AND RADIOLOGICAL HEALTH for general information, or arrow down for specific topics.

Dated: October 7, 1997.

Joseph A. Levitt,

Deputy Director for Regulations Policy, Center for Devices and Radiological Health.

[FR Doc. 97–32875 Filed 12–16–97; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Cardiovascular and Renal Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Cardiovascular and Renal Drugs Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA regulatory issues.

Date and Time: The meeting will be held on January 27, 1998, 8:30 a.m. to 5:30 p.m.; and January 28, 1998, 9 a.m. to 4 p.m.

Location: National Institutes of Health, Natcher Conference Center, 45 Center Dr., Bethesda, MD 20892.

Contact Person: Joan C. Standaert, Center for Drug Evaluation and Research (HFD–110), 419–259–6211, or Danyiel A. D'Antonio (HFD–21), 301–443–5455, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area), code 12533. Please call the Information Line for up-to-date information on this meeting.

Agenda: On January 27, 1998, the committee will review and discuss: (1) New drug application (NDA) 20–736, Verdia™ (tasosartan, Wyeth-Ayerst Research), as a therapy for hypertension; and (2) the unapproved outpatient use of intermittent intravenous positive inotropic agents. On January 28, 1998, the committee will review and discuss NDA 20–718, Integrilin™ (eptifibatide, Cor Therapeutics, Inc.), for use in the settings of percutaneous transluminal angioplasty and acute coronary syndrome.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by January 20, 1998. Oral presentations from the public will be scheduled between approximately 8:30 a.m. and 9:30 a.m. on January 27, 1998. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before January 20, 1998, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: December 11, 1997.

Michael A. Friedman,

Deputy Commissioner for Operations.

[FR Doc. 97–32874 Filed 12–16–97; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97D–0188]

International Conference on Harmonisation; Guidance on General Considerations for Clinical Trials

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a guidance entitled ''E8 General Considerations for Clinical Trials.'' 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 sets forth general scientific principles for the conduct, performance, and control of clinical trials.

DATES: Effective December 17, 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), 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 CBER's FAX Information System at 1–888–CBER–FAX or 301–827–3844.

FOR FURTHER INFORMATION CONTACT:

Regarding the guidance: G. Alexander Fleming, Center for Drug Evaluation and Research (HFD–510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–6391.

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, 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 (CDER) and CBER, 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 30, 1997 (62 FR 29540), FDA published a draft tripartite guideline entitled ''General Considerations for Clinical Trials.'' The notice gave interested persons an opportunity to submit comments by July 1, 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 17, 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 describes internationally accepted principles and practices in the conduct of clinical trials and development strategy for new drug products. It is intended to facilitate the evaluation and acceptance of foreign clinical trial data by promoting a common understanding of general principles and approaches. The guidance also presents an overview of ICH clinical safety and efficacy documents.

This guidance 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.

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/index.htm) or at CBER's World Wide Web site at ''http://www.fda.gov/cber/publications.htm''.

The text of the guidance follows:

E8 General Considerations for Clinical Trials[1]

1. Objectives of This Document

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

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 separate glossary of terms used in the ICH clinical safety and efficacy related documents that pertain to clinical trials and indicate which documents contain these.

For the sake of brevity, the term ''drug'' has been used in this document. It should be considered synonymous with ''investigational (medicinal) product,'' ''medicinal product,'' and ''pharmaceutical,'' including vaccines and other biological products. The principles established in this guidance may also be applied to other clinical investigations (e.g., radiotherapy, psychotherapy, surgery, medical devices and alternative therapies).

2. General Principles

2.1 Protection of Clinical Trial Subjects

The principles and practices concerning protection of trial subjects are stated in the ICH guidance 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 acceptably 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 qualified 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 important questions and answer them with appropriate studies. The primary objectives of any study should be clear and explicitly stated.

Clinical studies can be classified according to when the study occurs during clinical development or, as shown in Table 1, by their objectives. (The illustrative examples are not intended to be exhaustive.) 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 a therapeutic confirmatory study may suggest a need for additional human pharmacology studies.

The availability of foreign clinical data should obviate the need to generate similar data in an ICH region if the ICH E5 and ICH E6 guidances are followed (see ICH E5).

[1] This guidance 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.

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

Type of Study	Objective of Study	Study Examples
Human Pharmacology	• Assess tolerance • Define/describe PK[1] and PD[2] • Explore drug metabolism and drug interactions • Estimate activity	• Dose-tolerance studies • Single and multiple dose PK and/or PD studies • Drug interaction studies
Therapeutic Exploratory	• Explore use for the targeted indication • Estimate dosage for subsequent studies • Provide basis for confirmatory study design, endpoints, methodologies	• Earliest trials of relatively short duration in well-defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures • Dose-response exploration studies
Therapeutic Confirmatory	• Demonstrate/confirm efficacy • Establish safety profile • Provide an adequate basis for assessing the benefit/risk relationship to support licensing • Establish dose-response relationship	• Adequate, and well controlled studies to establish efficacy • Randomized parallel dose-response studies • Clinical safety studies • Studies of mortality/morbidity outcomes • Large simple trials • Comparative studies
Therapeutic Use	• Refine understanding of benefit/risk relationship in general or special populations and/or environments • Identify less common adverse reactions • Refine dosing recommendation	• Comparative effectiveness studies • Studies of mortality/morbidity outcomes • Studies of additional endpoints • Large simple trials • Pharmacoeconomic studies

[1] Pharmacokinetics
[2] Pharmacodynamics

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 the first studies in humans, the dose that is administered should be determined by careful examination of the prerequisite nonclinical pharmacokinetic, 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 and pharmacokinetic studies.* The basis and direction of the clinical exploration and development rests on the nonclinical pharmacokinetic and 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.

(e) Studies of absorption, distribution, metabolism, and excretion.

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 may be 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

Clinical drug development is often described as consisting of four temporal phases (Phases I–IV). It is important to recognize that the phase of development provides an inadequate basis for classification of clinical trials because one type of trial may occur in several phases (see Figure 1). A classification system using study objectives as discussed in section 2.2 is preferable. It is important to appreciate that the phase concept is a description, not a set of requirements. It is also important to realize that the temporal phases do not imply a fixed order of studies since for some drugs in a development plan the typical sequence will not be appropriate or necessary. For example, although human pharmacology studies are typically conducted during Phase I, many such studies are conducted at each of the other three stages, but nonetheless are 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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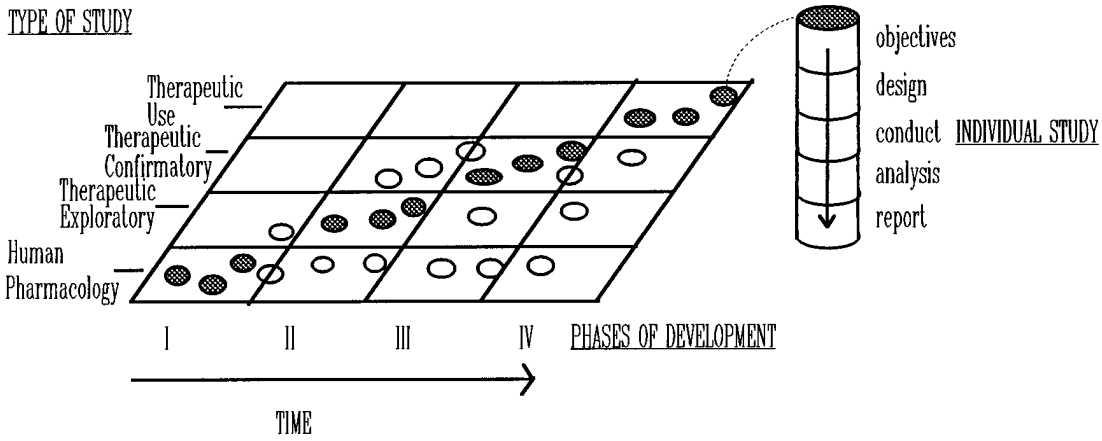
[1] This matrix graph illustrates the relationship between the phases of development and types of study by objective that may be conducted during each clinical development of a new medicinal product. The shaded circles show the types of study most usually conducted in a certain phase of development, the open circles show certain types of study that may be conducted in that phase of development but are less usual. Each circle represents an individual study. To illustrate the development of a single study, one circle is joined by a dotted line to an inset column that depicts the elements and sequence of an individual study.

Figure 1.—Correlation Between Development Phases and Types of Study[1]



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Drug development is ideally a logical, 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 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 efficacy 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. In addition, to support a new marketing application approval for the same drug, e.g., for a new indication, pharmacokinetic or therapeutic exploratory studies are considered to be in Phase I or Phase II of development.

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.

Although 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 and 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 is usually intended to determine the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions that can be expected. These studies typically include both single and multiple dose administration.

(b) Pharmacokinetics

Characterization of a drug's absorption, distribution, metabolism, and excretion continues throughout the development plan. Their preliminary characterization is an important goal of Phase I. Pharmacokinetics may be assessed via separate studies or as a part of efficacy, safety and tolerance studies. Pharmacokinetic studies are particularly important to assess the clearance of the drug and to anticipate possible accumulation of parent drug or metabolites and potential drug-drug interactions. 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; these are generally performed in phases beyond Phase I, but studies in animals and in vitro studies of metabolism and potential interactions may lead to doing such studies earlier.

(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 efficacy and may guide the dosage and dose regimen in later studies.

(d) Early measurement of drug activity

Preliminary studies of activity or potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage.

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 efficacy in patients.

Initial therapeutic exploratory studies may use a variety of study designs, including concurrent controls and comparisons with baseline status. Subsequent trials are usually randomized and concurrently 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 relatively narrow criteria, leading to a relatively homogeneous population, and who are closely monitored.

An important goal for this phase is to determine the dose(s) and regimen for Phase III trials. Early studies in this phase often utilize dose escalation designs (see ICH E4) to give an early estimate of dose response and later studies may confirm the dose response relationship for the indication in question by using recognized parallel dose-response designs (could also be deferred to phase III). Confirmatory dose response studies may be conducted in Phase II or 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 demonstrate, or confirm therapeutic benefit.

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 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 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. These studies carried out in Phase III complete the information needed to support adequate instructions for use of the drug (official product information).

3.1.3.4 *Phase IV (Variety of studies: Therapeutic use).* Phase IV begins after drug approval. Therapeutic use studies go beyond the prior demonstration of the drug's safety, efficacy 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 studies that were 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 use under the approved indication, e.g., mortality/morbidity studies, epidemiological studies.

3.1.3.5 *Development of an application unrelated to original approved use.* After initial approval, drug development may continue with studies 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, necessitating a new development plan.

The need for some studies may be obviated by the availability of data from the original development plan or from therapeutic use.

3.1.4 Special Considerations

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

3.1.4.1 *Studies of drug metabolites.* Major active metabolite(s) should be identified and deserve detailed pharmacokinetic study. 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 recommended. For drugs that are frequently coadministered, it is usually important that drug-drug interaction studies be performed in nonclinical and, if appropriate, in human studies. This is particularly true for drugs that are known to alter the absorption or metabolism of other drugs (see ICH E7), or whose metabolism or excretion can be altered by effects of 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 that need to be taken 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.

Particular attention should be paid to the ethical considerations related to informed consent from vulnerable populations and the procedures scrupulously followed (see ICH E6).

(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. Followup evaluation of the pregnancy, fetus, and child is very important. Similarly, for clinical trials that include pregnant women because the medicinal product is intended for use during pregnancy, followup of the pregnancy, fetus, and child is very 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 appropriate 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 guidances 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 efficacy and/or assessment of pharmacokinetic parameters and pharmacological, physiological, or biochemical effects.

3.2.2 Design

The appropriate study design should be chosen to provide the desired information. Examples of study design include parallel group, crossover, factorial, dose escalation, and fixed dose-dose response (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 (see ICH E9). 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 stage of development and the indication to be studied should be taken into account in selecting the subject population (e.g., normal healthy subjects, cancer patients or other special populations in early phase development) as should 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.

As a general principle, trial subjects should not participate concurrently in more than one clinical trial but there can be justified exceptions. Subjects should not be enrolled repetitively in clinical trials without time off treatment adequate to protect safety and exclude 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 that 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 have an adequate control group. Comparisons may be made with placebo, no treatment, active controls, or of different doses of the drug under investigation. The choice of the comparator depends on, among other things, the objective of the trial (see ICH E9 and E10). Historical (external) controls can be justified in some cases, but particular care is important to minimize the likelihood of erroneous inference.

3.2.2.3 *Number of subjects.* The size of a trial is influenced by the disease to be investigated, the objective of the study, and the study endpoints. Statistical assessments of sample size should be based on the expected magnitude of the treatment effect, the variability of the data, the specified (small) probability of error (see ICH E9), and the desire for information on subsets of the population or secondary endpoints. In some circumstances, a larger database may be needed to establish the safety of a 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 and may be insufficient in some cases (e.g., where long-term use in healthy individuals is expected).

3.2.2.4 *Response 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 that are chosen to assess drug effects that are related to pharmacokinetic parameters, pharmacodynamic measures, efficacy and safety. A primary endpoint(s) should reflect clinically relevant effects and is typically selected based on the principal objective of the study. Secondary endpoints assess other drug effects that 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 surrogate endpoint is an endpoint that is intended to relate to a clinically important outcome but does not in itself measure a clinical benefit. Surrogate endpoints may be used as primary endpoints when appropriate (when the surrogate is reasonably likely or well known to predict clinical outcome).

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

3.2.2.5 *Methods to minimize or assess 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 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 investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and analysis of data are also unaware of the treatment assignments, the study is double blind.

(c) Compliance

Methods used to evaluate 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 guidance and in accordance with other pertinent elements outlined in ICH E6 and other relevant ICH guidances (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 (see ICH E6). 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, on the content of safety reports, and on privacy and confidentiality of data (see ICH E2A, E2B, and E6).

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 response variables, specific hypotheses to be tested, and analytical approaches to common problems including early study withdrawal and protocol violations. A description of the statistical methods to be employed, including timing of any planned interim analysis(es), should be included in the protocol (see ICH E3, E6, and E9).

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 guidances on planning of the protocol (ICH E6), on the analysis plan and 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 (ICH E9).

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 (see ICH E2A).

3.2.5 Reporting

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

4. Annex 1

TABLE 2.—LIST OF RELEVANT ICH GUIDANCES 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
M3	Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals
S6	Safety Studies for Biotechnology-Derived Products

Dated: December 10, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 97–32877 Filed 12–16–97; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care Financing Administration

[Document Identifier: HCFA–R–26]

Agency Information Collection Activities: Proposed Collection; Comment Request

AGENCY: Health Care Financing Administration.

In compliance with the requirement of section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995, the Health Care Financing Administration (HCFA), Department of Health and Human Services, is publishing the following summary of proposed collections for public comment. Interested persons are invited to send comments regarding this burden estimate or any other aspect of this collection of information, including any of the following subjects: (1) The necessity and utility of the proposed information collection for the proper performance of the agency's functions; (2) the accuracy of the estimated burden; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) the use of automated collection techniques or other forms of information technology to minimize the information collection burden.

Type of Information Collection Request:

Extension of a currently approved collection; *Title of Information Collection:* Clinical Laboratory Improvement Amendment (CLIA) and the Information Collection Requirements (ICRs) contained in the Supporting Regulations 42 CFR 493.1–2001; *Form No.:* HCFA–R–26 (OMB# 0938–0612); *Use:* The ICRs referenced in 42 CFR 493.1–.2001 outline the requirements necessary to determine an entities compliance with CLIA. CLIA requires laboratories that perform testing on human specimens to meet performance requirements in order to be certified by HHS. HHS conducts inspections in order to determine a laboratory's compliance with the CLIA requirements. CLIA implements certificate, laboratory standards and inspection requirements.; *Frequency:* As needed; *Affected Public:* Individuals or Households, Business or other for profit, Not for profit institutions, Federal Government, State, local or tribal government; *Number of Respondents:* 149,700; *Total Annual Responses:* 631,459; *Total Annual Hours:* 9,133,625.

To obtain copies of the supporting statement and any related forms for the proposed paperwork collections referenced above, E-mail your request, including your address, phone number, OMB number, and HCFA document identifier, to Paperwork@hcfa.gov, or call the Reports Clearance Office on (410) 786–1326. Written comments and recommendations for the proposed information collections must be mailed within 60 days of this notice directly to the HCFA Paperwork Clearance Officer designated at the following address: HCFA, Office of Information Services, Information Technology Investment Management Group, Division of HCFA Enterprise Standards, Attention: Louis Blank, Room C2–26–17, 7500 Security Boulevard, Baltimore, Maryland 21244–1850.

Dated: December 5, 1997.

John P. Burke III,

HCFA Reports Clearance Officer, HCFA Office of Information Services, Information Technology Investment Management Group, Division of HCFA Enterprise Standards.

[FR Doc. 97–32859 Filed 12–16–97; 8:45 am]

BILLING CODE 4120–03–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care Financing Administration

Document Identifier: HCFA–R–205 and HCFA–R–206

Emergency Clearance: Public Information Collection Requirements Submitted to the Office of Management and Budget (OMB)

AGENCY: Health Care Financing Administration.

In compliance with the requirement of section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995, the Health Care Financing Administration (HCFA), Department of Health and Human Services, is publishing the following summary of proposed collections for public comment. Interested persons are invited to send comments regarding this burden estimate or any other aspect of this collection of information, including any of the following subjects: (1) The necessity and utility of the proposed information collection for the proper performance of the agency's functions; (2) the accuracy of the estimated burden; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) the use of automated collection techniques or other forms of information technology to minimize the information collection burden.

We are, however, requesting an emergency review of the information collections referenced below. In compliance with the requirement of section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995, we have submitted to the Office of Management and Budget (OMB) the following requirements for emergency review. We are requesting an emergency review because the collection of this information is needed before the expiration of the normal time limits under OMB's regulations at 5 CFR, Part 1320. This is necessary to ensure compliance with section 111 of HIPAA necessary to implement congressional intent with respect to guaranteeing availability of individual health insurance coverage to certain individuals with prior group coverage. We cannot reasonably comply with the normal clearance procedures because public harm is likely to result because eligible individuals will not receive the health insurance protections under the statute.

HCFA is requesting OMB review and approval of this collection by 12/31/97, with a 180-day approval period. Written comments and recommendations will be accepted from the public if received by the individuals designated below by 12/29/97. It should be noted that HCFA will continue to consider and respond as appropriate to the public comments received in response to the 04/08/97 **Federal Register** notices requesting public comment on the collections referenced below. During this 180-day period, we will publish a separate **Federal Register** notice announcing the initiation of an extensive 60-day agency review and public comment period on these requirements. We will submit the requirements for OMB review and an extension of this emergency approval.

Type of Information Request: Extension, without change, of a currently approved collection.

Title of Information Collection: Individual Health Insurance. Reform: Portability from Group to Individual Coverage; Federal Rules for Access in the Individual Market; State Alternative Mechanisms to Federal Rules BPD–882–IFC.

Form Number: HCFA–R–205 (OMB approval #: 0938–0703).

Use: These information collection requirements help ensure access to the individual insurance market for certain individuals and allows the States to