DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 94D–0028]

International Conference on Harmonisation; Guideline on Repeated Dose Tissue Distribution Studies; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a final guideline entitled ''Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution 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 provide guidance on the circumstances when nonclinical repeated dose tissue distribution studies to support drug registration should be considered and on the conduct of those studies.

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 repeated dose tissue distribution 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 9748), FDA published a draft tripartite guideline entitled, ''Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution 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 recommends that repeated dose tissue distribution studies should not be required uniformly for all compounds and should only be conducted when appropriate data cannot be derived from other sources. Repeated dose studies may be appropriate for compounds which have: (1) An apparently long half-life; (2) incomplete elimination; or (3) unanticipated organ toxicity. The guideline provides general guidance on the use of radio labelled compounds, dose and species selection, and duration of 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:

Pharmacokinetics: Guidance For Repeated Dose Tissue Distribution Studies

Introduction

A comprehensive knowledge of the absorption, distribution, metabolism, and elimination of a compound is important for the interpretation of pharmacology and toxicology studies. Tissue distribution studies are essential in providing information on distribution and accumulation of the compound and/or metabolites especially in relation to potential sites of action; this information may be useful for designing toxicology and pharmacology studies and for interpreting the results of these experiments.

In the European Union, United States, and Japan, there has been a general agreement on the need to conduct single dose tissue distribution studies as part of the nonclinical program. These studies often provide sufficient information about tissue distribution.

There has been no consistent requirement for repeated dose tissue distribution studies. However, there may be circumstances when assessments after repeated dosing may yield important information.

This paper provides guidance on circumstances when repeated dose tissue distribution studies should be considered and on the conduct of such studies.

Circumstances Under Which Repeated Dose Tissue Distribution Studies Should Be Considered

1. When single dose tissue distribution studies suggest that the apparent half-life of the test compound (and/or metabolites) in organs or tissues significantly exceeds the apparent half-life of the elimination phase in plasma and is also more than twice the dosing interval in the toxicity studies, repeated dose tissue distribution studies may be appropriate.

2. When steady-state levels of a compound/metabolite in the circulation, determined in repeated dose pharmacokinetic or toxicokinetic studies, are markedly higher than those predicted from single dose kinetic studies, then repeated dose tissue distribution studies should be considered.

3. When histopathological changes, critical for the safety evaluation of the test substances, are observed that would not be predicted from short-term toxicity studies, single dose tissue distribution studies and pharmacological studies, repeated dose tissue distribution studies may aid in the interpretation of these findings. Those organs or tissues which were the site of the lesions should be the focus of such studies.

4. When the pharmaceutical is being developed for site-specific targeted delivery, repeated dose tissue distribution studies may be appropriate.

Design and Conduct of Repeated Dose Tissue Distribution Studies

The objectives of these studies may be achieved using radiolabelled compounds or alternative methods of sufficient sensitivity and specificity.

Dose level(s) and species should be chosen to address the problem that led to the consideration of the repeated dose tissue distribution study.

Information from previous pharmacokinetic and toxicokinetic studies should be used in selecting the duration of dosing in repeated dose tissue distribution studies. One week of dosing is normally considered to be a minimum period. A longer duration should be selected when the blood/plasma concentration of the compound and/or its metabolites does not reach steady state. It is normally considered unnecessary to dose for longer than 3 weeks.

Consideration should be given to measuring unchanged compound and/or metabolites in organs and tissues in which extensive accumulation occurs or if it is believed that such data may clarify mechanisms of organ toxicity.

Summary

Tissue distribution studies are an important component in the nonclinical kinetics program. For most compounds, it is expected that single dose tissue distribution studies with sufficient sensitivity and specificity will provide an adequate assessment of tissue distribution and the potential for accumulation. Thus, repeated dose tissue distribution studies should not be required uniformly for all compounds and should only be conducted when appropriate data cannot be derived from other sources. Repeated dose studies may be appropriate under certain circumstances based on the data from single dose tissue distribution studies, toxicity and toxicokinetic studies. The studies may be most appropriate for compounds which have an apparently long half-life, incomplete elimination or unanticipated organ toxicity. The design and timing of repeated dose tissue distribution studies should be determined on a case-by-case basis.

Dated: February 23, 1995.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 95–4959 Filed 2–28–95; 8:45 am]

BILLING CODE 4160–01–F