments Due Date:* November 27, 2000.

ADDRESSES: Interested persons are invited to submit comments regarding this proposal. Comments should refer to the proposal by name and/or OMB approval number (2502–0369) and should be sent to: Joseph F. Lackey, Jr., OMB Desk Officer, Office of Management and Budget, Room 10235, New Executive Office Building, Washington, DC 20503.

FOR FURTHER INFORMATION CONTACT: Wayne Eddins, Reports Management Officer, Q, Department of Housing and Urban Development, 451 Seventh Street, Southwest, Washington, DC 20410; e-mail Wayne_Eddins@HUD.gov; telephone (202) 708–2374. This is not a toll-free number. Copies of the proposed forms and other available documents submitted to OMB may be obtained from Mr. Eddins.

SUPPLEMENTARY INFORMATION: The Department has submitted the proposal for the collection of information, as described below, to OMB for review, as required by the Paperwork Reduction Act (44 U.S.C. Chapter 35). The Notice lists the following information: (1) The title of the information collection proposal; (2) the office of the agency to collect the information; (3) the OMB approval number, if applicable; (4) the description of the need for the information and its proposed use; (5) the agency form number, if applicable; (6) what members of the public will be affected by the proposal; (7) how frequently information submissions will be required; (8) an estimate of the total number of hours needed to prepare the information submission including number of respondents, frequency of response, and hours of response; (9) whether the proposal is new, an extension, reinstatement, or revision of an information collection requirement; and (10) the name and telephone number of an agency official familiar with the proposal and of the OMB Desk Officer for the Department.

This Notice also lists the following information:

Title of Proposal: Uniform Physical Standards and Physical Inspection Requirements for Certain HUD Housing, Administrative Process for Assessment of Insured and Assisted Properties.

OMB Approval Number: 2502–0369.

Form Numbers: None.

Description of the Need for the Information and its Proposed Use: The uniform physical condition standards are intended to ensure that HUD program participants carry out their legal obligations to maintain HUD properties in a condition that is decent, safe, sanitary, and in good repairs.

Respondents: Business or Other For-Profit.

Frequency of Submission: Annually.

Reporting Burden:

Number of respondents	×	Frequency of response	×	Hours per response	=	Burden hours
7,100		1		9		153,900