DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 94D-0015]

International Conference on Harmonisation; Guideline on the Assessment of Systemic Exposure in Toxicity Studies; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a final guideline entitled "Toxicokinetics: Guidance on the Assessment of Systemic Exposure in Toxicity Studies." 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 help ensure that the assessment of systemic exposure in toxicity studies to support drug registration is carried out according to sound scientific principles. 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: 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 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 IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

Harmonization of the assessment of systemic exposure in toxicity studies was selected as a priority topic during the early stages of the ICH initiative. In the **Federal Register** of March 1, 1994 (59 FR 9755), FDA published a draft tripartite guideline entitled, "Tovicekingtics: A Cuidance on the

"Toxicokinetics: A Guidance on the Assessment of Systemic Exposure in Toxicity Studies." 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 toxicokinetics, which is the generation of pharmacokinetic data in nonclinical toxicity studies or ancillary studies to assess exposure. The objectives of toxicokinetics are: (1) To describe the systemic exposure achieved in animals, its relationship to dose level, and the time course of the toxicity study; (2) to relate the exposure achieved in toxicity studies to toxicological findings; (3) to support the choice of species and treatment regimen in nonclinical toxicity studies; and (4) to supply information which, along with the toxicity findings, will contribute to developing additional nonclinical toxicity studies.

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:

Toxicokinetics: Guidance on the Assessment

of Systemic Exposure in Toxicity Studies

l. Introduction

This Note for Guidance concerns toxicokinetics only with respect to the development of pharmaceutical products intended for use in human subjects.

In this context, toxicokinetics is defined as the generation of pharmacokinetic data, either as an integral component in the conduct of nonclinical toxicity studies or in specially designed supportive studies, in order to assess systemic exposure. These data may be used in the interpretation of toxicology findings and their relevance to clinical safety issues (see Note 1 for definitions of other terms used in this document).

The Note for Guidance has been developed in order to provide an understanding of the meaning and application of toxicokinetics and to provide guidance on developing test strategies in toxicokinetics. The guidance highlights the need to integrate pharmacokinetics into toxicity testing, which should aid in the interpretation of the toxicology findings and promote rational study design development.