## DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration [Docket No. 94D-0017]

International Conference on Harmonisation; Guideline on Dose Selection for Carcinogenicity Studies of Pharmaceuticals; Availability

**AGENCY:** Food and Drug Administration,

HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is publishing a final guideline entitled "Dose Selection for Carcinogenicity Studies of Pharmaceuticals." 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 examines criteria for establishing uniformity among international regulatory agencies for dose selection for carcinogenicity studies of human pharmaceuticals. The guideline is intended to help ensure that dose selection for carcinogenicity studies of pharmaceuticals to support drug registration is carried out according to sound scientific principles. DATES: Effective (insert date of publication in the Federal Register). 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: Roger L. Williams, Center for Drug Evaluation and Research (HFD-4), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–6740.

Regarding the 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 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 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 the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

Harmonization of dose selection for carcinogenicity studies of pharmaceuticals was selected as a priority topic during the early stages of the ICH initiative. In the **Federal Register** of March 1, 1994 (59 FR 9752), FDA published a draft tripartite guideline entitled, "Dose Selection for Carcinogenicity Studies of Pharmaceuticals." 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 discusses criteria for high dose selection for carcinogenicity studies of pharmaceuticals. Five generally acceptable criteria are dose limiting pharmacodynamic effects, maximum tolerated dose, a minimum of a 25-fold area under the concentration-time curve (AUC) ratio (rodent:human),

saturation of absorption, and maximum feasible dose. The guideline also considers other pharmacodynamic-, pharmacokinetic-, or toxicity-based endpoints in study design based on scientific rationale and individual merits.

FDA offers consultation and concurrence on carcinogenicity study designs and dose selection upon request. Regulatory consultation may be valuable when using any endpoint discussed in the guideline. However, it is considered especially important for sponsors to consult with FDA when planning carcinogenicity studies using pharmacodynamic endpoints and other product-specific designs to ensure their acceptability.

The guideline discusses a new pharmacokinetic endpoint, the 25X AUC ratio, developed specifically for carcinogenicity studies of nongenotoxic pharmaceuticals. The metabolism of the pharmaceutical should be qualitatively similar between humans and rodents to use the AUC ratio approach. Adequate data on comparative systemic exposure, metabolism and protein binding should be provided.

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 final 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 final 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: