

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

[Docket No. 97D-0188]

**International Conference on Harmonisation; Draft Guideline on General Considerations for Clinical Trials; Availability**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is publishing a draft guideline entitled, "General Considerations for Clinical Trials." 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 sets forth general scientific principles for the conduct, performance, and control of clinical trials.

**DATES:** Written comments by July 1, 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 (CBER), Food and Drug Administration, 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 CBERS's FAX Information System at 1-888-CBER-FAX or 301-827-3844.

**FOR FURTHER INFORMATION CONTACT:**

Regarding the draft guideline: G. Alexander Fleming, Center for Drug Evaluation and Research (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3490.

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, "General Considerations for Clinical Trials" should be made available for public comment. The draft guideline is the product of the Efficacy Expert Working Group of the ICH. Comments on this draft guideline will be considered by FDA and the Efficacy Expert Working Group.

The draft guideline is intended to describe internationally accepted principles and practices in the conduct of clinical trials and development strategy for new drug products, and to facilitate the evaluation and acceptance of foreign clinical trial data by promoting a common understanding of general principles and approaches. The

draft guideline also presents an overview of ICH clinical safety and efficacy documents.

This guideline represents the agency's current thinking on general considerations for the conduct, performance, and control of clinical trials. 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 July 1, 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 draft guideline is available on the Internet using the World Wide Web (WWW) (<http://www.fda.gov/cder/guidance.htm>) or through the CBERS home page (<http://www.fda.gov/cber/cberftp.html>).

The text of the draft guideline follows:

**General Considerations for Clinical Trials**

**1. Objectives of This Document**

In the three ICH regions, the evolution of drug development strategies and evaluation processes has led to the issuance of regional guidances on general considerations for clinical trials and the clinical development process. This harmonized guideline is derived from those regional documents as well as from ICH guidelines.

The ICH document "General Considerations for Clinical Trials" is intended to:

- (a) Describe internationally accepted principles and practices in the conduct of both individual clinical trials and overall development strategy for new medicinal products.
- (b) Facilitate the evaluation and acceptance of foreign clinical trial data by promoting a common understanding of general principles, general approaches, and the definition of relevant terms.
- (c) Present an overview of the ICH clinical safety and efficacy documents and facilitate the user's access to guidance pertinent to clinical trials within these documents. The relevant ICH documents are listed in Annex 1.
- (d) Provide a glossary of terms (under development) used in the ICH clinical safety and efficacy related documents that pertain to clinical trials and indicate which documents contain these terms.

For the sake of brevity, the term "drug" has been used in this document. It should be

considered synonymous with "medicinal product" and "pharmaceutical" including vaccines and other biological products.

## 2. General Principles

### 2.1 Protection of clinical trial subjects

The principles and practices concerning protection of trial subjects are stated in the ICH Guideline on Good Clinical Practice (ICH E6). These principles have their origins in The Declaration of Helsinki and should be observed in the conduct of all human drug investigations.

Before any clinical trial is carried out, results of nonclinical investigations or previous human studies should be sufficient to indicate that the drug is safe for the proposed investigation in humans. The purpose and timing of animal pharmacology and toxicology studies intended to support studies of a given duration are discussed in

ICH M3. The role of such studies for biotechnology products is cited in ICH S6.

Throughout drug development, emerging animal toxicological and clinical data should be reviewed and evaluated by competent clinicians and other experts to assess their implications for the safety of the trial subjects. In response to such findings, future studies and, when necessary, those in progress should be appropriately modified in a timely fashion to maintain the safety of trial participants. The investigator and sponsor share responsibility for the protection of clinical trial subjects together with the Institutional Review Board/Independent Ethics Committee. The responsibilities of these parties are described in ICH E6.

### 2.2 Scientific approach in design and analysis

Clinical trials should be designed, conducted, and analyzed according to sound

scientific principles to achieve their objectives, and should be reported appropriately. The essence of rational drug development is to ask key questions and answer them with well-controlled clinical studies. The primary objectives of any study should be clear and explicitly stated.

Clinical studies can be classified according to objective (see Table 1). The cardinal logic behind serially conducted studies of a medicinal product is that the results of prior studies should influence the plan of later studies. Emerging data will frequently prompt a modification of the development strategy. For example, results of controlled trials may suggest further need for pharmacology studies. The availability of foreign clinical data, which can be extrapolated, may obviate the need to generate similar data in the new region (see ICH E5).

TABLE 1.—AN APPROACH TO CLASSIFYING CLINICAL STUDIES ACCORDING TO OBJECTIVE

Type of Study	Objective of Study	Study Examples
Human Pharmacology	<ul style="list-style-type: none"> <li>•Assess tolerance</li> <li>•Define/describe pharmacokinetic (PK) and pharmacodynamic (PD)</li> <li>•Explore drug metabolism and drug interactions</li> <li>•Estimate activity</li> </ul>	<ul style="list-style-type: none"> <li>•Dose-tolerance studies</li> <li>•Single and multiple dose PK and/or PD studies</li> <li>•Drug interaction studies</li> <li>•Absorption, distribution, metabolism, excretion (ADME) studies</li> </ul>
Therapeutic Exploratory	<ul style="list-style-type: none"> <li>•Explore use for the targeted indication</li> <li>•Estimate dosage regimen</li> <li>•Provide basis for confirmatory study design, endpoints, methodologies</li> </ul>	<ul style="list-style-type: none"> <li>•Earliest controlled trials in narrow populations of relatively short duration, using surrogate or pharmacologic endpoints</li> </ul>
Therapeutic Confirmatory	<ul style="list-style-type: none"> <li>•Demonstrate/confirm effectiveness</li> <li>•Establish safety profile</li> <li>•Provide a basis for favorable benefit/risk relationship to support licensing</li> </ul>	<ul style="list-style-type: none"> <li>•Adequate and well controlled efficacy studies</li> <li>•Safety studies</li> <li>•Large simple trials</li> </ul>
Therapeutic Use	<ul style="list-style-type: none"> <li>•Refine understanding of benefit/risk relationship in general or special populations and/or environments</li> <li>•Identify less common adverse reactions</li> <li>•Refine dosing recommendation</li> </ul>	<ul style="list-style-type: none"> <li>•Comparative efficacy studies</li> <li>•Studies of mortality/morbidity outcomes</li> <li>•Large simple trials</li> <li>•Pharmacoeconomic studies</li> </ul>

## 3. Development Methodology

This section covers issues and considerations relating to the development plan and to its individual component studies.

### 3.1 Considerations for the development plan

#### 3.1.1 Nonclinical studies

Important considerations for determining the nature of nonclinical studies and their timing with respect to clinical trials include:

- (a) Duration and total exposure proposed in individual patients.
- (b) Characteristics of the drug (e.g., long half life, biotechnology products).
- (c) Disease or condition targeted for treatment.
- (d) Use in special populations (e.g., women of childbearing potential).
- (e) Route of administration.

The need for nonclinical information including toxicology, pharmacology, and pharmacokinetics to support clinical trials is addressed in the ICH M3 and S6 documents.

3.1.1.1 *Safety studies.* For first studies in humans, the dose that is administered should be determined by careful examination of the prerequisite nonclinical pharmacological and

toxicological evaluations (see ICH M3). Early nonclinical studies should provide sufficient information to support selection of the initial human dose and safe duration of exposure, and to provide information about physiological and toxicological effects of a new drug.

3.1.1.2 *Pharmacological studies.* The basis and direction of the clinical exploration and development rests on the nonclinical pharmacology profile, which includes information such as:

- (a) Pharmacological basis of principal effects (mechanism of action).
- (b) Dose-response or concentration-response relationships and duration of action.
- (c) Study of the potential clinical routes of administration.
- (d) Systemic general pharmacology, including pharmacological effects on major organ systems and physiological responses.

#### 3.1.2 Quality of investigational medicinal products

Formulations used in clinical trials should be well characterized, including information on bioavailability wherever feasible. The

formulation should be appropriate for the stage of drug development. Ideally, the supply of a formulation will be adequate to allow testing in a series of studies that examine a range of doses. During drug development different formulations of a drug are usually tested. Links between formulations established by bioequivalence studies or other means are important in interpreting clinical study results across the development program.

#### 3.1.3 Phases of clinical development

Although clinical studies may be classified according to their objectives, the concept that clinical drug development is comprised of four temporal phases (I–IV) is widely used. It is important to appreciate that this is a description, not a set of requirements, and that for some drugs and development programs the typical sequence will not be appropriate or necessary. Each of the four individual categories of studies by objective roughly corresponds to one of the four temporal phases of drug development. For example, human pharmacology studies are typically conducted during Phase I. However, many such studies are conducted at each of

the other three stages, but nonetheless sometimes labeled as Phase I studies. Figure 1 demonstrates this close but variable correlation between the two classification systems. The distribution of the points of the graph shows that the types of study are not synonymous with the phases of development.

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# Correlation between Development Phases and Types of Study

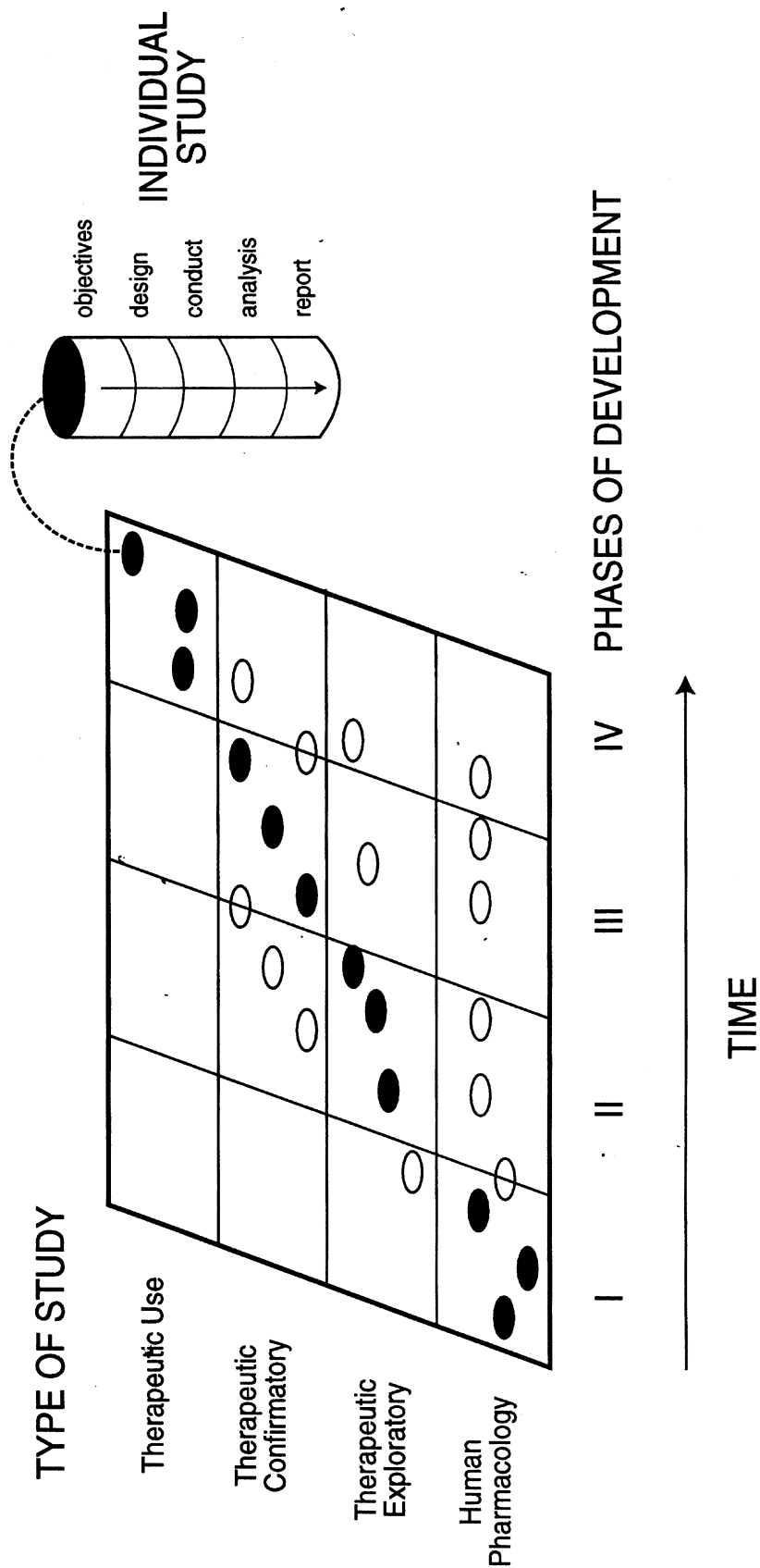


Figure 1—This matrix graph illustrates the relationship between the phases of development and types of study by objective that may be conducted during the clinical development of a new medicinal product. The shaded circles show the types of study most usually conducted in a certain phase of development; the open circles show certain types of study that may be conducted in a phase of development which may be less usual (see text for details). Each circle represents an individual study. To illustrate, one circle is joined by a dotted line to an inset column which depicts the elements and sequence of an individual study.

Drug development is ideally a step-wise procedure in which information from small early studies is used to support and plan later larger, more definitive studies. To develop new drugs efficiently, it is essential to identify important characteristics of the investigational medicine in the early stages of development and to plan an appropriate development based on this profile.

Initial trials provide an early evaluation of short-term safety and tolerability and can provide pharmacodynamic and pharmacokinetic information needed to choose a suitable dosage range and administration schedule for initial exploratory therapeutic trials. Later confirmatory studies are generally larger and longer and include a more diverse patient population. Dose-response information should be obtained at all stages of development, from early tolerance studies, to studies of short-term pharmacodynamic effect, to large effectiveness studies (see ICH E4). Throughout development, new data may suggest the need for additional studies that are typically part of an earlier phase. For example, blood level data in a late trial may suggest a need for a drug-drug interaction study or adverse effects may suggest the need for further dose finding and/or additional nonclinical studies. Other open circles represent preplanned studies conducted in a less usual phase, e.g., drug-drug interaction studies in Phase III. These studies are represented by open circles in Figure 1.

**3.1.3.1 Phase I (Most typical kind of study: Human pharmacology).** Phase I starts with the initial administration of an investigational new drug into humans.

While human pharmacology studies are typically identified with Phase I, they may also be indicated at other points in the development sequence. Studies in this phase of development usually have nontherapeutic objectives and may be conducted in healthy volunteer subjects or certain types of patients, e.g., patients with mild hypertension. Drugs with significant potential toxicity, e.g., cytotoxic drugs, are usually studied in patients. Studies in this phase can be open, baseline controlled or may use randomization with or without blinding, to improve the validity of observations.

Studies conducted in Phase I typically involve one or a combination of the following aspects:

(a) Estimation of initial safety and tolerability

The initial and subsequent administration of an investigational new drug into humans

are usually intended to determine the tolerability, and in particular, the highest dose with acceptable tolerability. These studies typically include both single and multiple dose administration.

(b) Determination of pharmacokinetics  
Preliminary characterization of a drug's absorption, distribution, metabolism, and excretion is almost always an important goal of Phase I. Pharmacokinetics may be assessed via separate studies or as a part of safety and tolerance studies. Pharmacokinetic studies are performed to assess the presence of accumulation of parent drug or metabolites and to assess pharmacokinetic changes over time. Some pharmacokinetic studies are commonly conducted in later phases to answer more specialized questions. For many orally administered drugs, especially modified release products, the study of food effects on bioavailability is important. Obtaining pharmacokinetic information in subpopulations such as patients with impaired elimination (renal or hepatic failure), the elderly, children, women, and ethnic subgroups should be considered. Drug-drug interaction studies are important for many drugs but are generally performed in phases beyond Phase I.

(c) Assessment of pharmacodynamics  
Depending on the drug and the endpoint studied, pharmacodynamic studies and studies relating drug blood levels to response (PK/PD studies) may be conducted in healthy volunteer subjects or in patients with the target disease. In patients, if there is an appropriate measure, pharmacodynamic data can provide early estimates of activity and potential effectiveness and may guide the dosage and dose regimen in later studies.

(d) Early measurement of activity  
Preliminary studies of activity or potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies may be appropriate when effectiveness is readily measurable with a short duration of drug exposure. At this early stage, use in patients and/or use in healthy volunteer subjects may be justified, depending on the drug.

**3.1.3.2 Phase II (Most typical kind of study: Therapeutic exploratory).** Phase II is usually considered to start with the initiation of studies in which the primary objective is to explore therapeutic effectiveness in patients.

Initial therapeutic exploratory studies may use a variety of study designs, such as randomized controls and comparisons with baseline status. Subsequent trials are usually randomized and controlled to evaluate the efficacy of the drug and its safety for a particular therapeutic indication. Studies in Phase II are typically conducted in a group of patients who are selected by clearly defined criteria and who are closely monitored.

An important goal for this phase is to determine the dose(s) and regimen for Phase III trials. Studies in this phase may utilize dose response designs (see ICH E4) to estimate and/or confirm the dose response relationship for the indication in question. Alternatively, confirmatory dose response studies may be left for Phase III. Doses used in Phase II are usually but not always less than the highest doses used in Phase I.

Additional objectives of clinical trials conducted in Phase II may include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications), and target populations (e.g., mild versus severe disease) for further study in Phase II or III. These objectives may be served by exploratory analyses, examining subsets of data, and by including multiple endpoints in trials.

**3.1.3.3 Phase III (Most typical kind of study: Therapeutic confirmatory).** Phase III usually is considered to begin with the initiation of studies in which the primary objective is to confirm therapeutic effectiveness.

Key studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. These well-controlled studies are intended to provide an adequate basis for marketing approval. Studies in Phase III may also further explore the dose-response relationship, or explore the drug's use in wider populations, in different stages of disease, or in combination with another drug. For drugs intended to be administered for long periods, trials involving extended exposure to the recipient population to the drug are ordinarily conducted in Phase III, although they may be started in Phase II (see ICH E1). ICH E1 and ICH E7 describe the overall clinical safety database considerations for chronically administered drugs and drugs used in the elderly.

**3.1.3.4 Phase IV (Variety of studies: See Table 1—Therapeutic Use).** Phase IV begins after drug approval. Therapeutic use studies are considered to be those trials that go beyond the prior demonstration of the drug's safety, effectiveness, and dose definition.

Studies in Phase IV are all studies (other than routine surveillance) performed after drug approval and related to the approved indication. They are not considered necessary for approval but are often important for optimizing the drug's use. They may be of any type but should have valid scientific objectives. Commonly conducted studies include additional drug-drug interaction, dose-response, or safety studies and studies designed to support an extended claim under the approved indication, e.g., mortality/morbidity studies.

Development of an application unrelated to the original approved use should be seen as needing a separate development program, though the need for some studies may be obviated by the availability of data from the original development program.

After initial approval, drug development may require continued study of new or modified indications, new dosage regimens, new routes of administration, or additional patient populations. If a new dose, formulation, or combination is studied, additional human pharmacology studies may be indicated.

#### 3.1.4 Special considerations

A number of special circumstances and populations require separate consideration when they are part of the development plan.

**3.1.4.1 Studies of drug metabolites.** Major active metabolite(s) should be identified and

receive detailed pharmacokinetic study when feasible. The rate of formation and elimination should be determined whenever possible. Timing of the metabolic assessment studies within the development plan depends on the characteristics of the individual drug.

3.1.4.2 *Drug-drug interactions.* If a potential for drug-drug interaction is suggested by metabolic profile, by the results of nonclinical studies, or by information on similar drugs, studies on drug interaction during clinical development are highly desirable. For drugs that are frequently coadministered, it is important that drug-drug interaction studies should be performed in nonclinical and/or in human studies, if appropriate. This is particularly true for drugs that are known to alter the absorption or metabolism of other drugs (see ICH E7), or to be susceptible to effects by other drugs.

3.1.4.3 *Special populations.* Some groups in the general population may require special study because they have unique risk/benefit considerations to take into account during drug development, or because they can be anticipated to need modification of use of the dose or schedule of a drug compared to general adult use. Pharmacokinetic studies in patients with renal and hepatic dysfunction are important to assess the impact of potentially altered drug metabolism or excretion. Other ICH documents address such issues for geriatric patients (ICH E7) and patients from different ethnic groups (ICH E5). The need for nonclinical safety studies to support human clinical trials in special populations is addressed in the ICH M3 document.

(a) Investigations in pregnant women

In general, pregnant women should be excluded from clinical trials where the drug is not intended for use in pregnancy. If a patient becomes pregnant during administration of the drug, treatment should generally be discontinued if this can be done safely. A followup study of the pregnancy, fetus, and child is very important. For clinical trials of a medicinal product for use during pregnancy a followup study of the pregnancy, fetus, and child is important.

(b) Investigations in nursing women

Excretion of the drug or its metabolites into human milk should be examined where applicable. When nursing mothers are enrolled in clinical studies their babies should be monitored for the effects of the drug.

(c) Investigations in children

The extent of the studies needed depends on the current knowledge of the drug and the possibility of extrapolation from adults and children of other age groups. Some drugs may be used in children from the early stages of drug development (see ICH M3).

For a drug expected to be used in children, evaluation should be made in the appropriate age group. When clinical development is to include studies in children, it is usually desirable to begin with older children before extending the trial to younger children and then infants.

### 3.2 Considerations for individual clinical trials

The following important principles should be followed in planning the objectives,

design, conduct, analysis, and reporting of a clinical trial (see ICH guidelines in Annex 1). Each part should be defined in a written protocol before the study starts (see ICH E6).

#### 3.2.1 Objectives

The objective(s) of the study should be clearly stated and may include exploratory or confirmatory characterization of safety and/or effectiveness and/or assessment of pharmacological, physiological, biochemical, or clinical effects.

#### 3.2.2 Design

The appropriate study design should be chosen to provide the desired information. Examples include parallel group, crossover, factorial, dose escalation, and historical controlled designs (see ICH E4, E6, E9, and E10). Appropriate comparators should be utilized and adequate numbers of subjects included to achieve the study objectives. Primary and secondary endpoints and plans for their analyses should be clearly stated. The methods of monitoring adverse events by changes in clinical signs and symptoms and laboratory studies should be described (see ICH E3). The protocol should specify procedures for the followup of patients who stop treatment prematurely.

3.2.2.1 *Selection of subjects.* The selection of the subject population will depend on the indication to be studied and should take account of the prior nonclinical and clinical knowledge. The variability of groups of patients or healthy volunteers studied in early trials may be limited to a narrow range by strict selection criteria, but as drug development proceeds, the populations tested should be broadened to reflect the target population.

Depending on the stage of development and level of concern for safety, it may be necessary to conduct studies in a closely monitored (i.e., inpatient) environment.

Subjects should not be enrolled repetitively in clinical trials without time off treatment adequate to protect safety and minimize carryover effects.

In general, women of childbearing potential should be using highly effective contraception to participate in clinical trials (see ICH M3).

For male subjects, potential hazards of drug exposure in the trial to their sexual partners or resulting progeny should be considered. When indicated (e.g., trials involving drugs which are potentially mutagenic, or toxic to the reproductive system), an appropriate contraception provision should be included in the trial.

3.2.2.2 *Selection of control group.* Trials should be adequately controlled. Comparators may be placebo, active controls, or of different doses of the same compound. The choice of the comparator depends on, among other things, the objective of the trial (see ICH E9 and E10). Historical or observational (external) controls may be employed when justified but additional care is important to minimize the likelihood of erroneous inference.

3.2.2.3 *Number of subjects.* The trial size should be based on consideration of the magnitude of the treatment effect, the disease to be investigated, the objective of the study, the endpoint criteria, and the number of trial

sites (see ICH E9). In some circumstances a larger database may be necessary to establish the safety of the drug. ICH E1 and ICH E7 suggest a minimum experience to assess safety for a registrational database for a new indication. These numbers should not be considered as absolute.

#### 3.2.2.4 Efficacy and safety variables.

Response variables should be defined prospectively, giving descriptions of methods of observation and quantification. Objective methods of observation should be used where possible and when appropriate (see ICH E9).

Study endpoints are the response variables, usually relating to efficacy, that are chosen to assess drug effects. A primary endpoint(s) represents clinically relevant changes and is typically selected based on the principal objective of the study. Secondary endpoints assess other drug effects which may or may not be related to the primary endpoint. Endpoints and the plan for their analysis should be prospectively specified in the protocol.

A validated surrogate endpoint is an endpoint which allows prediction of a clinically important outcome but in itself does not measure a clinical benefit. When appropriate, surrogate outcomes may be used as primary endpoints.

The methods used to make the measurements of the endpoints, both subjective and objective, should meet accepted standards for accuracy, precision, reproducibility, reliability, validity, and responsiveness (sensitivity to change over time).

3.2.2.5 *Methods to minimize bias.* The protocol should specify methods of allocation to treatment groups and blinding (see ICH E9 and E10).

#### (a) Randomization

In conducting a controlled trial, randomized allocation is usually the preferred means of assuring comparability of test groups and minimizing the possibility of selection bias.

#### (b) Blinding

Blinding is an important means of reducing or minimizing the risk of biased study outcomes. A trial where the treatment assignment is not known by the study participant because of the use of placebo or other methods of masking the intervention, is referred to as a single blind study. When the study clinician is also unaware of treatment assignment the study is double blind.

#### (c) Compliance

Methods used to survey patient usage of the test drug should be specified in the protocol and the actual usage documented.

### 3.2.3 Conduct

The study should be conducted according to the principles described in this guideline and in accordance with other pertinent elements outlined in ICH E6 and other relevant ICH guidelines (see Annex 1). Adherence to the study protocol is essential. If modification of the protocol becomes necessary, a clear description of the rationale for the modification should be provided in a protocol amendment. Timely adverse event reporting during a study is essential and should be documented. Guidance is available on expedited reporting of safety data to

appropriate officials and on the content of safety reports (see ICH E2A and E2B).

3.2.4 Analysis

The study protocol should have a specified analysis plan that is appropriate for the objectives and design of the study taking into account the method of subject allocation, the measurement methods of outcome variables, specific hypotheses to be tested, and analytical approaches to common problems including early study withdrawal and protocol violations. The plan for analyzing primary and secondary endpoints should be stated in the protocol.

The results of a clinical trial should be analyzed in accordance with the plan prospectively stated in the protocol and all deviations from the plan should be indicated in the study report. Detailed guidance is available in other ICH guidelines on planning of the protocol (ICH E6), statistical analysis of results (ICH E9), and on study reports (ICH E3).

Studies are normally expected to run to completion although in some studies the possibility of early stopping is formally recognized. In such cases this should be clearly described in the protocol with due statistical attention to the overall levels of

statistical significance and to the need to adjust the estimates of the size of treatment effects.

Safety data should be collected for all clinical trials, appropriately tabulated, and, with adverse events, classified according to their seriousness and their likely causal relationship.

3.2.5 Reporting

Clinical study reports should be adequately documented following the approaches outlined in other ICH guidelines (see E3 and E6).

4. Annex 1

LIST OF RELEVANT ICH GUIDELINES AND TOPICS

Code	Topic
E1	The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions
E2A	Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
E2B	Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
E2C	Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs
E3	Structure and Content of Clinical Study Reports
E4	Dose-Response Information to Support Drug Registration
E5	Ethnic Factors in the Acceptability of Foreign Clinical Data
E6	Good Clinical Practice: Consolidated Guideline
E7	Studies in Support of Special Populations: Geriatrics
E8	General Considerations for Clinical Trials
E9	Statistical Considerations in the Design of Clinical Trials
E10	Choice of Control Group in Clinical Trials
M1	International Medical Terminology
M2	Electronic Standards for the Transfer of Regulatory Information (ESTRI)
M3	Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals
S6	Safety Studies for Biotechnology-Derived Products

Dated: May 15, 1997.

**William K. Hubbard,**

*Associate Commissioner for Policy  
Coordination.*

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