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# Guidance for Industry

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

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**GUIDELINES FOR THE CLINICAL EVALUATION  
OF  
ANTI-INFECTIVE DRUGS (SYSTEMIC  
(ADULTS AND CHILDREN)**

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Comments on the contents of this publication are invited and should be addressed to the following office:

Group Leader for Anti-infective Drugs  
Division of Anti-infective Drug Products  
Bureau of Drugs  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

## ABSTRACT

The Food and Drug Administration, with the assistance of its scientific Advisory Committees and other outside consultants, the American Academy of Pediatrics' Committee on Drugs, and consultants to the Pharmaceutical Manufacturers' Association has developed guidelines for the clinical evaluation of new drugs. These guidelines present acceptable current approaches to the study of investigational drugs in man, and pertain to Phases I through III of the investigation. They represent generally accepted principles for arriving at valid conclusions concerning safety and effectiveness of new drugs, as well as the views of outstanding experts concerning appropriate methods of study of specific classes of drugs.

The FDA welcomes comments on the guidelines, and expects to keep them current by review and update at approximately two-year intervals.

## 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.

J. Richard Crout, M.D.  
Director  
Bureau of Drugs

Marion J. Finkel, M.D.  
Associate Director for  
New Drug Evaluation  
Bureau of Drugs

# GUIDELINES FOR THE CLINICAL EVALUATION OF ANTI-INFECTIVE DRUGS FOR SYSTEMIC ADMINISTRATION

## ADULT SECTION

### I. INTRODUCTION

"General Considerations for the Clinical Evaluation of Drugs" is an important companion piece and should be reviewed prior to reading these guidelines. It contains suggestions which are applicable to investigational drug studies for most classes of drugs and enables elimination of repetitious material in each of the specific guidelines.

The primary consideration in the early study of a potentially useful anti-infective drug is the action of the drug on microbial agents (bacteria, viruses, or other parasites). When this action has been thoroughly investigated *in vitro*, the next step is to study its effects in laboratory animals. In the case of anti-viral agents, studies in cell cultures are essential to indicate the effectiveness and toxicity of the agent. *In vivo* studies in various animal species will provide general information on the absorption, excretion, distribution of the drug and the metabolic changes in the drug and in the animal. Controlled experiments in suitable animal species infected with various microbes and treated with the drug at various doses may indicate its anti-infective potential. The *in vitro* studies and the *in vivo* studies in animals lead to investigational studies in man.

### II. PHASE I

(See "General Considerations for the Clinical Evaluation of Drugs")

Phase I studies should include determinations of absorption, excretion and plasma clearance of the drug, and, if feasible, metabolic pathways. Single dose studies may be used to obtain the above information. In addition, blood level and excretion data should be obtained employing repeated dose schedules and different dose levels, in order to obtain the optimum schedule which is safe and produces the desired concentration of drug in serum or other body fluids. The decision whether the agent should be studied only in patients who may potentially benefit from the agent will be made partly on the basis of potential toxicity of the drug.

Drug levels in cerebrospinal fluid, bile, other body fluids, organs and tissues should be determined when feasible.

### III. PHASE II

(Also, see "General Considerations for the Clinical Evaluation of Drugs")

#### A. PURPOSE

To obtain information on the efficacy, optimal dosage, and adverse effects in patients with infectious diseases due to a susceptible microbe(s) which are identified and characterized in *vitro*. To obtain additional information in the diseased patient, if needed, on absorption, excretion, distribution and metabolism of the drug.

#### B. SETTING

Such studies are best undertaken in hospitalized or institutionalized patients under 24 hour supervision. This provides great facility for observing the patient closely, adjusting dosage when necessary, and assuring that the drug is actually taken. Certain infectious diseases could also be evaluated in a suitable outpatient setting.

#### C. INVESTIGATORS

Investigators must be experienced in the diagnosis and treatment of infectious diseases.

#### D. INVESTIGATIONS

All studies in patients should include appropriate microbial evaluation. This means precise identification and, where appropriate and feasible, quantitation of the causal microbe(s). Minimal inhibitory concentrations (MIC) of the drug for the causative microbe(s) should be obtained immediately prior to administration of the drug. In the case of persistence of microorganisms, similar studies should also be done during and at the conclusion of therapy. Serologic confirmation of infections should be obtained when indicated and wherever possible. Whether or not microbial cure is achieved, changes in the clinical condition of the patient and in the infectious disease at the end of therapy should be described.

#### E. DURATION OF THERAPY AND OBSERVATION

The minimum duration of therapy will vary with the circumstances, i.e. the disease process, the microorganism involved, and the characteristics of the anti-infective drug. It should, however, be standardized as far as possible for each clinical situation. Observation should be continued for an appropriate period after therapy for complications and recurrences of infection, or the appearance of delayed untoward effects.

#### F. DESIGN

1. Phase II studies may be designed in one of two ways:
  - a. Preferably the drug under investigation should be compared with a drug of established efficacy for the disease under study. The drugs should be administered randomly. This type of study should preferably be blinded. When no effective drug control is available, a placebo control is desirable.

- b. When design (1) is not ethically, medically, or scientifically feasible or not necessary, the therapeutic response to a new drug may be compared with the therapeutic response obtained by an earlier regimen, preferably one with which the investigator has experience in the same institution.
2. In addition to the usual observations consonant with all good clinical investigations, the following are recommended:
  - a. The microbial status, including quantitation, before, during, and after therapy.
  - b. Concentrations of the drug in blood, urine, and whenever possible, in cerebrospinal fluid and other body fluids in selected patients in order, particularly, to attempt to relate these levels to outcome of therapy.
3. Documentation of the following is important:
  - a. The demographic background of the patient (age, sex, race, place of birth, prior medical history, etc.).
  - b. The physical status (clinical evaluation) before, during and after therapy.
  - c. The microbial status before, during and after therapy.
  - d. The range of dose and duration of therapy.
  - e. Concentrations of the drug in blood, urine and whenever possible, in cerebrospinal fluid and other body fluids.
  - f. Appropriate laboratory measurements before, during, and after therapy.
  - g. Concomitant drug therapy, if any.
  - h. Side effects associated with the administration of the drug under investigation. (Signs and symptoms.)
  - i. Investigator's comments about features of the patient relevant to the assessment of effect of the drug.
  - j. For out-patients: Evidence of compliance, such as urine excretion or serum levels of the drug.

#### **IV. PHASE III**

##### **A. PURPOSE**

Extension of clinical studies to evaluate the usefulness of the drug in a wide variety of conditions, so as to obtain a broad picture of safety and efficacy.

##### **B. PROCEDURES**

The data from a number of investigators who studied comparable populations of patients may be pooled to achieve an adequate number of patients for each specific infectious disease. Appropriate measures should be taken, however, to assure validity of such pooling.

The number of patients to be studied will depend on a number of factors: one is availability and suitability of patients; another is the drug under investigation. For example, if the drug under study is intended to be used for a wide variety of infectious diseases, a significant number of patients of all age groups for whom the drug is appropriate should be treated for each general indication, e.g. lower and upper respiratory tract infections, osteomyelitis, acute and chronic urinary tract infections, peritonitis, meningitis, encephalitis, etc.

Adverse effects should be recorded in detail. In addition to routine clinical evaluation and laboratory tests of hepatorenal and hematopoietic function, it may be necessary to carry out some special studies; for example, tests of auditory and vestibular function and observations for appearance of dermatologic, allergic, ophthalmic and dental abnormalities. If the drug has potential long-term toxic effects, there should be long-term followup.

## V. SPECIAL STUDIES

Studies of the kinetics of the drug in patients undergoing dialysis and in patients with varying degrees of renal failure may be desirable, depending upon the therapeutic indications of the drug.

## PEDIATRIC SECTION

### I. INTRODUCTION

"General Consideration for the Clinical Evaluation of Drugs in Infants and Children" should be reviewed prior to reading this section.

Guidelines for the evaluation of anti-infective agents in infants and children can only be formulated in general terms, because exceptions would need to be noted for many of the points made. For example, a drug with considerable potential toxicity might be life-saving under specialized circumstances, or certain agents might have their greatest use in limited age groups or specific situations, such as in the treatment of diseases occurring during the newborn period or a type not commonly encountered in hospitalized populations. Thus, guidelines should permit maximum flexibility, allow for modifications under suitable circumstances, and not attempt to proscribe certain approaches when these are appropriate. In general, the design of a study should utilize populations which are appropriate for the potential usefulness of the specific agent. For example, anti-infective drugs whose major application would primarily be in the treatment of gram-negative sepsis and meningitis in the newborn, should be tested in these patients, rather than in older children where similar diseases occur only rarely.

It is recognized, that there are no "ideal" anti-infective drugs which, theoretically, are agents whose use results in the prompt eradication of an offending pathogen without affecting the host or his normal flora. The best that can be done, under existing circumstances, is to attempt to approach this ideal. Thus, studies of anti-infective drugs in infants and children should determine the efficacy of an agent against a specific pathogenic organism and the disease produced by it, as well as the immediate, intermediate, and long-term toxicity of the drug in each specific age group, such as immature infants, newborns, and older children. Since the physiology of immature and newborn infants differs from each other and from that of older children, it is necessary to develop accurate information on specific phenomena important in the appropriate age group, such as albumin-binding and bilirubin displacement in the newborn period, the effect of an agent on a developing nervous system, its effect on protein synthesis, its propensity for sensitization, and its metabolism and excretion in more or less mature



organ systems. In other words, anti-infective agents should be evaluated in terms of the physiologic and pharmacologic characteristics of the age group for which they will be used. Furthermore, some of these drugs, although generally used for short periods of time, may need to be used repeatedly. Thus, information concerning cumulative toxicity and sensitization should be developed, if possible.

## II. CLINICAL STUDIES

Children should ordinarily not be included in clinical trials until late Phase II or Phase III unless the infection to be studied is restricted to the young age period. Even in these cases safety studies should first be performed in adults. Exceptions can be made for a life-threatening infection when the investigational drug offers greater promise than accepted therapy.

For design of clinical studies see Adult Section of these guidelines and the considerations outlined below under specific infections. In addition to studies of safety and effectiveness of the drug, pharmacokinetic studies should also be performed in children. Under appropriate circumstances, in order that basic pharmacokinetic data for the study drug may be obtained in the evaluation of an aminoglycoside antibiotic during the newborn period, a single dose of the drug under study may be substituted for a dose of the anti-infective agent which the patient is receiving as part of his regular therapy. Biostatistical consultation may greatly aid the design of studies in children to provide maximal information on metabolism, safety and efficacy on a minimal number of children with the least amount of physical and psychological trauma.

A number of common infectious diseases of children are selected and discussed below as an expression of some of the problems which accompany these disease states in children. Examples selected are not intended to limit the disease states in which anti-infective agents can be evaluated in children.

### Streptococcal Infections

The diagnosis of streptococcal infections, such as pharyngitis, pyoderma or otitis, must be confirmed by culture.

In the case of streptococcal pharyngitis, a defined clinical picture, which includes pharyngitis, must accompany the positive culture, as the carrier state is not rare. Cultures from the pharyngotonsillar area are considered positive for Group A beta hemolytic streptococci by the presence of 10 or more colonies on a blood agar plate from throat swabs incubated promptly, preferably in 5 percent CO<sub>2</sub>.

All initial isolates of streptococci should be saved. If follow-up cultures are positive for strep, the paired cultures should be compared by typing. If this is not possible, no conclusion can be drawn as to relapses vs. reinfection with a new strain.

Treatment with either the test drug or a control drug should be continued for 10 days. Because effective therapy may be available with several drugs, one of these, preferably a penicillin, should be used as a control. Clinical response to the drug should be monitored and recorded. At least three follow-up cultures are indicated (e.g., days 5, 14, and 31 after starting therapy). Comparisons of culture results at 5 days may be helpful in evaluating comparative efficacy.

It is essential in Phase II studies and desirable in Phase III studies to obtain acute and convalescent sera for titers to ASO and at least one other extracellular product.

There should be follow-up of the patients at 4-6 weeks. At the end of this time, clinical evaluation, throat culture and, if positive, grouping and typing, and urinalysis should be done. Distinction can now be made between cure, cure with relapse, cure with reinfection and failure. The goal of the treatment of streptococcal pharyngitis is the prevention of rheumatic fever and/or nephritis; therefore, it would be desirable to have data indicating that the drug is capable of preventing these complications.

#### **H. Influenzae Epiglottitis**

Diagnostic criteria should include clinical epiglottitis associated with a positive culture of *Hemophilus influenzae* Group B from the epiglottis or from a carefully obtained naso-pharyngeal culture. (A positive blood culture is further support of the diagnosis.)

The clinical response is assessed by duration and height of fever, occurrence of hoarseness, time for recovery, duration of hospitalization, and the necessity for non-routine tracheostomy or intubation. Comparison of culture results at appropriate times is also useful.

#### **Otitis Media, Acute**

To be included in the study, patients must have clinical evidence of acute otitis media (evidence of inflammation of the tympanic membrane and middle ear). It is necessary to confirm the presence of exudate in the middle ear by pneumotoscopy and needle aspiration to obtain fluid for culture.

Treatment is then begun with the study drug or an active control, usually administered for 10 days. Cultures of other sites such as the throat are usually not helpful. For a small number of patients, second needle aspiration is desirable, as it affords an opportunity to obtain data on antibiotic concentrations in the middle ear fluid and the promptness of bacteriologic cure. Concomitant therapy, such as decongestants, should be used in all patients or not used in any. The protocol must include some method of evaluating compliance.

Evaluation of results should be made on the basis of:

Estimate of need for reaspiration of fluid (preferably by pneumotoscopy).

Clinical course; remission of fever, pain and other symptoms.

Changes in appearance of tympanic membrane (perforation, presence of exudate, mobility, etc.).

Comparison of the group receiving the therapeutic regimen of aspiration and study drug to the active control group.

The follow-up period should include a check for relapse of infection, within 4 weeks.

In the absence of culture of middle ear fluid, no specific claim can be made regarding the effectiveness of any anti-infective drug.

#### **LOWER RESPIRATORY INFECTIONS**

The protocol should outline criteria by which the etiological diagnosis is made, including x-rays. Throat or naso-pharyngeal cultures cannot be used as evidence of infectious processes in the lungs. It is difficult to establish the diagnosis of bacterial pneumonia. A positive blood culture accompanying an appropriate clinical syndrome is strongly presumptive evidence. In children, transtracheal aspiration cultures are considered presumptive but not definitive evidence of etiology of lower respiratory infections.

Aspiration of pleural fluid and lung puncture are acceptable mechanisms for establishing a diagnosis. The detection of bacterial antigen in appropriate fluids by counter-immune electrophoresis may represent a suitable method for etiologic diagnosis under certain circumstances, as may serologic studies for rises in specific antibody to microbes such as mycoplasma, pneumococci, etc.

In the absence of bacteriological diagnosis, no specific claim can be made for an anti-infective drug.

Efficacy evaluation should include clinical, laboratory and x-ray changes.

(N.B., the culture media and incubation techniques chosen for the diagnosis of lower respiratory infections should support the growth of fastidious strains such as *H. influenzae*, etc.)

## **ACUTE URINARY TRACT INFECTIONS**

In any study of urinary tract infections, patients with anatomical abnormalities should be considered subgroups of the patient population.

### **Diagnosis**

In infants and young children, needle aspiration of the bladder is safer and less traumatic than catheterization. In this age group, this method is preferable. Diagnosis of infection may be made from a single specimen if any pathogens are present. The majority of patients with urinary tract infections have 100,000 colonies/ml or more.

A colony count of 10,000 - 100,000/ml in a clean catch, catheterized or aspirated specimen is suspicious and should be repeated. For a diagnosis of infection from clean catch specimens, there should be two successive specimens showing 100,000 colonies or greater per ml. Clean catch specimens are feasible and should be encouraged in older patients. Recognized standard methods for collecting should be described in each protocol.

*E. coli* strains should be serotyped, when possible, to differentiate between relapse and reinfection with a new serotype.

The usual *in vitro* susceptibility measurements reflect serum rather than urinary levels of the drug, and thus may be unsuitable for predicting the susceptibility of urinary tract infections. Concentration of active antibiotic in the urine may convert relatively ineffective serum levels to extremely effective urinary levels. Therefore, a good indication of drug efficacy is a determination as to whether the organism is eradicated after 48-72 hours of treatment.

### **Follow-up**

Urine specimens should be cultured at these intervals:

1. Pre-treatment.
2. The first 48-72 hours of therapy.
3. Post-treatment (as soon as the drug is no longer present in the urine).
4. 7-10 days after completion of therapy.

To be considered efficacious, bacteria should be eradicated (or sharply reduced in colony count) by 72 hours after initiation of drug therapy.

If the original organism recurs following completion of therapy, the patient is classified as "cure with relapse." If the urine remains sterile following therapy, the patient is classified as "cured." If the original organism is eradicated and infection with a different strain occurs during follow-up, the patient is classified as a "cure with reinfection."

#### **DIARRHEAL DISEASE RELATED TO RECOGNIZED ENTEROPATHOGENS**

(Shigella, Salmonella, Enteropathogenic and/or Enterotoxic E. coli, Parasites and Protozoa)

Patients under study in Phase II should be hospitalized. During treatment of the infection, effects on kidney, liver and bone marrow should be monitored. The effect of the drug on the bowel flora and infectious organism should be evaluated by daily stool cultures using techniques which will allow recognition of overgrowth with fungi, *Klebsiella-Enterobacter*, etc.

If orally "non-absorbable" drugs are administered to patients with enteritis, studies should be done to determine possible absorption of the drug through the inflamed bowel wall.

Taking into consideration baseline data on the natural history of the disease (including duration of finding pathogens in the stool), studies should include daily rectal swabs or stool cultures during therapy and follow-up specimen examinations after completion of therapy and at weekly intervals for at least 4 weeks to evaluate persistence and carrier state.

Evaluation of drug efficacy is based primarily on elimination of the pathogen from the stool. Other parameters of efficacy may include number and character of the stools, clinical assessment of hydration and degree and duration of fever. The day on which the character of the stools changes from diarrheal to "normal" should be recorded. For infants, the day of onset of steady weight gain should be recorded.

Concomitant therapy should include fluids and electrolytes, but not symptomatic antidiarrheal therapy.

It is desirable to estimate the optimum duration of therapy on the basis of clinical studies.

#### **MENINGITIS**

##### **Diagnosis**

The bacteriologic diagnosis must be based on examination of spinal fluid including culture with appropriate procedures. CSF culture must be positive for inclusion of a patient in the study. In a great number of central nervous system infections, the infection may be caused by a variety of infecting organisms. Therefore, until the pathogen is positively identified, the drugs employed must have a spectrum of activity to cover both gram positive and gram negative organisms. Immediately upon identification of the causative organism, more specific therapy is indicated.

##### **Treatment**

Ideally, these early studies should be confined to small numbers of patients. Depending on the clinical course, it is usually desirable to evaluate drug efficacy by daily lumbar punctures until cultures are sterile. Some of the fluid so obtained may be used for determination of antibiotic concentrations, which should be compared to concomitant serum concentrations to evaluate steady state equilibration. (One parameter of

effectiveness is how long it takes to sterilize the spinal fluid, particularly in meningitis due to bacteria other than pneumococcus, meningococcus and *H. influenzae*. "Sterile" spinal puncture is negative both on smear and culture.) Because daily lumbar puncture may not be without inherent dangers, this evaluation should be carried out only in small numbers of children.

All medication should be administered intravenously initially. Duration of treatment should be based initially on experience with the standard drug for the causative organism.

During therapy, renal, hepatic and hematologic function should be carefully monitored.

#### **Follow-Up**

The children should be followed for an appropriate time to determine gross psychomotor development and presence or absence of any neurologic defects. Whenever possible, follow-up should include vestibular and auditory function one year post-treatment compared with a control group. A year or more after the illness the following should be noted: Subsequent development of seizures, evaluation of psychomotor function, presence or absence of neurological deficit, subsequent development of intellectual function, and personality or behavioral changes.

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