DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97D–0147]

International Conference on Harmonisation; Guidance on Nonclinical Safety 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 guidance entitled ''M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals.'' The guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guidance 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: Effective November 25, 1997. Submit written comments at any time.

ADDRESSES: Submit written comments on the guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Copies of the guidance 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 guidance may be obtained by mail from the Office of Communication, Training and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research (CBER), 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 guidance: Robert E. Osterberg, Center for Drug Evaluation and Research (HFD–520), Food and Drug Administration, 9201 Corporate Blvd., Rockville, MD 20850, 301–827–2123.

Regarding 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 (EU), 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.

In the **Federal Register** of May 2, 1997 (62 FR 24320), FDA published a draft tripartite guideline entitled ''Guideline on the Timing of Nonclinical Studies for the Conduct of Human Clinical Trials for Pharmaceuticals'' (M3). The notice gave interested persons an opportunity to submit comments by June 16, 1997.

After consideration of the comments received and revisions to the guidance, a final draft of the guidance was submitted to the ICH Steering Committee and endorsed by the three participating regulatory agencies on July 16, 1997.

In accordance with FDA's Good Guidance Practices (62 FR 8961, February 27, 1997), this document has been designated a guidance, rather than a guideline.

The guidance 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 pharmacology studies, and pharmacokinetic studies. The guidance discusses these types of studies, their duration, and their relation to the conduct of human clinical trials. The guidance should facilitate the conduct of clinical trials and reduce the unnecessary use of animals and other resources, which in turn should promote safe and ethical development of drugs and the availability of new pharmaceuticals.

This guidance represents the agency's current thinking on nonclinical safety 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.

As with all of FDA's guidances, 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 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. An electronic version of this guidance is available on the Internet (http://www.fda.gov/cder/guidance.htm) or through the CBER home page (http://www.fda.gov/cber/cberftp.html).

The text of the guidance follows:

M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals[1]

1. Introduction

1.1 Objectives of the Guidance

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 facilitate the timely conduct of clinical trials and reduce the unnecessary use of animals and other resources. This should promote safe and ethical development and 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 scientific justification for these differences and whether it would be possible to develop a mutually acceptable guidance.

The present guidance 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 Guidance

The nonclinical safety study recommendations for the marketing approval of a pharmaceutical usually include single and repeated dose toxicity studies, reproduction toxicity studies, genotoxicity studies, local tolerance studies, and for drugs that have special 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 (absorption, distribution, metabolism, and excretion (ADME)) studies. These types of studies and their relation to the conduct of human clinical trials are presented in this guidance.

This guidance applies to the situations usually encountered during the conventional development of pharmaceuticals and should be viewed as providing general guidance for drug development. Animal safety studies and human clinical trials should be planned and designed to represent an approach that is scientifically and ethically appropriate for the pharmaceutical under development.

There have been marked changes in the kinds of therapeutic agents being developed (e.g., biotechnology-derived products), and the existing paradigms for safety evaluation may not always be appropriate or relevant. The safety evaluation in such cases should be considered on a case-by-case basis as described in the ICH guidance ''Safety Studies in Biotechnological Products'' (Ref. 1). Similarly, pharmaceuticals under development for indications in life-threatening or serious diseases without current effective therapy may also warrant a case-by-case approach to both the toxicological evaluation and clinical development to optimize and expedite drug development. In these cases, particular studies may be abbreviated, deferred, or omitted.

1.4 General Principles

The development of a pharmaceutical 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 under the conditions of the supported clinical trial.

Human clinical trials are conducted to demonstrate the efficacy and safety 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 guidance ''General Considerations for 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 exploratory efficacy and safety studies in patients (Phase II studies—Therapeutic Exploratory studies). This is followed by confirmatory clinical trials for efficacy and safety 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 ADME in animals should be made available to compare human and animal metabolic pathways. Appropriate information should usually be available by the time the 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 considered an acceptable alternative to the single dose design.

5. Repeated Dose Toxicity Studies

The recommended duration of the repeated dose toxicity studies is usually related to the duration, therapeutic indication, 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 up to the maximum recommended duration of the repeated dose toxicity studies (Tables 1 and 2).

In certain circumstances, where significant therapeutic gain has been shown, trials may be extended beyond the duration of supportive repeated dose toxicity studies on a case-by-case basis.

5.1 Phase I and II Studies

A repeated dose toxicity study in two species (one nonrodent) for a minimum duration of 2 to 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. Six-month rodent and chronic nonrodent studies (Ref. 11) would support clinical trials of longer duration than 6 months.

[1] This guidance represents the agency's current thinking on nonclinical safety 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.

Table 1.—Duration of Repeated Dose Toxicity Studies to Support Phase I and II Trials in the EU and Phase I, II, and III Trials in the United States and Japan[1]

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

[1] In Japan, if there are no Phase II clinical trials of equivalent duration to the planned Phase III trials, conduct of longer duration toxicity studies should be considered as given in Table 2.

[2] In the EU and the 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, as an alternative to 2-week studies, single dose toxicity studies with extended examinations can support single dose human trials (Ref. 4).

[3] See Ref. 11. Data from 6 months of administration in nonrodents should be available before the initiation of clinical trials longer than 3 months. Alternatively, if applicable, data from a 9-month nonrodent study should be available before the treatment duration exceeds that which is supported by the available toxicity studies.

5.2 Phase III Studies

For the Phase III (Therapeutic Confirmatory) studies, the recommendations for the United States and Japan are the same as those in Table 1. In the EU, a 1-month toxicity study in two species (one nonrodent) would support clinical trials of up to 2 weeks duration (Table 2). Three-month toxicity studies would support clinical trials for up to 1 month duration, while 6-month toxicity studies in rodents and 3-month studies in nonrodents would support clinical trials of a duration up to 3 months. For longer term clinical trials, a 6-month study in rodents and a chronic study in nonrodents are recommended.

Table 2.—Duration of Repeated Dose Toxicity Studies to Support Phase III Trials in the EU and Marketing in All Regions[1]

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

[1] The above table also reflects the marketing recommendations in the three regions except that a chronic nonrodent study is recommended for clinical use > 1 month.

[2] See Ref. 11.

6. Local Tolerance Studies

Local tolerance should be studied in animals using routes relevant to the proposed clinical administration. 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 the ICH document (Ref. 7).

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

9. Reproduction Toxicity Studies

Reproduction 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 reproduction 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 reproduction toxicity studies to support the inclusion of women of childbearing potential in clinical trials.

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. In the EU, assessment of embryo-fetal development should be completed prior to Phase I trials in women of childbearing potential and female fertility studies prior to Phase III trials.

In the United States, women of childbearing potential may be included in early, carefully monitored studies without reproduction 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 3), 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 of 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.

In the three regions, the pre- and postnatal development study should be submitted for marketing approval or earlier if there is cause for concern. For all regions, all female reproduction 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 3) or whose pregnancy status is unknown.

9.4 Pregnant Women

Prior to the inclusion of pregnant women in clinical trials, all the reproduction 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 Studies

Additional nonclinical studies may be needed if previous nonclinical or clinical findings with the product or related products have indicated special safety 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 information and should generally be available before pediatric clinical trials. The necessity for adult human data would be determined on a case-by-case basis.

In addition to appropriate repeated dose toxicity studies, all reproduction 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 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 guidance. However, differences remain in a few areas. These include toxicity studies to support first entry into man and the recommendations for reproduction toxicity studies for women of childbearing potential. 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 guidances.

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 has usually been conducted prior to the inclusion of men in clinical trials. However, an assessment of male fertility by careful histopathological examination in the rodent 4-week repeated dose toxicity study has been found to be more sensitive in detecting effects on male reproductive organs than fertility studies (Ref. 9), and is now recommended to be performed prior to the first clinical trial in 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 A highly effective method of birth control is defined as one that results in a low failure rate (i.e., less than 1 percent per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices (IUD's), sexual abstinence, or a vasectomized partner. For subjects using a hormonal contraceptive method, information regarding the product under evaluation and its potential effect on the contraceptive should be addressed.

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: The Assessment of Systemic Exposure in Toxicity Studies.''

4. FDA, ''Single Dose Acute Toxicity Testing for Pharmaceuticals; Revised Guidance,'' 61 FR 43934 to 43935, August 26, 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 Carcinogenicity Studies for 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.

11. ICH Topic S4 Document ''Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent Toxicity Testing).''

Dated: November 18, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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