DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration [Docket No. 94D-0029]

International Conference on Harmonisation; Guideline on the Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a final guideline entitled "The Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-lifethreatening Conditions." This guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guideline is intended to present an accepted set of principles for the safety evaluation of drugs intended for the long-term treatment (chronic or repeated intermittent use for longer than 6 months) of non-life-threatening diseases.

DATES: Effective on March 1, 1995. Submit written comments at any time. ADDRESSES: Submit written comments on the guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Copies of the guideline are available from CDER Executive Secretariat Staff (HFD–8), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

FOR FURTHER INFORMATION CONTACT:

Regarding the guideline: Leah Ripper, Center for Drug Evaluation and Research (HFD–500), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301– 443–2544.

Regarding ICH: Janet J. Showalter, Office of Health Affairs (HFY-20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1382.

SUPPLEMENTARY INFORMATION: 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 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 Industry 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 Association (IFPMA).

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

Harmonization of the safety evaluation of drugs intended for the long-term treatment of non-lifethreatening diseases was selected as a priority topic during the early stages of the ICH initiative. In the **Federal** Register of March 1, 1994 (59 FR 9746), FDA published a draft tripartite guideline entitled "Draft Guideline on the Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions." The notice gave interested persons an opportunity to submit comments by May 16, 1994.

After consideration of the comments received and revisions to the guideline, a final draft of the guideline was submitted to the ICH Steering Committee and endorsed by the three participating regulatory agencies at the ICH meeting held in October 1994.

The guideline presents an accepted set of principles for the safety evaluation of drugs intended for the long-term treatment of non-lifethreatening diseases. The guideline distinguishes between clinical data on adverse drug events (ADE's) derived from studies of shorter duration of exposure and data from studies of longer duration, which frequently include nonconcurrently controlled studies. The principles discussed in the guideline are summarized as follows: (1) Regulatory standards are valuable for the extent and duration of treatment needed to provide the safety data base for drugs intended for long-term treatment of non-life-threatening conditions; however, there are a number of circumstances where harmonized regulatory standards for the clinical safety evaluation may not be applicable; (2) further investigation is needed about the occurrence of ADE's in relation to duration of treatment for different drug classes; (3) because most ADE's first occur within the first 3 to 6 months of drug treatment, many patients should be treated and observed for 6 months at dosage levels intended for clinical use; and (4) because some serious ADE's may occur only after drug treatment for more than 6 months, some patients should be treated with the drug for 12 months.

In the past, guidelines have generally been issued under § 10.90(b) (21 CFR 10.90(b)), which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but are acceptable to FDA. The agency is now in the process of revising § 10.90(b). Therefore, this guideline is not being issued under the authority of § 10.90(b), and it does not create or confer any rights, privileges, or benefits for or on any person, nor does it operate to bind FDA in any way.

As with all of FDA's guidelines, the public is encouraged to submit written comments with new data or other new information pertinent to this guideline. The comments in the docket will be periodically reviewed, and, where appropriate, the guideline will be amended. The public will be notified of any such amendments through a notice

in the Federal Register.

Interested persons may, at any time, submit written comments on the guideline 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 guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the guideline follows: