DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 92N–0136]

Single Dose Acute Toxicity Testing for Pharmaceuticals; Revised Guidance; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a revised guidance entitled ''Single Dose Acute Toxicity Testing for Pharmacueticals.'' This guidance was originally published as part of a proposed implementation document entitled ''U.S. FDA's Proposed Implementation of ICH Safety Working Group Consensus Regarding New Drug Applications.'' The agency has revised the guidance based on comments it received on the proposed implementation document.

DATES: Written comments on the revised guidance may be submitted at any time.

ADDRESSES: Submit written requests for single copies of the revised guidance entitled ''Single Dose Acute Toxicity Testing for Pharmaceuticals'' to the Division of Communications Management (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855. Send two self-addressed adhesive labels to assist that office in processing your requests. An electronic version of this guidance is also available via Internet using FTP, Gopher or the World Wide Web (WWW). For FTP, connect to the Center for Drug Evaluation and Research (CDER) anonymous FTP server at CDVS2.CDER.FDA.GOV and change to the ''guidance'' directory. For Gopher, connect to the CDER Gopher server at GOPHER.CDER.FDA.GOV and select the ''Industry Guidance'' menu option. For WWW, connect to the FDA Home Page at WWW.FDA.GOV and go to the CDER section. Submit written comments on the revised guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Requests and comments should be identified with the docket number found in brackets in the heading of this document. A copy of the guidance and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT:

Regarding the toxicity testing document: Joseph J. DeGeorge, Center for Drug Evaluation and Research (HFD–150), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5758.

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

In the Federal Register of April 15, 1992 (57 FR 13105), FDA published a notice of availability of a proposed implementation document entitled ''U.S. FDA's Proposed Implementation of ICH Safety Working Group Consensus Regarding New Drug Applications.'' The proposed implementation document was developed by the Safety Working Group of the ICH and described scientific and technical aspects of conducting pharmacology and toxicology studies, including single dose (acute toxicity studies), to be submitted to FDA. That notice gave interested persons an opportunity to submit written comments by June 15, 1992. In the Federal Register of July 31, 1992 (57 FR 33965), FDA reopened the comment period until August 14, 1992, in response to a request for an extension of the comment period.

The FDA draft guidance on Single Dose (acute) Toxicity Studies placed in the docket (92N–0136) for comment was considered compatible with the ICH participant regulatory agencies policies and with the consensus opinion of ICH Safety Working Group members on single dose toxicity testing. The main intent of the guidance was to have all regulatory regions confirm that LD_{50} studies were not necessary as part of acute toxicity testing. The agency received 15 comments on the proposed implementation document. In response to comments on the draft guidance, FDA modified its proposed guidance to provide information that would allow for use of single-dose toxicity studies to support single dose studies in humans. This approach, designed to facilitate the early stages of pharmaceutical development, is not an ICH consensus position although it is considered to be in general agreement with the ICH position on acute toxicity testing. It is, however, an FDA specific modification of the Single Dose Toxicity guidance of regional applicability.

Although this guidance does not create or confer any rights for or on any person and does not operate to bind FDA, it does represent the agency's current thinking on single dose acute toxicity testing for pharmaceuticals.

The public is encouraged to submit written comments with new data or other new information pertinent to this guidance. The comments in the docket will be periodically reviewed, and, where appropriate, the guidance 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 guidance 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 guidance 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 revised guidance follows:

Single Dose Acute Toxicity Testing for Pharmaceuticals

Introduction

Acute toxicity studies in animals are usually necessary for any pharmaceutical intended for human use. The information obtained from these studies is useful in choosing doses for repeat-dose studies, providing preliminary identification of target organs of toxicity, and, occasionally, revealing delayed toxicity. Acute toxicity studies may also aid in the selection of starting doses for Phase 1 human studies, and provide information relevant to acute overdosing in humans.

Definition

Acute toxicity is the toxicity produced by a pharmaceutical when it is administered in one or more doses during a period not exceeding 24 hours.

Testing Procedures

The test compound should be administered to animals to identify doses causing no adverse effect and doses causing major (life-threatening) toxicity. The use of vehicle control groups should be considered. For compounds with low toxicity, the maximum feasible dose should be administered.

Acute toxicity studies in animals should ordinarily be conducted using two routes of drug administration: (1) The route intended for human administration, and (2) intravenous administration, if feasible. When intravenous dosing is proposed in humans, use of this route alone in animal testing is sufficient.

Studies should be conducted in at least two mammalian species, including a nonrodent species when reasonable. The objectives of acute studies can usually be achieved in rodents using small groups of animals (for instance, three to five rodents per sex per dose). Where nonrodent species are appropriate for investigation, use of fewer animals may be considered. Any data providing information on acute effects in nonrodent species, including preliminary dose-range finding data for repeat-dose toxicity studies, may be acceptable.

Observation

Animals should be observed for 14 days after pharmaceutical administration. All mortalities, clinical signs, time of onset, duration, and reversibility of toxicity should be recorded. Gross necropsies should be performed on all animals, including those sacrificed moribund, found dead, or terminated at 14 days.

In addition, if acute toxicity studies in animals are to provide the primary safety data supporting single dose safety/kinetic studies in humans (e.g., a study screening multiple analogs to aid in the selection of a lead compound for clinical development), the toxicity studies should be designed to assess dose-response relationships and pharmacokinetics. Clinical pathology and histopathology should be monitored at an early time and at termination (i.e., ideally, for maximum effect and recovery).

Note: Animal Protection

Studies should be designed so that the maximum amount of information is obtained from the smallest number of animals. Calculating lethality parameters (e.g., LD_{50}) using large numbers of animals, as was done previously, is not recommended (see the Federal Register of October 11, 1988, 53 FR 39650).

To avoid causing excessive pain or tissue damage in the animals, pharmaceuticals with irritant or corrosive characteristics should not be administered in concentrations that produce severe toxicity solely from local effects.

Dated: August 15, 1996.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 96–21651 Filed 8–23–96; 8:45 am]

BILLING CODE 4160–01–F