DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 99D–3082]

International Conference on Harmonisation; Choice of Control Group and Related Issues in Clinical Trials; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance entitled “E10 Choice of Control Group and Related Issues in Clinical Trials.” The guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guidance sets forth general principles that are relevant to all controlled trials and are especially pertinent to the major clinical trials intended to demonstrate drug (including biological drug) efficacy. The guidance describes the principal types of control groups and discusses their appropriateness in particular situations. The guidance is intended to assist sponsors and investigators in the choice of control groups for clinical trials.

DATES: This guidance is effective [insert date of publication in the Federal Register]. Submit written comments on agency guidances at any time.

ADDRESSES: Submit written requests for single copies of the guidance to the Drug Information Branch (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, or the Office of Communication, Training and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research (CBER), 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–3844, FAX: 888–CBERFAX. Send two self-addressed adhesive labels to assist the 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. See the SUPPLEMENTARY INFORMATION section for electronic access to the guidance. Requests and comments should be identified with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT:

Regarding the guidance: Robert Temple, Center for Drug Evaluation and Research (HFD–4), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–6758.

Regarding the ICH: Janet J. Showalter, Office of International Affairs (HFG–1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–0864.

SUPPLEMENTARY INFORMATION:

I. Background

In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and the Pharmaceutical
Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

In accordance with the agency’s regulation on good guidance practices (GGP) (21 CFR 10.115; 65 FR 56468, September 19, 2000), this document is being called a guidance, rather than a guideline.

To facilitate the process of making ICH guidances available to the public, the agency has changed its procedures for publishing ICH guidances. Beginning April 2000, we no longer include the text of ICH guidances in the Federal Register. Instead, we will publish a notice in the Federal Register announcing the availability of an ICH guidance. The ICH guidance is placed in the docket and can be obtained through regular agency sources (see the ADDRESSES section). Draft ICH guidances are left in the original ICH format. Final guidances are reformatted to conform to the GGP style before publication.

In the Federal Register of September 24, 1999 (64 FR 51767), FDA published a draft tripartite guidance entitled “E10 Choice of Control Group in Clinical Trials.” The notice gave interested persons an opportunity to submit comments by December 23, 1999.

After consideration of the comments received and revisions to the guidance, a final draft of the guidance was submitted to the ICH Steering Committee and endorsed by the three participating regulatory agencies in July 2000.

This guidance sets forth general principles that are relevant to all controlled trials and are especially pertinent to the major clinical trials intended to demonstrate drug (including biological drug) efficacy. The guidance includes a description of the five principal types of controls, a discussion of two important purposes of clinical trials, and an exploration of the critical issue
of assay sensitivity, i.e., whether a trial could have detected a difference between treatments when there was a difference, a particularly important issue in noninferiority/equivalence trials. In addition, the guidance presents a detailed description of each type of control and considers, for each: (1) Its ability to minimize bias; (2) ethical and practical issues associated with its use; (3) its usefulness and the quality of inference in particular situations; (4) modifications of study design or combinations with other controls that can resolve ethical, practical, or inferential concerns; and (5) its overall advantages and disadvantages.

This guidance represents the agency’s current thinking on the choice of control group in clinical trials. 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 (address above) written comments on the guidance at any time. 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 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 document at http://www.fda.gov/cder/guidance/index.htm or http://www.fda.gov/cber/publications.htm.

Dated: \( \frac{4}{5} \) 2001


Margaret M. Dotzel,
Associate Commissioner for Policy.

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