CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

General Considerations for the Clinical Evaluation of Drugs

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Food and Drug Administration

FOREWORD

The purpose of these guidelines is to present acceptable current approaches to the study of investigational drugs in man. These guidelines contain both generalities and specifics and were developed from experience with available drugs. It is anticipated that with the passage of time these guidelines will require revision. In order to keep them current a re-review will be performed approximately every 18 to 24 months.

These guidelines are not to be interpreted as mandatory requirements by the FDA to allow continuation of clinical trials with investigational drugs or to obtain approval of a new drug for marketing. These guidelines, in part, contain recommendations for clinical studies which are recognized as desirable approaches to be used in arriving at conclusions concerning safety and effectiveness of new drugs; and in the other part they consist of the views of outstanding experts in the field as to what constitutes appropriate methods of study of specific classes of drugs. In some cases other methods may be equally applicable or newer methods may be preferable, and for certain entirely new entities it is possible that the guidelines may be only minimally applicable.

Under FDA regulations (21 CFR 10.90(b)) all clinical guidelines constitute advisory opinions on an acceptable approach to meeting regulatory requirements, and research begun in good faith under such guidelines will be accepted by the Agency for review purposes unless this guideline (or the relevant portion of it) has been formally rescinded for valid health reasons. This does not imply that results obtained in studies conducted under these guidelines will necessarily result in the approval of an application or that the studies suggested will produce the total clinical information required for approval of a particular drug.

Many of the clinical guidelines have been developed largely, or entirely, by FDA's Advisory Committees and consultants. Others were originally developed by intramural committees and consultants of FDA and of the Pharmaceutical Manufacturers Association; in these cases the guidelines were reviewed and revised, as appropriate, by FDA's Advisory Committees.

The general guidelines for the evaluation of drugs in infants and children and most of those for study of various drug classes in children were developed by the Committee on Drugs of the American Academy of Pediatrics (AAP). Some of the pediatric guidelines for specific classes were written by FDA's Advisory Committees. There was cross review and comment on the pediatric guidelines by both the Committee on Drugs of the AAP and FDA's Advisory Committees.

The Bureau of Drugs of the FDA wishes to thank the many individuals who devoted so much time and effort to the development of these guidelines.

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GENERAL CONSIDERATIONS FOR THE CLINICAL EVALUATION OF DRUGS

INTRODUCTION

The objective of clinical investigations is to assess whether a drug is of value in the treatment or prophylaxis of a disease or condition, its risks or undesirable effects, and the relative relationship of these assessments. Investigations of this nature must be conducted in such a way that the participating subjects, or patients, are exposed to the least possible risk consistent with the anticipated benefit.

These guidelines have been developed from experience with prior drugs. The guidelines will require modification with completely new entities, active in a way never before experienced, although it is anticipated that the general principles will remain valid. The guidelines must not be used to force new compounds into their mold else the fruit of original ideas may be lost. History is replete with discoveries that could not have been made if the investigation was constrained by established methods.

The investigator, the sponsor, and the regulatory agencies must recognize the need in drug evaluation for the exercise of sound scientific clinical judgement by the investigator, based on his experience in the field of study, together with the highest regard for the rights, safety, comfort and well-being of the test subject or patient. Obviously, any aspect of an individual study, the nature and frequency of laboratory tests, period of drug administration, interval between visits, etc., while generally outlined, must remain subject to modification in the best interest of the patient. Because the investigator is responsible for administration of the investigational drug, he also must have the ultimate responsibility for the welfare of the subject or the patient. Institutional review and informed consent will provide additional safeguards for the test subject. The principles concerning institutional review and informed consent are stated in the March 13, 1975 FEDERAL REGISTER, Technical Amendments concerning "Protection of Human Subjects" (45 CFR Part 46) and the following have been extracted for the purpose of this guideline.

A. Institutional Review

1. An institutional Review Board must be composed of no less than five persons with varying backgrounds to assure complete and adequate review of activities commonly conducted by the institution. In addition to possessing the professional competence necessary to review specific activities, the Boarc must be able to ascertain the acceptability of applications and proposals in terms of institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. The Board must therefore include persons whose concerns are in these areas.

2. No member of a Board shall be involved in either the initial or continuing review of an activity in which he has a conflicting interest, except to provide information requested by the Board.

3. No Board shall consist entirely of persons who are officers, employees, or agents of, or are otherwise associated with the institution, apart from their membership on the Board.

B. Principles of Informed Consent

1. A fair explanation of the procedures to be followed, and their purposes, including identification of any procedures which are experimental;

2. a description of any attendant discomforts and risks reasonably to be expected;

3. a description of any benefits reasonably to be expected;

4. a disclosure of any appropriate alternative procedures that might be advantageous for the subject;

5. an offer to answer any inquiries concerning the procedures; and

6. an instruction that the person is free to withdraw his consent and to discontinue participation in the project or activity at any time without prejudice to the subject.

Prior to onset of studies, investigators must determine criteria which will be used to reach a decision to discontinue the test drug. These criteria may be altered during the studies as safety dictates. To help protect the safety of the subject or patient, the sponsor must assume the responsibility of initiating and maintaining proper follow-up of patients through the investigator. There is some risk associated with every investigational drug; despite guidelines, complete safety cannot be assured.

The guidelines are intended as overall guides to the clinical investigation of drugs and as such must be concerned primarily with generalities. The place for specifics is in the protocols of individual investigators in which details can be specified much more precisely in relationship to the preclinical and clinical data available on the compound at the time of the proposed investigation.

While there are obvious advantages to outlining the general sequence for phases of drug evaluations, the cardinal logic behind serially conducted studies is that the result of each prior study influences the plan of the following study. Frequently, natural landmarks are apparent for the review of data and modification of plans. The early clinical data should be reviewed and evaluated by the sponsor and the FDA as they become available so that the continuing and expanding evaluation of the compound can proceed expeditiously.

While it is both rational and desirable to design studies with a specific plan to obtain specific information, the generation of data justifying conclusions other than those originally anticipated is a very valuable result of clinical investigation, and the significance of the data is in no way reduced because it was not anticipated in the original design.

These guidelines are concerned with human studies. For evey set of clinical guidelines, it is assumed that adequate preclinical investigations have been conducted to indicate that the drug does indeed merit human trials and that animal pharmacology and toxicology appropriate for the proposed clinical trials have been accomplished. Some of the specific guidelines describe in vitro or animal pharmacologic tests which are particularly appropriate for the drug class under study. Animal findings relevant, or possibly relevant, to the safety and effectiveness of the drug should be considered in designing specific clinical protocols.

DESIGN AND ANALYSIS CONSIDERATIONS

1. Statistical expertise is helpful in the planning, design, execution and analysis of clinical investigations and clinical pharmacology in order to ensure the validity of estimates of safety and efficacy obtained from these studies.

2. It is the objective of clinical studies to draw inferences about drug responses in well defined target populations. Therefore, study protocols should specify the target population, how patients or volunteers are to be selected, their assignment to the treatment regimens, specific conditions under which the trial is to be conducted and the procedures used to obtain estimates of the important clinical parameters.

3. Good planning usually results in questions being asked which permit direct inferences. Since studies are frequently designed to answer more than one question, it is useful in the planning phase to consider listing of the questions to be answered in order of priority.

4. Certain principles are generally followed in the conduct of clinical trials. These are, to a large extent, stated in the May 8, 1970 Federal Register Statement concerning "adequate and well-controlled clinical investigations" (21 CFR 314.111). The principles are as follows:

The need:

a. To clearly state the objective(s) of the study.

b. To define the selection criteria (including diagnostic criteria and reasons for exclusion) and to show comparability of the population studied with the population likely to receive the medication (target population).

c. To document the method of randomization and the analysis performed to verify how well the randomization procedure worked.

d. To plan the suitable size of a clinical experiment. This will also depend upon appropriate decisions concerning the precision desired:

(1) the degree of response one wishes to detect,

(2) the desired assurance against a false positive finding, and

(3) the acceptable risk of failure to demonstrate the response when it is, in fact, present in the population.

e. To include, when appropriate, comparison group(s), usually simultaneous.

f. To perform studies blind whenever feasible, as a means of avoiding patient and physician response bias and selection bias.

g. To use objective methods of observation where possible and appropriate.

h. To rigorously define response variables (parameters), including description of methods of observation and quantification.

i. To maintain strict adherence to the protocol, if possible, or to document any modifications that may be necessary or desirable.

j. To specify limitations imposed upon the study by failure to comply with the written protocol (withdrawals, failure of randomization to produce similar groups, etc.) with some idea of the effect the limitation might have on the result.

5. A statement as to the rationale for a particular length of the study may be helpful. A clinical trial should be of sufficient length so that efficacy or the lack of it can be clearly demonstrated.

6. Any pooling of data across investigators or studies should be accompanied by specific summaries for each investigator or study and a statement as to the rationale for pooling the results.

7. The report of findings should include a description and documentation of the statistical methods used. This description of the methods used should be adequate to demonstrate their appropriateness.

SELECTION OF SUBJECTS

The propriety of any given study and the selection of the subjects for the study must be viewed in the total context of the study. This includes, among other considerations, the qualifications of the responsible investigator, the investigational facilities available to him, the proposed plan of investigation, the amount of information available on the compound, the patient population available to the investigator, and the availability of adequate peer review.

However, drugs should be studied in all age groups, including the geriatric, for which they will have significant utility. See Sections on "Women of Childbearing Potential" and "Evaluation in Children."

NUMBER OF PATIENTS

Some of the specific drug class guidelines suggest the number of patients which should be included in certain types of studies, based upon previous experience with these studies. These numbers must not be considered as absolute. The overriding consideration should be that the planned studies will provide the desired data while keeping to a minimum the number of subjects at risk. This often requires the contribution of the clinical biostatistician in sample size estimation.

RANDOMIZATION OF PATIENTS

Although randomization of patients among various treatment groups is generally satisfactory when one is treating the same disease, it is often preferable to stratify patients prior to grouping them. This will help to ensure appropriate analysis of results among subgroups that may be more or less responsive to the drug.

STUDY CONTROL

Some of the guidelines suggest that placebo groups should be included in the very earliest trials of the drug. This is desirable, but need not be interpreted as a strict requirement. The purpose of the earliest human trials of a new compound is gradually to build up the dose to a pharmacologic effect or side-effect level. This can often best be done on an open (non-blind) basis. The most important requirement for this phase of clinical trial is that the patient be under careful and continuous observation. In some instances, initial efficacy evaluation can also be accomplished with least risk by open studies against a historic baseline. The speed with which blind comparisons with placebo and/or positive controls can be fruitfully undertaken varies with the nature of the compound.

During all phases of clinical investigation the objective in using a placebo is to control the study adequately. It should be recognized that there are other methods of adequately controlling studies. In some studies, and in some diseases, the use of an active control drug rather than a placebo is desirable, primarily for ethical reasons. If a drug gives a positive dose response, this in itself may constitute adequate control in some studies. In some diseases or conditions where the natural course of the disease or the condition is predictable and in which objective measurements of therapeutic or prophylactic response can be made, carefully executed open studies may be compared to the historical data to provide acceptable evidence

of efficacy. Some studies should be designed to ascertain the degree of safety and effectiveness of the investigational drug in comparison with one or more marketed drugs for the same indication.

With the majority of investigational drugs, placebo and/or active drug controlled studies are necessary.

PATIENT COMPLIANCE

A serious problem in clinical drug evaluation is the degree of adherence by the patient to the dosage schedule. Protocols for controlled studies should state clearly how compliance is to be monitored and the degree of compliance acceptable for continuation in the study. If it is apparent at follow-up visits that patients are not complying, the reasons for their noncompliance should be determined. Efforts to keep these patients in the study should be as conscientious as those for the patients who are complying. All patients initially included in studies must be reported regardless of the degree of compliance. Inclusion of data on patient compliance and noncompliance enhances the credibility of a study. Certain aspects of noncompliance may necessitate evaluation within special subgroups, e.g., failure to take the drug under study, excessive use of alcohol, or use of other medications.

DOSAGE CONSIDERATIONS

It is desirable to ascertain a range of effectiveness so that the lowest effective dose and, when feasible, the highest safe and effective dose are determined.

Consideration should be given to varying dosage according to patient response in some double-blind placebo-controlled studies involving drugs where individual patient response is expected to be quite variable.

DRUG DYNAMICS STUDIES

Metabolic studies have on occasion led to the discovery of new drugs with a variety of therapeutic uses. Present knowledge of metabolic pathways may give clues to the chemist as to what metabolites will be formed.

In view of the well-established variations in metabolism among animal species, each drug must be evaluated individually regarding how much of the metabolic assessment is meaningful at each stage of the investigation. Uniform requirements for metabolic studies are therefore not appropriate.

The one standard requirement should be an attempt, at or soon after initial introduction into humans, to assess absorption characteristics (with exception of i.v. preparations) and plasma half-life by chemical determination of blood, urine, and fecal levels after single and multiple doses. Metabolic studies in humans may confirm whether man's metabolic disposition of the compound is similar to one or more of the animal species used in the preclinical pharmacology, toxicology and metabolic studies.

A search for drug metabolites is frequently incorporated in the study of a new drug, but at this time, with certain exceptions, not enough is understood about the relevance of these findings to assessment of safety and effectiveness. Animal studies, however, will often allow a judgement about whether drug action or toxicity involves a metabolite. A complete study of drug metabolism should be contingent upon the specific drug in question, its potential usefulness and stage of development.

Generally, early detailed metabolic studies in humans are not warranted. The technical problems involved may be great enough to preclude such studies altogether. Where feasible,

however, they should be performed along with the clinical studies since they may be of assistance in the design of the later clinical trials.

In the later stages of clinical trial, since the drug is administered to large numbers of patients, more detailed investigations on metabolism and protein binding are indicated.

Controlled studies for drug interactions and enzyme induction are highly desirable during the course of the clinical trials. Drugs which are frequently administered concomitantly should be studied in patients with the disease under treatment by the investigational drug. Obviously, from the practical standpoint, a selection must ordinarily be made. For example, a patient with arteriosclerotic heart disease and angina pectoris, receiving an investigational coronary vasodilator, may be on concomitant diuretic, anti-hypertensive, sedative, or hypoglycemic drugs. Drugs from these categories should be chosen. A patient on a gastric secretory depressant investigational drug for peptic ulcer might also be expected to be on a sedative and/or antacid concomitantly. Whichever drugs are chosen for the study of drug interactions, the information developed should ultimately be placed in the package insert.

TESTS FOR SAFETY

Both the nature and frequency of laboratory and other tests necessary for safe clinical evaluation vary with the compound. At times a clinical observation can be an earlier and more dependable index of an effect than a laboratory test with which that effect correlates. While specific laboratory tests are listed in some of the guidelines, it should be remembered that the most desirable tests to be used change with evolvement of new technology.

DEFINITIONS AND GUIDANCE

DEFINITIONS

Phase I, Clinical Pharmacology is intended to include the initial introduction of a drug into man. It may be in the usual "normal" volunteer subjects to determine levels of toxicity, and, when appropriate, pharmacologic effect, and be followed by early dose-ranging studies in patients for safety and in some cases early evidence of effectiveness.

Alternatively, with some new drugs, for ethical or scientific considerations, the initial introduction into man is more properly done in selected patients. When normal volunteers are the initial recipients of a drug, the very early trials in patients which follow are also considered part of Phase I.

The number of subjects and patients in Phase I will, of course, vary with the drug but may generally be stated to be in the range of 20-80 on drug.

Drug dynamic and metabolic studies, in whichever stage of investigation they are performed, are considered to be Phase I clinical pharmacologic studies. While some, such as absorption studies, are performed in the early stages, others, such as efforts to identify metabolites, may not be performed until later in the investigations.

Phase II, Clinical Investigation consists of controlled clinical trials designed to demonstrate effectiveness and relative safety. Normally, these are performed on closely monitored patients of limited number. Seldom will this phase go beyond 100-200 patients on drug.

Phase III, Clinical Trials are the expanded controlled and uncontrolled trials. These are performed after effectiveness has been basically established, at least to a certain degree, and are intended to gather additional evidence of effectiveness for specific indications, and more precise definition of drug-related adverse effects.

Phase IV, Postmarketing Clinical Trials are of several types:

1. Additional studies to elucidate the incidence of adverse reactions, to explore a specific pharmacologic effect, or to obtain more information of a circumscribed nature.

2. Large scale, long-term studies to determine the effect of a drug on morbidity and mortality.

3. Additional clinical trials similar to those in Phase III, to supplement premarketing data where it has been deemed in the public interest to release a drug for more widespread use prior to acquisition of all data which would ordinarily be obtained before marketing.

4. Clinical trials in a patient population not adequately studied in the premarketing phase, e.g., children.

5. Clinical trials for an indication for which it is presumed that the drug, once available, will be used.

PHASE I STUDIES

A. Subject and Setting

The studies should ordinarily be performed in adults who are hospitalized or are in other settings permitting close observation. Females who are pregnant, or are at risk of becoming pregnant, should be excluded.

In most cases, "normal" volunteers are involved in the initial studies, except when their use is contraindicated because of the potentially toxic or pharmacologic nature of the drug. With respect to the use of "normal" subjects it should be recognized that few people are literally normal in all respects. This term should be interpreted with caution and should mean volunteers who are free from abnormalities which would complicate the interpretation of the experiment or which might increase the sensitivity of the subject to the toxic potential of the drug. Individuals with mild, but stable, illnesses may be considered for inclusion in the initial study of a drug, e.g., patients with mild, uncomplicated hypertension or arthritis. It is permissible, even desirable, to include subjects with certain abnormalities for which the drug is indicated, e.g., otherwise healthy subjects with hyperlipoproteinemia if an antilipemic agent is being studied.

In lieu of, or supplemental to, the use of "normal" volunteers, in some or many cases, it may be feasible (and in some cases desirable or mandatory) to utilize patients with the disease to be treated. Several small, closely-followed studies may be performed in a metabolic ward or other institutionalized situation. In most cases, women of childbearing potential, children, and patients with serious primary disease and serious unrelated problems (e.g., cardiac, hepatic, renal, hematologic abnormalities) should be excluded from Phase I. In general, patients receiving concomitant drug therapy should be excluded, except perhaps where the concomitant therapy is considered mandatory (e.g., malignancy) or routine (e.g., salicylates in rheumatoid arthritis). Even when concomitant therapy is considered routine, every effort should be made to design and execute trials excluding the concomitant therapy, provided this is consistent with ethical principles of patient care. In general, outpatients should not be utilized as initial recipients of an investigational drug. Exceptions may include but are not limited to:

1. A drug which has been extensively studied abroad.

2. Combinations of well-known drugs.

3. Drugs which have been studied previously for other indications.

4. Drugs whose pharmacologic activity is so well-known that it is considered safe to utilize outpatients, e.g., corticosteroids, estrogens.

5. Marketed drugs which are being investigated by other manufacturers.

6. New formulations of known drugs.

7. Topical preparations.

In cases 1, 3, 5, and 6 it is usually feasible to bypass Phase I and proceed directly to Phase II.

Hospital employees or adult students (volunteers) may, in some cases, be utilized as initial recipients of an investigational drug since they can be under the supervision of the clinical investigator by day, and, if an emergency situation should arise during nights or week-ends, they are knowledgeable with respect to contacting the investigator or other physician.

B. Qualifications of Investigators

Phase I studies involving "normal" volunteers should ordinarily be performed by investigators skilled in initial evaluation of a variety of compounds for safety and pharmacologic effect. Where patients with a specific disease are being studied, the investigators involved should be experts in the particular disease categories to be treated and/or in evaluation of drug effects on the disease process.

C. Procedures

Pretreatment physical examinations and the following laboratory tests should be performed to screen out individuals with medically significant abnormalities: CBC including platelet estimate, urinalysis, BUN (or serum creatinine), liver function studies, FBS (or 2 hour postprandial blood sugar), ECG and any other specifically indicated for the drug under study.

For individuals who will probably be involved in repeated drug testing, G-6-PD deficiency screen should be performed.

Prior to administration of a new drug, whenever feasible, all patients or subjects shall have been off previous drugs (including "over-the-counter" drugs) for at least two and preferably four weeks. In some cases where the previous drug has a prolonged duration of action, a longer "washout" period will be required for return to physiologic state.

1. Single Dose Studies

In a rising single dose study, no subjects should be placed upon the next higher dose until sufficient exposure has occurred with the immediately preceding dose to ascertain that serious adverse effects have not occurred.

The number of subjects in the prolonged dose study is optional. It is desirable to begin with a small group, e.g., 5 on drug and 5 on placebo for a period of 5-7 days to observe for adverse effects, and then move to larger groups. The inclusion of a placebo group is desirable because of the high incidence of side effects reported in institutionalized subjects involved in drug studies (sometimes as many as 40-50% of subjects on placebo report side effects) and because of the possibility of intercurrent infections which may produce laboratory abnormalities and symptoms which could be attributed erroneously to the drug.

In this connection, because of the occasional occurrence of infectious hepatitis outbreaks in an institutionalized setting with resultant hepatic function abnormalities which could be attributed to drug (if the placebo patients happen to be uninvolved

in the outbreak), it may be desirable to perform the prolonged dose study in two or more institutions. Despite the limitations of the test, it may be of interest to determine the presence of Hepatitis-Associated Antigen when one is uncertain about the etiology of hepatic function abnormalities occurring during drug testing.

The prolonged dose placebo-controlled study is usually performed double-blind. The subjects should be seen at least once daily, physical examinations should be performed during and post-therapy and all laboratory examinations should be repeated at least once weekly. The duration of drug administration in the prolonged dose Phase I study, will, of course, vary with the nature of the drug. Where a drug is intended for chronic administration, a period of at least 4-6 weeks of continuous administration is usually utilized unless contraindicated by the toxicity or pharmacologic effect of the drug.

D. Additional Considerations

1. Recent experience with ECG's in supposedly normal adults has demonstrated the occurrence of T wave ST segment abnormalities, bundle branch block, arrhythmias, etc. In cases where these occurred only in the drug group, the sponsors and the FDA have had to conclude that the changes may have been drug related. Therefore, it is desirable to gather a significant amount of ECG data under standardized conditions in "normal" volunteers, monitored and interpreted by experts, to provide information on incidence of various ECG changes.

2. Specialized laboratory tests are indicated from the safety and pharmacologic standpoint when animal studies have demonstrated a potential problem in a target organ or when it is desirable to measure certain pharmacologic effects.

3. Special attention to the possible appearance of certain physical findings is indicated when previous experience with a class of drugs has revealed the occurrence of such abnormalities in animals or man.

4. Blood level studies should be performed with single and with multiple doses of the drug. Sometime during the clinical trials of Phase II and III, methods for determination of blood levels of drug using the non-tagged compound should be developed, if feasible; such delay in development of these methods should be considered only when it is likely that their development would be too difficult and time-consuming to be worth the effort during Phase I.

PHASES II AND III STUDIES

A. Subjects

Patients selected for early Phase II studies should ordinarily be free of hematologic, hepatic, renal, cardiac or other serious diseases. To avoid possible interference with assessment of safety and effectiveness of the investigational drug, they should be receiving no concomitant therapy, if feasible.

Patients in later Phase II studies and Phase III studies may be included (cautiously) if they have concomitant diseases and concomitant therapy since they would be expected to be representative of certain segments of the population who will be receiving the investigational drug following approval for marketing.

B. Qualifications of Investigators

Phase II studies should be performed by investigators who are considered experts in the particular disease categories to be treated and/or in evaluation of drug effects on the disease process. Phase III studies may be performed by experts and/or experienced clinicians, depending upon the nature of the studies.

C. Procedures and Additional Considerations

In Phase II, the frequency of the visits and of the laboratory tests will vary depending upon the nature of, and the safety of, the drug. For some drugs, daily supervision may be necessary. Patients should ordinarily be seen by the investigator at least weekly (or more frequently) for two or four weeks (the duration is dependent upon the number of and the results of Phase I studies and the chemical nature of the drug). Specialized "safety" and pharmacologic laboratory tests should be performed as required by the nature of the drug. Ordinarily, visits should then be biweekly for another six to eight weeks. After three months patients may be seen at monthly intervals for two or three months and bimonthly thereafter. Routine "safety" laboratory tests should be performed at frequent intervals. (CBC's should include platelet estimates.)

When the investigational drug or another active compound is altered significantly in manufacture or use of excipients in order to accomodate a single or double-blind trial, blood level studies (or urinary excretion studies, if blood level studies are not feasible) should be performed to indicate that the alteration has not materially affected its absorption or excretory process. Merely placing a crushed tablet in a gelatin capsule as a means of blinding, for example, would not require bioavailability studies, if dissolution rates are not affected. Any significant change in formulation or manufacture of the investigational drug during the course of late Phase II or Phase III clinical trials will require bioavailability studies so that meaningful comparison can be made among the clinical trials performed with the various formulations.

For chronically administered drugs which are known to be absorbed, complete ophthalmologic examinations (pre- and post-drug) should be performed in a representative number of patients followed for six months, or, preferably longer, on drug. For drugs that are administered for shorter periods in clinical trials, eye examinations should be performed at the end of drug administration; however, the possibility of delayed effects on the eye should be considered.

WOMEN OF CHILDBEARING POTENTIAL

A woman of childbearing potential is defined as a premenopausal female capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception; women who are single; women whose husbands have been vasectomized or whose husbands have received or are utilizing mechanical contraceptive devices. Women in certain institutions, e.g., prisions, although of childbearing potential, could be considered as not in the appropriate environment to become pregnant during administration of an investigational drug. However, women in mental institutions could become pregnant.

In general, women of childbearing potential should be excluded from the earliest dose ranging studies. If adequate information on efficacy and relative safety has been amassed during Phase II, women of childbearing potential may be included in further studies provided Segment II and the female part of Segment I of the FDA Animal Reproduction Guidelines have been completed. All three Segments should be completed before large-scale clinical trials are initiated in women of childbearing potential.

In some cases, women of childbearing potential may receive investigational drugs in the absence of adequate reproduction studies in animals. These include, for example, the use of the drug as a life-saving or life-prolonging measure; use of a drug belonging to a class of compounds (e.g., anti-metabolites) where a teratogenic potential has already been established in animals; use of women who have been institutionalized for a time period adequate to establish a non-pregnant state.

When an investigational drug is used in a woman of childbearing potential for treatment of a serious disease and animal reproduction studies have not been performed, the lack of reproduction studies should be pointed out and fully informed consent should be obtained.

Pregnancy tests should be performed prior to introduction of the investigational drugs and the patient should be advised about suitable contraceptive measures.

For drugs that are absorbed systemically, transplacental passage and secretion in milk of the drug should be assumed until proven otherwise. Fetal follow-up should be carried out in women who become pregnant while on the drug. Excretion of the drug or its metabolites in the milk of lactating women should be determined, when feasible, prior to use of the drug in nursing mothers.

MALE REPRODUCTIVE SYSTEM

Where testicular abnormalities or abnormalities of spermatogenesis have occurred in experimental animals or where chromosomal abnormalities are anticipated (e.g., alkylating agents), the criteria for inclusion of males in Phases I, II and III depend upon the nature of the abnormalities, the dosage at which they occurred, the disease being treated, the importance of the drug, and the duration of drug administration. In some cases, special written consent forms, even in Phase III, may be required.

EVALUATION IN CHILDREN

Drugs with a significant potential for use in children and neonates should be evaluated in these age groups. Usually, studies in children are not attempted until there has been considerable experience in adults (i.e., late Phase II or early Phase III in adults). With certain drugs, of course, early use in children is warranted.

When studies are performed in children, it is preferable to begin with older children, followed by younger children, infants and prematures.

Detailed comment on pediatric studies is contained in the Guideline entitled "General Considerations for the Clinical Evaluation of Drugs in Infants and Children."

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