

[www.fda.gov/dockets/ecomments](http://www.fda.gov/dockets/ecomments). See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

**FOR FURTHER INFORMATION CONTACT:**

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**SUPPLEMENTARY INFORMATION:**

**I. Background**

In March 1995, the agency issued a guidance entitled "Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women". The agency was revising the 1995 guidance when the results of a substudy of the National Institutes of Health (NIH) Women's Health Initiative (WHI) trial were made available to the public.<sup>1</sup> In light of the interim results of the WHI substudy, on September 10, 2002 (67 FR 57432), the agency withdrew the 1995 guidance. Once finalized, this guidance will replace the 1995 guidance.

In the WHI substudy, postmenopausal women who took conjugated estrogen 0.625 milligram (mg) combined with medroxyprogesterone acetate 2.5 mg had higher risks of several serious adverse events relative to those women who took placebo. Conjugated estrogens alone also increased the rates of cardiovascular disease compared to placebo. Other doses of conjugated estrogens and medroxyprogesterone acetate and other combinations of estrogens and progestins were not studied in the WHI. However, in the absence of comparable data, the risks of serious adverse events should be assumed to be similar because other studies show that estrogens and progestins are associated with these types of events.

This draft guidance revises the 1995 guidance in several ways. For example, the draft guidance no longer uses the phrase "hormone replacement" because neither estrogen alone nor estrogen/progestin treatments for symptoms of menopause should be considered replacement hormones. The guidance only addresses two indications (moderate to severe vasomotor symptoms and moderate to severe vulvar and vaginal atrophy symptoms) and explains under what conditions both indications can be studied concurrently in a single trial. For other indications, such as the prevention of

osteoporosis, sponsors are asked to direct inquiries to the appropriate review division in the Center for Drug Evaluation and Research. A section entitled Primary Endpoints has been added for each indication, and the Study Analysis section has been modified to clarify analyses of the primary endpoints. The Monitoring section for drug products containing estrogen plus progestin has been expanded. The additions to this section were made to address diagnostic ambiguities in the efficacy evaluation for protection of the endometrium.

This level 1 draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance represents the agency's current thinking on recommendations for clinical evaluation of estrogen and estrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms. 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.

**II. Comments**

Interested persons may submit to the Dockets Management Branch (see **ADDRESSES**) written or electronic comments regarding the draft guidance. Submit a single copy of electronic comments to <http://www.fda.gov/dockets/ecomments> or two hard copies of any written comments, except that individuals may submit one hard copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guidance and received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

**III. Electronic Access**

Persons with access to the Internet may obtain the draft document at either <http://www.fda.gov/cder/guidance/index.htm> or <http://www.fda.gov/ohrms/dockets/default.htm>.

Dated: January 23, 2003.

**Margaret M. Dotzel,**

*Assistant Commissioner for Policy.*

[FR Doc. 03-2213 Filed 1-30-03; 8:45 am]

**BILLING CODE 4160-01-S**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

[Docket No. 01D-0488]

**Guidance for Industry on Food-Effect Bioavailability and Fed Bioequivalence Studies; 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 "Food-Effect Bioavailability and Fed Bioequivalence Studies." This guidance provides recommendations to sponsors and/or applicants planning to conduct food-effect bioavailability (BA) and fed bioequivalence (BE) studies for orally administered drug products as part of investigational new drug applications (INDs), new drug applications (NDAs) and abbreviated new drug applications (ANDAs), and supplemental applications.

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

**ADDRESSES:** Submit written requests for single copies of this guidance to the Division of Drug Information (HFD-240), 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. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

**FOR FURTHER INFORMATION CONTACT:**

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**SUPPLEMENTARY INFORMATION:**

**I. Background**

FDA is announcing the availability of a guidance for industry entitled "Food-Effect Bioavailability and Fed Bioequivalence Studies." This guidance document is intended to provide information to sponsors and/or applicants planning to include food-effect BA and fed BE studies for orally

<sup>1</sup> The results of the NIH Women's Health Initiative trial were reported in the *Journal of the American Medical Association*, 288: 321-333, 2002.