DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97D–0147]

International Conference on Harmonisation; Draft Guideline on the Timing of Nonclinical Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft guideline entitled ''Guideline for the Timing of Nonclinical Studies for the Conduct of Human Clinical Trials for Pharmaceuticals.'' The draft guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft guideline is intended to recommend international standards for and to promote harmonization of the nonclinical safety studies needed to support human clinical trials of a given scope and duration.

DATES: Written comments by June 16, 1997.

ADDRESSES: Submit written comments on the draft guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Copies of the draft guideline are available from the Drug Information Branch (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–4573. Single copies of the draft guideline may be obtained by mail from the Office of Communication, Training and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, MD 20852–1448, or by calling the CBER Voice Information System at 1–800–835–4709 or 301–827–1800. Copies may be obtained from CBER's FAX Information System at 1–888–CBER–FAX or 301–827–3844.

FOR FURTHER INFORMATION CONTACT:

Regarding the guideline: Lisa D. Rarick, Center for Drug Evaluation and Research (HFD–580), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–4260.

Regarding the ICH: Janet J. Showalter, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–0864.

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 Industries 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 Associations (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.

At a meeting held on November 7, 1996, the ICH Steering Committee agreed that a draft guideline entitled ''Guideline for the Timing of Nonclinical Studies for the Conduct of Human Clinical Trials for Pharmaceuticals'' should be made available for public comment. The draft guideline is the product of the Multidisciplinary (Safety/Efficacy) Expert Working Group of the ICH. Comments about this draft will be considered by FDA and the Multidisciplinary (Safety/Efficacy) Expert Working Group.

The draft guideline is intended to recommend international standards for and to promote harmonization of the nonclinical safety studies needed to support human clinical trials of a given scope and duration. The nonclinical safety study requirements for the marketing approval of pharmaceuticals usually include single and repeat dose toxicity studies, reproductive toxicity studies, genotoxicity studies, local tolerance studies, an assessment of carcinogenic potential, safety pharmocology studies, and pharmacokinetic studies. The draft guideline discusses these types of studies, their duration, and their relation to the conduct of human clinical trials. The draft guideline should minimize delays in the conduct of clinical trials and reduce the unnecessary use of animals and other resources, which in turn should expedite the ethical development of drugs and facilitate the availability of new pharmaceuticals.

In publishing this draft guideline, a note from a prior draft (Note 4) has been deleted because it could have been read to suggest, incorrectly, that FDA lacks the authority to require the inclusion of certain populations in particular clinical trials. FDA has such authority under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 *et seq.*, and the Public Health Service Act, 42 U.S.C. 201 *et seq*. The note was deleted because it was subject to misinterpretation and was unnecessary.

This guideline represents the agency's current thinking on the timing of nonclinical studies for the conduct of human clinical trials for pharmaceuticals. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Interested persons may, on or before June 16, 1997, submit to the Dockets Management Branch (address above) written comments on the draft guideline. 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 draft guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. An electronic version of this guideline is available via Internet using the World Wide Web (WWW)(http://www.fda.gov/cder/guidance.htm). To connect to CBER's WWW site, type http://www.fda.gov/cber/cberftp.html.

The text of the draft guideline follows:

Draft Guideline for the Timing of Nonclinical Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

1. Introduction

1.1 Objectives of the Guideline

The purpose of this document is to recommend international standards for and to promote harmonization of the nonclinical safety studies needed to support human clinical trials of a given scope and duration.

Harmonization of the guidance for nonclinical safety studies will help to define the current recommendations and reduce the likelihood that substantial differences will exist between regions. This guidance should minimize delays in the conduct of clinical trials and reduce the unnecessary use of animals and other resources. This should expedite the ethical development of drugs and facilitate the availability of new pharmaceuticals.

1.2 Background

The recommendations for the extent of nonclinical safety studies to support the various stages of clinical development differ among the regions of Europe, the United States, and Japan. This raises the important question of whether there is any scientific justification for these differences and whether it would be possible to develop a mutually acceptable guidance.

The present guideline represents the consensus that exists among the ICH regions regarding the scope and duration of nonclinical safety studies to support the conduct of human clinical trials for pharmaceuticals.

1.3 Scope of the Guideline

The nonclinical safety study requirements for the marketing approval of a pharmaceutical agent usually include single and repeated dose toxicity studies, reproductive toxicity studies, genotoxicity studies, local tolerance studies, and for drugs which have cause for concern or are intended for a long duration of use, an assessment of carcinogenic potential. Other nonclinical studies include pharmacology studies for safety assessment (safety pharmacology) and pharmacokinetic (ADME) studies. These various types of studies, their duration, and the relation to the conduct of human clinical trials are presented in this guideline.

This guideline applies to the situations usually encountered during the development of conventional pharmaceutical agents and should be viewed as providing general guidance for drug development and not rigid requirements. The animal safety study and human clinical trial plans should be designed to represent that approach which is the most scientifically and ethically appropriate for the pharmaceutical agent under development.

There have been marked advances in the innovation of therapeutic agents (e.g., biotechnology-derived products) for which the existing paradigms for safety evaluation may not always be appropriate or relevant and they should therefore be evaluated on a case-by-case basis (Ref. 1). Similarly, pharmaceuticals in development for indications in life-threatening diseases or diseases without current effective therapy may also warrant a case-by-case approach to both the toxicological evaluation and clinical development to optimize or expedite drug development. In certain cases, studies may be abbreviated, deferred, or omitted.

1.4 General Principles

The development of a pharmaceutical agent is a stepwise process involving an evaluation of both the animal and human safety information. The goals of the nonclinical safety evaluation include: A characterization of toxic effects with respect to target organs, dose dependence, relationship to exposure, and potential reversibility. This information is important for the estimation of an initial safe starting dose for the human trials and the identification of parameters for clinical monitoring for potential adverse effects. The nonclinical safety studies, although limited at the beginning of clinical development, should be adequate to characterize potential toxic effects.

Human clinical trials are conducted to demonstrate the safety and efficacy of a pharmaceutical, starting with a relatively low exposure in a small number of subjects. This is followed by clinical trials in which exposure usually increases by dose, duration and/or size of the exposed patient population. Clinical trials are extended based on the demonstration of adequate safety in the previous clinical trial(s) as well as additional nonclinical safety information that is available as the clinical trials proceed. Serious adverse clinical or nonclinical findings may influence the continuation of clinical trials and/or suggest the need for additional nonclinical studies and a reevaluation of previous clinical adverse events to resolve the issue.

Clinical trials are conducted in phases for which different terminology has been utilized in the various regions. This document uses the terminology as defined in the ICH guideline ''General Considerations for the Clinical Trials'' (Ref. 2). Clinical trials may be grouped by their purpose and objectives. The first human exposure studies are generally single dose studies, followed by dose escalation and short-term repeated dose studies to evaluate pharmacokinetic parameters and tolerance (Phase I studies—Human Pharmacology studies). These studies are often conducted in healthy volunteers but may also include patients. The next phase of trials consists of small scale studies for additional safety and clinical pharmacology as well as preliminary efficacy studies in patients (Phase II studies—Therapeutic Exploratory studies). This is followed by large scale clinical trials for safety and efficacy in patient populations (Phase III studies—Therapeutic Confirmatory studies).

2. Safety Pharmacology

Safety pharmacology includes the assessment of effects on vital functions (such as cardiovascular, central nervous, and respiratory systems) and these should be evaluated prior to human exposure. These evaluations may be conducted as additions to toxicity studies or as separate studies.

3. Toxicokinetic and Pharmacokinetic Studies

Exposure data in animals should be evaluated prior to human clinical trials (Ref. 3). Further information on absorption, distribution, metabolism, and excretion in animals should be made available to compare human and animal metabolic pathways. Appropriate information should usually be available by the time the early Phase I (Human Pharmacology) studies have been completed.

4. Single Dose Toxicity Studies

The single dose (acute) toxicity for a pharmaceutical should be evaluated in two mammalian species prior to the first human exposure (Note 1). A dose escalation study is an acceptable alternative to the single dose design.

5. Repeated Dose Toxicity Studies

The recommended duration of the repeated dose toxicity studies is related to the duration and scale of the proposed clinical trial. In principle, the duration of the animal toxicity studies conducted in two mammalian species (one nonrodent) should be equal to or exceed the duration of the human clinical trials (Table 1).

5.1 Phase I and II Studies

A repeated dose toxicity study in two species (one nonrodent) for a minimum duration of 2–4 weeks (Table 1) would support Phase I (Human Pharmacology) and Phase II (Therapeutic Exploratory) studies up to 2 weeks in duration. Beyond this, 1-, 3-, or 6-month toxicity studies would support these types of human clinical trials for up to 1, 3, or 6 months, respectively.

TABLE 1.—DURATION OF REPEATED DOSE TOXICITY STUDIES TO SUPPORT PHASE I AND II TRIALS IN EU AND JAPAN AND PHASE I, II, AND III TRIALS IN THE UNITED STATES

Duration of Clinical Trials[1]	Duration of Repeated Dose Toxicity Studies
Single Dose	2–4 Weeks[2]
Up to 2 Weeks	2–4 Weeks[2]
Up to 1 Month	1 Month
Up to 3 Months	3 Months
Up to 6 Months	6 Months

TABLE 1.—DURATION OF REPEATED DOSE TOXICITY STUDIES TO SUPPORT PHASE I AND II TRIALS IN EU AND JAPAN AND PHASE I, II, AND III TRIALS IN THE UNITED STATES—Continued

Duration of Clinical Trials[1]	Duration of Repeated Dose Toxicity Studies
>6 Months	6–12 Months[3]

[1] In special circumstances, trials may be extended beyond the duration of completed repeat dose toxicity studies on a case-by-case basis.
[2] EU and United States: 2-week studies are the minimum duration. In Japan: 2-week nonrodent and 4-week rodent studies are needed (Also, see Note 2). In the United States, single dose toxicity studies with extended examinations can support single dose human studies (Ref. 4).
[3] In EU and Japan, 6-month studies are adequate. In the United States, a 12-month nonrodent study is usually needed (See Note 3).

5.2 Phase III Studies

For the Phase III (Therapeutic Confirmatory) studies, a 1-month toxicity study in two species (one nonrodent) would support clinical trials of up to 2 weeks in duration (Table 2). Three-month toxicity studies would support clinical trials for up to 1-month duration, while 6-month toxicity studies would support clinical trials for a longer duration.

TABLE 2.—DURATION OF REPEATED DOSE TOXICITY STUDIES TO SUPPORT PHASE III TRIALS IN THE EU AND JAPAN[1]

Duration of Clinical Trials[2]	Duration of Repeated Dose Toxicity Studies
Up to 2 Weeks	1 Month
Up to 1 Month	3 Months
> 1 Month	6 Months

[1] The durations in this table also indicate the marketing requirements in the United States and EU. In addition, in the United States, for drugs used for duration in excess of 6 months, a 12-month nonrodent study is generally considered an important part of the safety evaluation for marketing.
[2] In special circumstances, trials may be extended beyond the duration of completed repeat dose toxicity studies on a case-by-case basis.

6. Local Tolerance Studies

Local tolerance should be studied in animals using a route which is relevant to the proposed clinical administration site. The evaluation of local tolerance should be performed prior to human exposure. The assessment of local tolerance may be part of other toxicity studies.

7. Genotoxicity Studies

Prior to first human exposure, in vitro tests for the evaluation of mutations and chromosomal damage are generally needed. If an equivocal or positive finding occurs, additional testing should be performed (Ref. 5).

The standard battery of tests for genotoxicity (Ref. 6) should be completed prior to the initiation of Phase II studies.

8. Carcinogenicity Studies

Completed carcinogenicity studies are not usually needed in advance of the conduct of clinical trials unless there is cause for concern. Conditions relevant for carcinogenicity testing are discussed in ICH document ''Guideline on the Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals'' (Ref. 7).

For pharmaceuticals developed to treat certain serious diseases, carcinogenicity testing, if needed, may be conducted postapproval.

9. Reproductive Toxicity Studies

Reproductive toxicity studies (Refs. 8 and 9) should be conducted as is appropriate for the population that is to be exposed.

9.1 Men

Men may be included in Phase I and II trials prior to the conduct of the male fertility study since an evaluation of the male reproductive organs is performed in the repeated dose toxicity studies (Note 2).

A male fertility study should be completed prior to the initiation of Phase III trials (Refs. 8 and 9).

9.2 Women Not of Childbearing Potential

Women not of childbearing potential (i.e., permanently sterilized, postmenopausal) may be included in clinical trials without reproductive toxicity studies provided the relevant repeated dose toxicity studies (which include an evaluation of the female reproductive organs) have been conducted.

9.3 Women of Childbearing Potential

For women of childbearing potential there is a high level of concern for the unintentional exposure of an embryo/fetus before information is available concerning the potential benefits versus potential risks. There are currently regional differences in the timing of reproductive toxicity studies to support the inclusion of women of childbearing potential in clinical trials.

In the EU and in Japan, assessment of female fertility and embryo-fetal development should be completed prior to the inclusion of women of childbearing potential using birth control in any type of clinical trial. The pre- and postnatal development study should be submitted for marketing approval.

In the United States, women of childbearing potential may be included in early, carefully monitored studies without reproductive toxicity studies provided appropriate precautions are taken to minimize risk. These precautions include pregnancy testing (for example, based on the b-subunit of HCG), use of a highly effective method of birth control (Note 5), and entry after a confirmed menstrual period. Continued testing and monitoring during the trial should be sufficient to ensure compliance with the measures not to become pregnant during the period of drug exposure (which may exceed the length of study). To support this approach, informed consent should include any known pertinent information related to reproductive toxicity, such as a general assessment of potential toxicity in pharmaceuticals with related structures or pharmacological effects. If no relevant information is available, the informed consent should clearly note the potential for risk.

In the United States, assessment of female fertility and embryo-fetal development should be completed before women of childbearing potential using birth control are enrolled in Phase III trials. Unless there is cause for concern, the pre- and postnatal development study should be submitted for marketing approval. For all regions, all female reproductive toxicity studies (Ref. 8) and the standard battery of genotoxicity tests (Ref. 6) should be completed prior to the inclusion, in any clinical trial, of women of childbearing potential not using highly effective birth control (Note 5) or whose pregnancy status is unknown.

9.4 Pregnant Women

Prior to the inclusion of pregnant women in clinical trials, all the reproductive toxicity studies (Refs. 8 and 9) and the standard battery of genotoxicity tests (Ref. 6) should be conducted. In addition, safety data from previous human exposure are generally needed.

10. Supplementary Toxicity Studies

Special toxicity studies may be needed if previous nonclinical or clinical findings with the study product or related product have indicated special toxicological concerns.

11. Clinical Trials in Pediatric Populations

When pediatric patients are included in clinical trials, safety data from previous adult human exposure would usually represent the most relevant safety data and should

generally be available before pediatric clinical trials (Note 6).

In addition to appropriate repeated dose toxicity studies, all reproductive toxicity studies (Ref. 8) and the standard battery of genotoxicity tests (Ref. 6) should be available prior to the initiation of trials in pediatric populations. Juvenile animal safety studies should be considered on an individual basis when previous animal data and human safety data are insufficient.

The need for carcinogenicity testing should be addressed prior to long-term exposure in pediatric clinical trials considering the length of treatment or cause for concern (Ref. 7).

12. Continuing Efforts to Improve Harmonization

It is recognized that significant advances in harmonization of the timing of nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals have already been achieved and are detailed in this guideline. However, differences remain in a few areas. These include toxicity studies to support first entry into man, the recommendations for reproductive toxicity studies for women of childbearing potential, and the duration of nonclinical safety studies for trials and marketing of drugs intended for greater than 6 months clinical use. Regulators and industry will continue to consider these differences and work towards further improving the drug development process.

13. Endnotes

Note 1 For the conduct of single dose toxicity studies, refer to the ICH–1 recommendations (Ref. 10) and the regional guidelines (e.g., Ref. 4).

Note 2 There are currently regional differences for the minimum duration of repeated dose toxicity studies: 2 weeks in the EU and the United States, and 2-weeks nonrodent and 4-weeks rodent in Japan. In Japan, unlike the EU and the United States, the male fertility study is expected prior to the inclusion of men in clinical trials. As an alternative, an assessment of male fertility by careful histopathological examination in rodents can be made in the 4-week repeated dose toxicity study (Ref. 9) and thus fulfills this requirement for Japan. In the EU and the United States, 2-week repeated dose studies are considered adequate for an overall assessment of the potential toxicity of a drug to support clinical trials for a short duration.

Note 3 In the United States, if the 12-month nonrodent study will not be completed before clinical trials exceed 6 months, the U.S. Food and Drug Administration should be consulted. The nature of the pharmaceutical being developed, the patient population being treated, and the available nonclinical toxicity information should be considered. If, for example, 6-month studies in two species (one rodent and one nonrodent) have been completed and there is no cause for concern for the safety of the subjects being studied, the 12-month nonrodent study should be ongoing such that it exceeds the duration of the clinical trial. This lead should be sufficient to allow application of the findings from the nonclinical study to influence monitoring and conduct of the clinical study if additional unexpected hazards are identified to ensure patient safety and efficient evaluation of potential clinical hazards.

Note 4 Deleted.

Note 5 A highly effective method of birth control is defined as one which results in a low failure rate when used consistently and correctly (i.e., less than 1 percent per year), such as implants, injectables, combined oral contraceptives, some IUD's, sexual abstinence, or vasectomized partner. For subjects using hormonal contraceptive method, information regarding the product under evaluation and its potential effect on the contraceptive should be addressed.

Note 6 The necessity for adult human data would be determined on a case-by-case basis.

14. References

1. ICH Topic S6 Document ''Preclinical Testing of Biotechnology-Derived Pharmaceuticals.''

2. ICH Topic E8 Document ''General Considerations for Clinical Trials.''

3. ICH Harmonised Tripartite Guideline (S3A) Note for ''Toxicokinetics—Guidance on the Assessment of Systemic Exposure in Toxicity Studies.''

4. Food and Drug Administration, ''Single Dose Acute Toxicity Testing for Pharmaceuticals,'' Guidance for Industry, August 1996.

5. ICH Harmonised Tripartite Guideline (S2A) ''Guidance on Specific Aspects of Regulatory Genotoxicity Tests.''

6. ICH Topic S2B Document ''Standard Battery of Genotoxicity Tests.''

7. ICH Harmonised Tripartite Guideline (S1A) ''Guideline on the Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals.''

8. ICH Harmonised Tripartite Guideline (S5A) ''Detection of Toxicity to Reproduction for Medicinal Products.''

9. ICH Harmonised Tripartite Guideline (S5B) ''Toxicity to Male Fertility.''

10. Arcy, P. F., and D. W. G. Harron, ''Proceeding of The First International Conference on Harmonisation, Brussels 1991,'' Queen's University of Belfast, pp. 183–184, 1992.

Dated: April 25, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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