Guidance for Industry

Developing Antimicrobial Drugs — General Considerations for Clinical Trials

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4573, or from the Internet at http://www.fda.gov/cder/guidance/index.htm.

For questions on the content of the draft document contact Renata Albrecht 301-827-2336.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
July 1998
Clin-Anti

X:\TRANSFER\GUIDANCE\ANTI-\2580DFT.WPD
7/21/98

TABLE OF CONTENTS

Draft - Not for Implementation

GUIDANCE FOR INDUSTRY[1]

Developing Antimicrobial Drugs — General Considerations for Clinical Trials

I. INTRODUCTION

This is one in a series of guidance documents intended to assist the pharmaceutical industry in the development of antimicrobial drug products. This document presents general guidance on designing, implementing, and analyzing data from clinical trials for antimicrobial drug products. Additional companion guidances are being developed to address issues specific to individual indications.

The Agency believes that providing this information will be useful to drug sponsors as they plan the necessary clinical studies, design clinical protocols, implement and monitor the conduct of clinical studies, collect the relevant data for analysis, and perform the appropriate types and numbers of analyses of the study data. Clinical trials planned and conducted as recommended in this Agency guidance should yield the kind of information the Agency can use to determine whether the antimicrobial drug under study is safe and effective in the treatment of the specific infection studied.

The Agency intends this guidance to serve as a focus for continued communication among the divisions in ODE IV and with the pharmaceutical industry, the infectious disease academic community, and the public. As the collective knowledge of these classes of drug products expands and as the clinical trial process involving these drug products matures, The Agency anticipates that this document will change to reflect that new knowledge. In addition, in the coming years, the Agency plans to develop guidance on other individual indications and add them to this series. Guidance on the development of antiviral drug products will be provided in future documents.

---

[1] This guidance has been prepared by the Office of Drug Evaluation IV, representing the Division of Anti-Infective Drug Products, the Division of Special Pathogens and Immunological Drug Products, and the Division of Anti-Viral Drug Products, in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on antimicrobial drug product development. 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.

II. BACKGROUND

Over the years, the Agency has issued guidance to the pharmaceutical industry on the development of antimicrobial drugs for the treatment of infections in a variety of forms. The intent of this general guidance and its companion guidances on individual indications is to provide basic information on antimicrobial drug product development. This guidance document is a result of efforts to collect all pertinent information on antimicrobial drug development and present it in one location. Where appropriate, this guidance contains relevant information from several sources, including

- *Clinical Evaluation of Anti-Infective Drugs (Systemic)*, FDA, 1977
- *Guidelines for the Evaluation of Anti-Infective Drug Products,* IDSA,1992[2]
- *Points to Consider, Division of Anti-Infective Drug Products, Clinical Development and Labeling of Anti-Infective Drug Products* (1992) (*Points to Consider*), an FDA document on issues related to evaluating new drug applications for anti-infective drug products
- *Evaluating Clinical Studies of Antimicrobials in the Division of Anti-Infective Drug Products* (February 1997), an early draft FDA guidance that was discussed at a March 1997 advisory committee meeting on anti-infective drug products and which this guidance will supersede once it is issued in final form.

Antimicrobial drug products do not usually exert their intended therapeutic effect directly on the human, as do most other human drug products. Rather, the human therapeutic effect is the result of the drug's ability to kill or inhibit the growth of microorganisms. Pharmacologic effects on humans are usually unintended adverse events. Standardized in-vitro techniques may be used on antimicrobial drug products to generate reproducible data on the amount of drug required to kill or inhibit the growth of certain microorganisms in an in-vitro setting. The in-vitro setting, however, does not reproduce the exact conditions of drug/microbe interface in the human host.

Techniques for assessing the pharmacokinetic properties of certain antimicrobial drug products in humans provide information on the rate and extent of drug present in various body tissues and fluids. The human host normally does not present a constant level of antimicrobial exposure to the microorganism, and the in-vitro methodology does not replicate the intrinsic defense mechanisms of the human host. Nonetheless, one can gain useful knowledge when in-vitro and human pharmacokinetic data are applied in concert. Primary questions in establishing clinical

[2] This guideline appeared in IDSA's (Infectious Disease Society of America) supplement to *Clinical Infectious Diseases* (formerly *Reviews of Infectious Diseases)*, vol. 15, Sup. 1, November 1992.

effectiveness of an antimicrobial drug product include how much and what kind of human clinical data are required to corroborate and confirm the in-vitro/pharmacokinetic assumptions about the product.

In the sections that follow, guidance on a variety of issues, including microbiology, toxicology, chemistry, and the design and conduct of clinical trials is provided and recommendations are made as to what information should be included in the application submission.

If, after consulting these guidance documents, questions about any of these areas remain, manufacturers may wish to contact appropriate Agency staff to discuss specific issues that arise in the development of a specific antimicrobial drug product to facilitate product review, approval, and labeling. In particular, applicants wishing to develop a unique antimicrobial drug should discuss clinical development plans with the applicable division prior to the initiation of a capital-intensive development program.

III. MICROBIOLOGY

Before an anti-infective drug is used in humans, it should be tested in vitro and in animals to characterize its antimicrobial effects. Such studies yield important information on the drug's biological activity against representative microorganisms and potential efficacy in model systems. In-vitro studies are designed to (1) demonstrate anti-infective activity against target microorganisms in vitro, (2) examine culture conditions that might affect the assessment of antimicrobial activity, (3) determine interactions (synergistic, additive, and antagonistic) with other anti-infective agents, (4) provide information on mechanisms of action and on the potential for the development of resistance, and (5) develop interpretation criteria and quality control ranges for in-vitro susceptibility testing.

In general, studies in animals are designed to (1) provide preliminary information useful in selection of dosage schedules for humans, (2) determine potential antimicrobial activity in general and in specific infections, and (3) evaluate the potential activity of drugs that cannot be adequately evaluated using in-vitro methods. The following parameters should be considered.

A. Mechanism Of Action

If known, information on the mechanisms of action of the therapeutic agent should be reported. This provides insight regarding the static or cidal nature of the drug’s action, the development of resistance through alterations in the drug's target sites, the potential for inactivation by enzymes, and/or elimination by efflux mechanisms.

B. Antimicrobial Spectrum

The activity of a new drug against a panel of pathogenic bacteria including Gram-positive and Gram-negative species, aerobes, facultative anaerobes, and obligate anaerobes should be determined. In addition to type strains obtained from the American Type Culture Collection (ATCC), the panel should include isolates with known mechanisms of resistance such as those available in the form of *challenge sets* from the Center for Disease Control and representative recent isolates from a variety of clinical settings, such as outpatient and inpatient settings and community, teaching, and government hospitals. Repeat isolates from the same patient should not be used. Other organisms that may be considered for testing are rickettsiae, mycoplasmas, chlamydiae, spirochetes, and mycobacteria. Similar panels of microorganisms should be collected for assessing the activity of antifungal and antiprotozoal agents. The activity measured should be compared with that of currently approved drugs, especially those of the same class as the new agent. This information will provide insight on the potential clinical efficacy of the drug.

C. Susceptibility Testing Systems

Susceptibility testing methods should be standardized prior to clinical trials of the drug. The methods should be standardized with respect to the inoculum concentration, the chemical composition and physical state (solid or liquid) of the growth medium, pH, osmolarity, ionic strength, concentrations of cations and growth factors, as well as environmental conditions such as temperature, partial pressure of various gases, and moisture. Once the methods have been standardized, the tentative breakpoints should be chosen largely to differentiate subpopulations of isolates according to factors such as pharmacokinetic properties, serum protein binding, and agreement with alternate susceptibility testing methods. The tentative breakpoints usually become the final approved breakpoints for the drug, but the final breakpoints may be adjusted from the tentative breakpoints to accommodate host-parasite interactions that affect the activity of the drug. Breakpoints should be incorporated into dosage form labeling when standardized susceptibility testing methods are available or proposed for a particular antimicrobial drug.

Adjustments also may be made to accommodate organisms such as *Haemophilus* spp. and *Streptococcus pneumoniae*, whose nutritional and cultural needs do not fit the typical patterns of most bacteria. These anomalous species frequently require separate standardization and separate breakpoints.

Historically, FDA has asked for performance standards for susceptibility testing systems. Today, these performance standards take the form of quality control (QC) limits.

Tentative QC limits should be based on statistical analyses of the central tendencies of replicate susceptibility testing measurements using specific well-characterized bacterial isolates. Tentative QC limits can be adjusted to accommodate a perceived need to move most clinical susceptibility testing results away from false susceptible readings.

D. Emergence and Mechanism(s) of Resistance

Accepted in-vitro methods should be used to provide for detection of emerging antimicrobial resistance. The potential for cross-resistance to anti-infective agents of the same class or other classes should be evaluated.

The development of resistance in organisms outside the population of organisms targeted by the anti-infective should be evaluated. Information on the mechanism of resistance and the method by which this resistance might be transferred to other microorganisms should be included in the submission if known.

Information on whether the anti-infective agent can induce the production of enzymes or other methods of resistance, if known, should be included in the submission. Any information on the ability of the anti-infective to inhibit enzymes known to degrade anti-infective agents should also be included in the submission. These data will be evaluated to determine whether the anti-infective is susceptible to known mechanisms of resistance to the same class of drugs.

E. Synergistic, Additive, Antagonistic, and Indifferent Effects

Drug interactions can result in synergistic, additive, antagonistic, and indifferent effects. These effects can be determined using a variety of techniques. One technique involves measuring the activity of combinations of serial dilutions of two anti-infectives in an isobologram (checkerboard titration). The use of time-kill curves may help complete the characterization of these effects.

F. Intracellular and Subcellular Concentrations

Where appropriate with certain anti-infective agents, the determination of the degree of intracellular penetration or the subcellular concentration may be helpful. This information is particularly useful if the target pathogen is phagocytized, but not killed by host defenses. Ex-vivo studies may be appropriate. Any ability of the anti-infective to diminish or enhance the activity of phagocytic cells should be included in the submission.

G. Evaluation of Anti-infective Drugs in Animals

The potential use of anti-infective drugs for treatment of some well-defined infections can be examined in animals. Animals can be used to identify which diseases in humans may be most suitable for clinical trials of a new anti-infective drug. Testing in animals can help explore the advantages and disadvantages of combination therapy, pharmacodynamic considerations, the penetration of the drug into infected sites, the timing of prophylaxis, the clearance of organisms by the reticuloendothelial system, and intracellular killing. Several useful models have been developed to determine a drug's potential in treating infective endocarditis, meningitis, pneumonia, peritonitis, and pyelonephritis, as well as infections in the neutropenic host.

IV. PHARMACOLOGY AND TOXICOLOGY

In general, animal toxicity studies are intended to inform the clinical investigators about the potential toxicities associated with the investigational drugs so that those effects may be monitored during the clinical investigations. Baseline evaluation of safety includes monitoring for signs and symptoms of adverse events and laboratory screening (e.g., chemistry, hematology, urinalysis). However, if animal testing suggests specific toxicities to organs or tissues (e.g., hearing loss, renal toxicity, hyperplasias, bleeding), monitoring should be carried out during the clinical study to detect such potential toxicities.

Results of animal studies also should be considered when selecting dosage regimens to be tested in humans. They should be considered when determining what organ systems might be at risk for toxicity and what safety monitoring should be undertaken. Preclinical toxicology tests should identify the toxicologic profile (e.g., the complete spectrum of toxicities that a drug might elicit). Animal toxicity data may identify toxicities not produced in humans. Conversely, animal toxicity data may not always identify a toxicity that is produced in humans.

In most circumstances, acute and repeat dose toxicity studies should be completed in a rodent and a nonrodent mammalian species. The routes of drug administration in the animal studies should mimic the intended clinical route, and the durations of animal testing should be equal to or exceed the durations of the anticipated clinical trials. In addition, Segment I, II and III reproductive toxicity studies as well as various in-vitro and in-vivo clastogenicity and mutagenicity studies, should be undertaken according to recommended guidance. (See also guidance developed as part of the International Conference on Harmonisation (ICH).)

Chronic, carcinogenicity, and special studies (e.g., photo co-carcinogenicity) should be performed when appropriate. Pharmacokinetic studies in the animal species should be performed to identify

those pharmacokinetic parameters comparable to humans and to verify the applicability of the animal species used in the toxicity tests.

Certain potential toxicities cannot be investigated ethically in humans. In such cases, tests should be undertaken in either animal models or in in-vitro assays. The results of these studies should be included in the appropriate sections of the product label to inform prescribers. Examples of such studies include investigations for impairment of fertility, teratology, mutagenicity, carcinogenicity, and overdosage. Chronic and carcinogenicity studies generally do not need to be done because anti-infective drugs are used for short-course therapy except in special circumstances (e.g., cystic fibrosis).

Dose selection should be made in consultation with the reviewing division (e.g., reviewing pharmacologist and clinical reviewer) and should be based on the doses shown to have an acceptable safety profile in animals.

V. CHEMISTRY ISSUES

Chemistry issues pertinent to clinical trials and the evaluation of data that should be considered include the stability of a compound under various storage conditions, stability over time, and purity of the compound, including any possible toxic impurities or breakdown products. A number of Agency guidance documents are available on a range of chemistry issues.

VI. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Clinical pharmacology includes the study of drug pharmacokinetics and pharmacodynamics in humans to optimize treatment of patients. Pharmacokinetics (absorption, distribution, metabolism, and excretion) and biopharmaceutics (dissolution, bioavailability, including drug/food interactions) information should be available prior to beginning clinical studies with patients. For example, an oral drug product should not be administered to patients with meals before the effect of food on the bioavailability is known. Food has been shown to significantly diminish the rate (peak plasma concentration (CMAX)) and/or extent (area-under-the-curve (AUC)) of absorption of anti-infective drugs. This reduction in systemic availability may diminish the therapeutic effect of a drug.

The extent of availability, effective concentration range, and drug clearance are pharmacokinetic parameters that will help define the appropriate dosing rate of a drug for a particular route of administration. Knowledge of additional pharmacokinetic parameters (volume of distribution, blood/plasma concentration ratio, extent of protein binding, and extent of metabolism) also can

be used to anticipate changes in the disposition of the drug in different disease states.

The plasma half-life of the drug is an important pharmacokinetic parameter in deciding the dosing frequency. The time needed to achieve steady-state drug concentrations in plasma, as well as the time needed to establish new steady-state concentrations after a change in dosage regimen, is a function of the drug elimination half-life. However, alterations in half-life should be carefully interpreted since half-life is a function of both drug clearance and volume of distribution. Clearance and volume of distribution may change with a given disease state or with alterations in normal physiological function.

Pharmacodynamics can establish the relationship between the dose of the anti-infective drug and its antimicrobial activity. A combined pharmacokinetics/pharamacodynamics (PK/PD) evaluation includes relating drug concentrations in plasma to the in-vitro susceptibility of the target microorganisms and/or clinical outcomes. Usually, plasma drug concentrations are related to minimum inhibitory concentrations (MIC). In addition, the drug concentration-time profile can be transformed to a single measure of exposure (e.g., AUC or time above the minimum inhibitory concentration (T>MIC)) and related to microbiological and/or clinical outcome to determine the optimal dosage regimen. The choice of pharmacodynamic variable (e.g., AUC/MIC, CMAX/MIC, T>MIC) will depend upon the mechanism of antimicrobial effect. This type of PK/PD assessment should be conducted throughout the drug development program. Incorporation of a PK/PD assessment in clinical trials can be a useful addition to the efficacy and safety database.

In the clinical study of anti-infective drug products, dose selection, dose regimen, and duration of therapy should take into account the biopharmaceutics, pharmacokinetics, and pharmacodynamics of the drug/drug product, as well as consideration of the disease state or other patient characteristics that may alter these properties.

Half-life is also important in considering the time intervals for evaluating treatment outcomes after drug therapy, that is, the test-of-cure visit. (In general, it takes approximately seven half-lives for more than 90 percent of the drug to be eliminated from the body.) For drugs with short half-lives (e.g., one hour), the time interval for plasma concentrations to decrease to insignificant levels after the last dose may be seven hours. For drugs with longer half-lives, this time interval can extend to a period of weeks. However, half-life of the drug is not the only consideration to determine when a test-of-cure visit should take place. The development of a schedule to evaluate treatment outcomes should consider the pharmacokinetic and pharmacodynamic characteristics of the drug, the site of infection, the infecting organism, and host factors. Issues related to appropriate follow-up and other changes to protocol design in clinical development of agents with long half-lives or unusual pharmacokinetic and pharmacodynamic characteristics should be brought to the attention of the reviewing division and addressed at the time of protocol design and

implementation.

Tissue distribution studies that demonstrate (at the dosing regimen requested in the NDA) that the investigative agent diffuses into the infected body site and maintains concentrations equal to or above the MIC_{90} of the claimed pathogens for an adequate time period may provide data that are supportive of clinical effectiveness. This suggestion does not imply that the adequacy of all such testing methodology has been verified for all infected sites or that the relevance of all such data to clinical effectiveness has been established. Rather, these are simply suggested studies to obtain data to help support the data derived from the adequate and well-controlled clinical trials to which the antimicrobial drug product has been subjected.

VII. PROTOCOL PLANNING

When planning a protocol, it is important to consider the purpose and objective of the study, the indication being sought, the various questions about the drug's safety and efficacy that should be answered, the probable labeling and marketing strategies, and how the pursuit of a given indication fits into the overall drug development plan.

Planning should also take into account the uniqueness of the particular drug under study. Although it is desirable to have clear and detailed guidance for individual indications and include specific steps, procedures, and time points for evaluation for each infectious disease indication, it may be impossible to apply the criteria literally to each possible study scenario because of differences among drugs, drug classes, disease states, and patient populations. Failure to consider these kinds of critical issues in the protocol planning could result in a flawed clinical trial.

VIII. PROTOCOL ISSUES AND ELEMENTS

A. Purpose and Objective

The purpose and objective of the protocol should be stated clearly at the beginning of each protocol. The statement should include, but not be limited to, a discussion of the drug, dose, target population, and goal of the study.

B. Trial Design

1. Blinding

Studies should be double-blinded (the investigator and the patient are blinded) whenever possible to ensure that no bias is introduced. When double blinding is not possible, a sound justification should be offered, and the protocol should state how the objectivity of the participants will be ensured. For example, an objective primary endpoint, such as microbiological culture, may be used when the laboratory is masked to the patient's treatment regimen and to whether the specimen was obtained at entry, at the on-therapy visit, or at the test-of-cure visit. If radiographic examination or histological examination were considered the primary endpoint, blinding of the evaluators to all aspects of the patient's treatment would be expected.

2. Open Trial

Because of concern about selection bias on the part of the investigator in open trial designs, a patient registration log should be maintained by each investigator or site (as appropriate). All patients with the disease under investigation presenting to the investigator (or co-investigators) should be entered by initial in this registration log. The log should document the reason for not enrolling a given patient in the trial. Registration log books should be submitted as part of any NDA in which such trial results serve as critical effectiveness data. Generally, any appearance that patients were pre-selected for the study could invalidate the study unless adequate explanation is provided.

C. Randomization

See Section XX, Statistical Considerations.

D. Inclusion Criteria

Patients enrolled in the study should have the disease intended for study. The specific characteristics that determine whether the patient meets the inclusion criteria are specified in the companion guidances on individual indications. As specified originally in *Points to Consider*, patients can be evaluated for their clinical response to treatment, or they may be evaluated for clinical and microbiological response to treatment. The circumstances and conditions under which these evaluations are appropriate are described in the companion guidances according to the individual indication.

Patients should have a complete history and physical examination at entry, both to confirm the diagnosis under study and to exclude other diagnoses.

E. Exclusion Criteria

Exclusion criteria generally are designed to (1) exclude patients who do not have the disease under study, (2) exclude patients whose disease has progressed to a stage where drug intervention may be too late or inadequate to assess activity, (3) protect patients from a potentially unacceptable risk of adverse event, or (4) exclude patients with a serious underlying disease in whom drug safety evaluation is confounded by already existing morbidity. In general, therefore, patients should be excluded from studies if there is a risk that their disease, underlying condition, and situation make it unlikely that their participation would yield information on a drug's efficacy and safety. Otherwise, the risk of participation in the study may not result in benefit either for the patient or the study outcome.

Depending on the drug under study, patients can be excluded from clinical studies for any of the following reasons:

- Patients with known or suspected hypersensitivity to or a known or suspected serious adverse reaction to the agent under study or a related member of that class of agents.

- Patients who have received any other investigational drug within 1 month prior to screening or enrollment.

- Patients who have received antimicrobial therapy for the same condition within 7 days prior to enrollment.

- Patients at risk for serious drug interactions because of concomitant drugs.

- Patients who are receiving other medications or who have other disease conditions that could interfere with the evaluation of drug efficacy or drug safety.

- Patients who were previously enrolled in the trial.

- Patients with any concomitant condition that, in the opinion of the investigator, would preclude evaluation of response or make it unlikely that the contemplated course of therapy and follow-up could be completed.

- Patients with a concomitant infection that needs to be treated with an additional antimicrobial agent.

- Patients with renal failure who are on hemodialysis, peritoneal dialysis, plasmapheresis, or hemoperfusion.

F. Distinguishing Severity of Infection from Complexity of Infection

Applicants should carefully distinguish in their protocol and proposed product labeling between the severity of a disease entity (mild, moderate, or severe) and the complexity of a disease entity (complicated or uncomplicated). Often these terms are used interchangeably and result in confusion on the part of investigator, applicant, and FDA reviewer. A severe case of an uncomplicated disease should not generally equate with a complicated disease. Likewise, a mild case of a complicated disease entity should not routinely equate with an uncomplicated disease.

G. Clinical Microbiology Issues

1. Laboratory Expertise

The microbiologists should be experienced in routine microbiology procedures as well as in recovering anaerobic and fastidious organisms, identification of organisms to the species level, susceptibility testing, storage, and retrieval.

To qualify for participation in clinical trials the laboratory should participate in a recognized inspection and quality control or proficiency program. The laboratory should be certified to perform testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). (See 42 CFR 493.3 for laboratories exempt from regulation by CLIA.)

Note: Laboratories under the jurisdiction of the Department of Veterans Affairs (VA) are regulated by the VA and not by CLIA.

Outside the U.S., a variety of certification agencies exist. If foreign laboratories are used, due to variation in regulations, the quality control and quality assurance procedures and standard operating protocols should be made available for review.

2. Standard Guidance for Diagnosis and Case Definitions

Each study protocol should outline specific clinical and microbiological procedures for diagnosis and follow-up as well as criteria for the specific infection under study. All protocols used during the clinical trials (specimen collection, transport, primary isolation, identification, susceptibility testing, and quality control) should

be submitted in as much detail as possible. Examples of criteria to be considered for optimal diagnosis and case definition are listed here.

a. Timing of Specimen Collection

Protocols should designate how long before and after administration of the study drug a specimen should be collected. Prior therapy should be noted since it may distort the evaluation of clinical efficacy and obscure the detection of valid pathogens. It is essential to define an acceptable interval for transport.

b. Specimen Collection and Transport

The technique used for collecting specimens should be defined for each type of infection studied. It is especially important that specific, uniform criteria be established for sites of infection that are not readily accessible or for circumstances in which the specimen is expected to contain normal flora. Examples of problematic infections include osteomyelitis, in which drainage, aspirates, and/or surgical specimens may be collected; endometritis, in which specimens may be collected by protected brush or by aspiration or by biopsy; and urinary tract infection, in which defined clean-voided procedures and culture methods and uniform interpretive guides differentiating infection from colonization or contamination should be used. Specimens should be transported to the laboratory as promptly as possible, and specimen storage conditions and methods of transport should be defined. The maximal interval allowable from collection to processing in the laboratory should be specified for all specimen types.

3. Quality of Specimens

Direct smears and Gram staining as well as other types of stains, if relevant, should routinely be used as an aid in evaluating specimen quality and the relevance of subsequent growth. Assessment of respiratory tract specimens, especially expectorated sputum, underscores the importance of careful adherence to strict clinical criteria and uniform clinical microbiology laboratory procedures. Protocols should take into account semi-quantitative estimates of numbers of white blood cells, epithelial cells, and bacterial morphotypes in smears, to aid in evaluating and interpreting the amounts of growth of potential pathogens in cultures.

4. Identification of Microorganisms and Parasites to the Species Level

In general, identification to the species level should be done routinely. Procedures such as those outlined in the *Manual of Clinical Microbiology, Clinical Microbiology Procedures Handbook,* or those used with FDA-approved commercial kits can be used to identify isolates that are likely to be the cause of infection.

5. Serological Diagnosis and Direct Immunologic or Molecular Detection Procedures

A variety of detection procedures have been developed, but each procedure should be validated and verified as to its sensitivity and specificity. For example, for detection of *Mycoplasma pneumoniae* in respiratory specimens, culture procedure may not be as sensitive as direct fluorescent antibody or direct genetic-probe procedures. Likewise, the evaluation of nasopharyngeal specimens may be superior to that of sputum samples, depending on the clinical situation and the test used. Each protocol should define the diagnostic criteria and acceptable methodologies to be used when serological or molecular procedures are recommended and should indicate when appropriate serological or molecular data can be used as a diagnostic alternative if the agent is not isolated from primary specimens (e.g., *Legionalla* or *Mycoplasma).*

6. Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing (AST) procedures should be standardized and should include testing of appropriate quality-control strains at least on each day susceptibility testing is done. Clinical strains (recovered during clinical trials) that are considered pathogenic should be frozen (at -70^{o} C) and saved by the study laboratory. In selected circumstances (e.g., when the patient fails to respond clinically to treatment and/or the presumed pathogen is not eradicated), these microorganisms can be sent to the sponsor or to a reference facility for confirmatory speciation, repeat AST, and characterization of the mechanism of resistance when appropriate.

7. Disk Diffusion

Disk diffusion procedures should follow standardized guidelines. For clinical trials, the detailed protocols should be submitted and zone diameters recorded.

8. Dilution Methods

Standard dilution procedures should be followed. A full range of dilutions should be tested to yield on-scale (rather than off-scale) end points. MIC_{50} and MIC_{90} values for all of the pathogens collected during the clinical trial should be determined. Limited screening dilutions or breakpoint concentrations, rather than full twofold dilution series, are not recommended.

9. Testing of Anaerobes

During clinical trials, testing of anaerobes by broth disk elution screening tests is problematic. In mixed infections, routine antimicrobial susceptibility testing is clinically warranted only for occasional selected anaerobic isolates to guide clinical management. Only when the clinical investigator determines that the research value substantiates the need for the individual patient should more than one anaerobic species from polymicrobial infections be tested. Anaerobes should be considered likely pathogens and antimicrobial susceptibility testing performed when they are recovered in pure culture from specimens such as blood, pleural fluid, or cerebral spinal fluid, or when they are present as pure or predominant isolates from tissue or deep-abscess specimens.

10. Quality-Control Standards

Systematic definition of quality-control standards is important for monitoring the reproducibility and accuracy of in-vitro AST during clinical trials. QC standards for disk diffusion tests using the selected disk concentration should be derived from a study including at least 5 laboratories. At least 5 lots of medium from 2 manufacturers as well as a reference lot of Mueller-Hinton agar medium should be used. Appropriate ATCC quality-control strains should be tested in parallel to the clinical isolates using the same susceptibility testing methodology. Procedures should follow standardized guidelines.

11. Grouping of Pathogenic Species and Special Strain Subsets

In an evaluation of microbiological results and clinical efficacy, the assessment of clinical relevance can be enhanced by approaches such as the following:

a. Collation of infections by broad groups of pathogens (e.g., Gram-positive and Gram-negative) and analysis by species.

b. Analysis of specific resistant isolates within a specific genus and species of an organism such as methicillin-resistant *Staphylococcus*

aureus (MRSA) as a subset distinct from methicillin-susceptible *S. aureus* strains.

c. Comparative analysis of *Haemophilus influenzae, S. aureus, Neisseria gonorrhoeae,* and *Moraxella catarrhalis* based on production of beta lactamase (i.e., beta-lactamase-positive vs beta-lactamase-negative strains), especially if the regimen under study is a beta-lactam antimicrobial drug with or without a beta-lactamase inhibitor.

d. Analysis of penicillin-resistant *Streptococcus pneumoniae* as a subset distinct from the penicillin-susceptible *S. pneumoniae* strains.

e. Analysis of vancomycin-resistant *Enterococcus* as a subset distinct from vancomycin-susceptible *Enterococcus*.

f. Analysis of any subset of Gram-negative organisms demonstrating the production of extended-spectrum beta-lactamases.

g. Analysis of any subset of organisms demonstrating potentially unique resistance patterns and/or mechanism(s) of resistance.

12. Emergence of Resistance

The emergence of resistance should be monitored using speciation, antimicrobial susceptibility testing, and characterization of the mechanism of resistance. Any apparent change in zone diameter or MIC should be confirmed by concurrent testing of the pre- and post-therapy isolates. Likewise, the appearance of a new pathogen (with clinical signs of new infection) should also prompt speciation and antimicrobial susceptibility testing and characterization of the mechanism of resistance.

In general, a fourfold or greater increase in MIC or an equivalent decrease in zone diameter (e.g., more than 3 to 6 mm) suggests a significant change in antimicrobial susceptibility. Such changes should be recorded even if the shift in end point does not represent a change in the proposed interpretive category. Changes in zone diameter or MIC in tests with other drugs should also be recorded in such instances, especially for representative drugs in the same class. The biochemical profile of original and follow-up strains, and the mechanisms of resistance should be recorded when resistant variants or new pathogens emerge. The use of this

procedure may aid in distinguishing a resistant variant of the original isolate from a new superinfecting strain. Additional typing techniques, such as plasmid analysis, may be useful in differentiating such strains definitively. Routine use of these methods is not necessary in clinical trials. However, such typing procedures should be available for application to selected pertinent isolates such as via reference laboratories.

13. Pharmacokinetics/Pharmacodynamics

Pharmacokinetic data at the site of infection for the treatment regimen in question should be determined. Data from pharmacology studies should also be considered when defining susceptible and resistant breakpoints.

Concentrations of the antimicrobial agent in the blood, serum, or urine should be obtained during phase 2 or 3 studies, according to the pharmacokinetic/dynamic profile of the agent under study. Results of such testing may be useful in determining therapeutic versus ineffective drug levels. Similarly, drug levels may help with understanding safety issues.

H. Drug Selection and Dosage Regimen

Decisions about drug selection and dosage regimens, control drug, and any concomitant medications, should be made based on the pharmacokinetic characteristics of the drugs, expected patient outcomes, known information on the control drug, and the role of concomitant medications.

1. Study Drug

The choice of the drug formulation to test and the dosage regimen to be tested should consider the microbiology, toxicology, chemistry, pharmacokinetic data and knowledge of the disease to be studied and the population to be tested.

In protocols where the study involves conversion from intravenous therapy to oral therapy, a complete clinical evaluation should be repeated before the patient is switched from intravenous to oral therapy. Clear clinical and microbiological responses need to be defined in the protocol. In many cases, a microbiological reassessment at the time of the switch would be helpful. The results of the tests and findings should be documented.

In studies of antimicrobials for infections characterized by multiple potential

etiological pathogens, significant morbidity or even mortality in the absence of treatment, or conditions where the causative pathogen is unknown (e.g., febrile neutropenia), consideration should be given to whether the drug to be studied has adequate in-vitro and pharmacokinetic properties to be tested as a single agent or whether the clinical indication to be studied and condition of the patient warrant that initial therapy covers potential pathogens.

Ultimately, the conditions under which a drug is tested would be reflected in the product labeling to enable physicians to use the drug appropriately.

2. Choice of Comparator Agent

The control regimen for the study should be selected based on the following considerations: (1) the drug is approved by the FDA for the treatment of the disease under study — although it may not be feasible to find one that is approved for all the desired target pathogens in the proposed marketing portfolio; (2) the drug continues to have acceptable efficacy rates in the treatment of the disease, as demonstrated by its efficacy in other recent marketing applications or in the peer-reviewed literature; (3) the drug continues to have good in-vitro activity against the bacteria causing the disease; and (4) the drug can be tested in a double-blind manner. Other considerations may also be applicable. The purpose of this is to ensure that the study drug is adequately tested, and a valid assessment of its role in the therapeutic armamentarium can be made. Compliance monitoring should be performed.

In active controlled trials, an applicant can choose a comparator that is approved in the United States for the treatment of that infection. If an applicant chooses to use a comparator agent or dosing regimen (in a trial designed to demonstrate equivalence of the two treatment arms) that is not approved in the United States, it is the responsibility of the applicant to submit in the NDA the data substantiating the comparator agent or regimen as safe and effective therapy.

Applicants should be aware that the so-called *bio-creep* phenomenon is always of concern to the Agency. This phenomenon is the selection of successively less effective comparator agents, each of which individually fits a statistical confidence interval relative to the product to which it was compared. This process, over time, may result in the presumed equivalence of statistically and clinically inequivalent products. Also, the recognized effectiveness of certain products changes with time due to alterations in resistance patterns and development of new knowledge, and the labeling of the products may not keep pace with this experience. To prevent

the occurrence of bio-creep, we advise applicants to discuss comparator agents with the division, if they have any doubts, prior to the initiation of their clinical development program. Products establishing *equivalence* to less effective products should have such information readily available to physicians in the product label. Promotion of such products should also include balanced information regarding the data upon which the product was approved for marketing.

In a clinical trial designed to test an agent that has activity against various resistant organisms and where it is impossible to use a control regimen with equally good coverage against the resistant organisms, the reviewing division should be consulted to determine whether it is appropriate to (1) conduct a clinical study comparing the study drug to a standard but unapproved regimen, (2) establish the natural history of the disease and use a historical control for comparison of efficacy, or (3) consider another alternative.

3. Concomitant Medication

Within individual indications, prescription and nonprescription drugs that may act to alter the signs and symptoms of infections (e.g., antipyretics, analgesics, antihistamines, cough suppressants) should be documented. The use of other antimicrobial therapy in the preceding few days or week (approximately), as well as during the study and through the test-of-cure evaluation period, may affect the patient's clinical course and should be reported. All of this information should be taken into account when evaluating the study results, ideally while blinded to drug therapy, so the reviewer (or the applicant during its analysis) can independently conclude whether or not the patient responded to therapy.

I. Evaluation

The protocol should provide a schedule of the patient evaluation visits and should specify when these visits should take place and what procedures should be performed at each visit. In all studies, a minimum of two evaluation visits, the entry visit and the test-of-cure visit, should be scheduled, and the findings obtained at these visits should be documented in the case report form. In most studies, however, additional visits may be needed. The individual companion documents should be consulted for specific number and timing of the evaluation visits.

In general, evaluation visits can be classified as follows:

1. Entry Visit (Pre-Therapy Visit)

This visit is usually conducted before any antimicrobial treatment is started. Patients are evaluated for baseline signs and symptoms of the disease, have a medical history taken, a physical examination performed, and blood and urine taken for laboratory tests. In most studies, a specimen is obtained for microbiology culture or other appropriate diagnostic testing. Other procedures (x-rays, diagnostic procedures) may be performed depending on the indication under study.

2. On-Therapy Visit

This visit is usually performed to assess whether the patient is responding to treatment and tolerates the test drug. This visit can also be used to review the results of any baseline microbiology cultures and susceptibility testing to determine whether treatment should be modified. This visit is generally considered optional for the purposes of drug evaluation.

3. End-of -Therapy Visit

At this visit, the patient's response to treatment can be assessed. In addition, the patient should be queried about any adverse reactions to the drug, and laboratory tests to evaluate safety also should be performed. This visit should not be used mistakenly as a substitute for the test-of-cure visit.

4. Test-of-Cure Visit (Post-Therapy Visit)

This visit should be available for all patients. Without this visit, it is impossible to make a final assessment of the patient's response to treatment.

The timing of this visit should take into consideration the disease under study and the pharmacokinetic properties of the drug. Thus, for many drugs with a short half-life, the test-of-cure visit would be scheduled within several days or weeks of the completion of treatment. If the drug has a long half-life, the test-of-cure visit should be scheduled more than one or two weeks after completing therapy.

In other infections, where assessment of long-term sequela is important, the test-of-cure visit should be scheduled at an appropriate time after the completion of treatment. For some indications, more than one post-treatment visit is recommended to enable the investigator and reviewer to obtain a complete time

course and clinical picture of the patient's outcome. Specific recommendations are made for individual indications in the companion guidances.

5. Chronic Administration

(Reserved)

J. Safety Evaluation

Patients typically have blood and urine samples submitted for laboratory tests before and after therapy to evaluate drug safety. If any of the post-treatment laboratory values are abnormal, the patient should be followed and the laboratory test repeated to document whether the value returns to normal.

K. Monitoring

Adequate, timely, and appropriate monitoring is critical to ensure completeness and validity of the data submitted. A concern in studies that are poorly designed and/or monitored is having large numbers of unevaluated or inadequately followed patients.

IX. STUDY POPULATIONS

In most clinical studies, both male and female adult patients are enrolled with their age ranges specified. In general, populations who will be taking the drug once it is approved should be included in clinical trials. Any questions about enrolling population subgroups, such as pediatric patients, pregnant or lactating patients, or patients with renal failure should be discussed with the reviewing divisions at the time of protocol design. Once a patient is enrolled in the study based on a presumptive or confirmed diagnosis of the infection under study, every attempt should be made to ensure that the necessary information is collected and that the patient completes the study. Maximizing protocol compliance and obtaining complete documentation on a patient is particularly important in assessing the results of the study and reaching conclusions about the drug's safety and efficacy.

A. Pediatric Patients

Because infectious diseases frequently occur in the pediatric population, the Agency is committed to providing in drug product labeling scientific data regarding appropriate use of antimicrobial drug products in children. In addition, the Modernization Act of 1997 provides incentives to sponsors who perform certain pediatric studies. (See Agency

guidance for industry on *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug and Cosmetic Act*, May 1998.)

Many elements of disease manifestation in children are different from their adult counterparts, and these elements should be considered to ensure that the use of an antimicrobial drug product in a specific pediatric infection will be safe and effective. Some elements include (1) the growth and development characteristics of children; (2) the drug absorption, distribution, and elimination characteristics of children at different ages, including immaturity of detoxification and elimination mechanisms and immaturity of the blood-brain barrier; (3) the diseases that occur specifically in the pediatric population; and (4) the microbiology of certain infectious diseases may be unique to the subgroups of the pediatric population as compared to the same disease in adults.

The Agency has previously stated that it is unnecessary for an applicant to reestablish a drug's effectiveness in children, assuming the applicant has adequately established the drug's effectiveness in adults and assuming the disease pathophysiology and microbiology are the same in children and adults (59 FR 64240, December 13, 1994). In these situations, the correct dosage of the medication in the specific pediatric population under consideration should be established by correlating it with the established effective dose in adults. Likewise in this situation, any specific pediatric safety concerns should be adequately addressed. When it is necessary to conduct pediatric clinical trials to establish efficacy and safety in disease entities different in physiology or microbiology from adult disease entities, where possible, the same scientific standards as for adults should apply to clinical trials to establish effectiveness and safety of a drug product in pediatric populations.

The INDICATIONS AND USAGE and the DOSAGE AND ADMINISTRATION sections and the *Pediatric Use* subsection of the PRECAUTIONS section of final product labeling should be used to detail data from trials as outlined in the three preceding paragraphs.

B. Geriatric Patients

Special concerns are associated with the use of prescription drugs in geriatric patients. The medical community has become increasingly aware that prescription drugs can produce effects in elderly patients that are significantly different from those produced in younger patients. Although both young and old patients can exhibit a range of responses to drug therapy, factors contributing to different responses are comparatively more common among the elderly. For example, elderly patients are more likely to have impaired mechanisms of drug excretion (e.g., deceased kidney function), or to be on other

medications that can interact with a newly prescribed drug, or to have another medical condition that can affect drug therapy.

FDA has encouraged sponsors to include more elderly subjects, especially those over 75 years old, in clinical studies. On March 5, 1990, FDA announced the availability of a guidance for industry entitled *Guideline for the Study of Drugs Likely to be Used in the Elderly*. The guidance emphasizes FDA's recommendation that drugs should be studied in the full range of the patients who will receive them, including the elderly, and that efforts should be made to discover differences in pharmacokinetics related to age, or to conditions associated with age (e.g., decreased renal function, concomitant drugs, concomitant illness), and that clinical data should be analyzed to see whether the drug has different effects, favorable or unfavorable, in the elderly. The guidance provides detailed advice on how to evaluate new drugs in older patients and is intended to encourage routine and thorough evaluation of the effects of drugs in elderly populations so that sufficient information can be provided to physicians. The guidance did not call for, or anticipate, an increase in the number of patients or the number of clinical studies needed to evaluate a new therapy. Based on several FDA surveys, patients over 65 years of age already represented a significant portion of study subjects in most cases. The guidance advised not to exclude the very old, to analyze the data already collected, and to obtain modest additional pharmacokinetic data.

As part of its international harmonization efforts (ICH), the FDA published in the Federal Register of August 2, 1994 (59 FR 39398) a guidance regarding the use of drugs in geriatric populations entitled *E7 Studies in Support of Special Populations: Geriatrics*. The guidance reflects sound scientific principles for testing drugs in geriatric populations and for submitting marketing applications to regulatory authorities worldwide and is consistent with the Agency's 1990 guidance, discussed previously.

Related rulemakings containing additional information pertinent to the use of drugs in geriatric populations include a final rule entitled "Specific Requirements on Content and Format of Labeling for Human Prescriptions Drugs; Addition of a 'Geriatric Use' Subsection in the Labeling," published on August 27, 1997 (62 FR 45313) and a final rule entitled "Investigational New Drug Applications and New Drug Applications," published on February 11, 1998 (63 FR 6854).

The 1997 rulemaking amended FDA regulations governing the content and format of labeling for human prescription drug products, including biological products, to include information pertinent to the appropriate use of drugs in the elderly and to facilitate access to this information by establishing a *Geriatric Use* subsection in the labeling. The 1998 rulemaking amended FDA regulations pertaining to new drug applications (NDAs) to

clearly define in the NDA format and content regulations the requirement to present effectiveness and safety data for important demographic subgroups, specifically gender, age, and racial subgroups. FDA also amended its regulations pertaining to investigational new drug applications (INDs) to require sponsors to tabulate in their annual reports the numbers of subjects enrolled to date in clinical studies for drug and biological products according to age group, gender, and race.

C. Pregnant Patients

Adequate and well-controlled, randomized clinical trials are not typically conducted in pregnant women, except in rare circumstances (e.g., topical vaginal products for certain infections). Most clinical trials of new antimicrobials in phases 1, 2, and 3 do not intentionally include pregnant women. However, women of reproductive age are routinely included in these trials because they reflect the anticipated patient population once the drug is marketed. It is therefore likely that, as for marketed drugs, pregnancy exposures will occur during those trials. When this happens, information on maternal and fetal safety and outcomes should be aggressively pursued, including follow-up to delivery with ascertainment of fetal and neonatal outcomes. Because antibiotics are among the most commonly prescribed drugs in pregnant women, it is important to collect data and provide available information in product labeling on the use of antimicrobial drugs in pregnant women, to the extent possible.

There may be circumstances under which it is reasonable and appropriate to include (or not uniformly exclude) pregnant women in clinical trials of antimicrobial drugs. Examples include trials for topical products, combinations of products already known to be safe for use in pregnancy, or treatments of drug-resistant or life-threatening infections. In these cases, discussion with the reviewing division is advisable for consideration of whether additional protections for the patient should be put in place and what additional data might be collected. For example, pregnant women have altered physiology that includes increased blood volume, increased glomerular filtration, altered gastrointestinal motility and altered cellular immunity. At a minimum, the opportunity to collect basic pharmacokinetic data on an investigational drug in the gravid patient should not be lost. Pharmacodynamic and clinical response data in this population may be very useful, even if from only a few patients. Also, there may be targeted maternal safety information that would be useful to collect based on concerns raised by preclinical studies, keeping in mind the changes in baseline laboratory parameters that accompany the physiologic changes of pregnancy. For drugs that are likely to be used in women of reproductive age, especially those that may require multiple courses or prolonged administration, sponsors should consider the establishment of a prospective pregnancy registry or other studies to collect maternal and fetal safety data either in phase 3 or phase 4 of development.

X. PROTOCOL DESIGN AND IMPLEMENTATION

A clinical trial is only as good as the protocol serving as its foundation. Any successfully performed and completed study starts with a sound, clearly written, thoroughly developed protocol. The protocol serves as the template for all the procedures, tests, or steps that are undertaken, all the data that are collected, and all the information that is recorded in the case record form, during the conduct of a clinical trial. It should follow that if a protocol is well-designed with a clear objective and purpose, if all of its sections clearly address the procedures that should be followed and data that should be collected and if the protocol is implemented correctly and monitored appropriately, the resulting data should be complete and valid and yield useful information on the drug's safety and effectiveness. Particularly in the present climate when drug development and drug review times are being shortened, it becomes very important to *get it right the first time*. Often studies are designed as Phase 1/ 2 or Phase 2/3 trials, each trying to capture earlier in the development process information that can be used to support approval for marketing.

Although a well-designed, scientifically and medically valid protocol is important, a good protocol does not automatically ensure a *well-conducted* clinical trial. The clinical trial will only be considered successful and its results plausible if the protocol is carefully followed, if protocol compliance is high, and if protocol violations of any type are kept to a minimum. This means that the information requested by the protocol should be obtained and documented under the conditions and in the time frames specified in the protocol.

XI. CASE REPORT FORMS

The natural corollary of a good protocol is a clear, logical, organized and complete case report form (CRF). For any protocol submitted to the Agency for review, the sponsor should also provide a sample CRF to identify which data are being collected and how the data collection is organized.

The CRF should contain a field or place to record all individual data points and elements that are described within each section of the protocol. They should be organized either by date or visit or by category of domain or data. It may even be a good idea to plan for case report form annotation early in the process, so that entries made in the CRF can easily be transferred into an electronic data base for subsequent review and analysis.

Under 21 CFR Part 11 (Electronic Signature and Records), some sponsors have elected to collect patient data from clinical trials in electronic form. When this form of data collection is

undertaken, it should be consistent with the regulations. (See Agency guidance on submitting NDAs in electronic format.)

XII. CONSENT FORMS

Consent forms should be written in compliance with 21 CFR Part 50 and should be submitted to the IND along with the protocol. One of the key elements reviewers look for in the consent form, in addition to the required elements, is the clarity and completeness of explaining the risk versus the benefit of the proposed trial and drug and protection of study participants. In pediatric studies, special guidance and attendance to age-specific assent also are important.

XIII. STUDY MONITORING

In addition to good planning and protocol design, a successful study also contains sound monitoring and auditing programs. Such programs should ensure that the protocol was correctly implemented and followed and that investigators and others at the study site, as well as the patients, adhered to the steps and requirements of the protocol. The study sites and their records should be available for examination by staff from the Division of Scientific Investigations (21 CFR 312.62 and 21 CFR 312.68).

XIV. EVALUATING SAFETY

To be eligible for safety assessment, a patient should have received at least one dose of the study drug (or control drug). The safety evaluation is based on the observation of adverse events and the results of pre-treatment and post-treatment laboratory changes.

The challenge in the assessment of safety is to determine whether the event is due to the drug being tested, or whether the event is due to the underlying disease. Therefore, an evaluation is made of findings before therapy compared to findings after therapy, including clinical signs and symptoms volunteered by the patient or noted by the investigator and laboratory results from hematology, chemistry, coagulation, urinalysis, or other tests.

A variety of analyses may be used to characterize the safety profile of a drug. Some of the usual analyses should determine whether effects are related to dose, duration of therapy, age (pediatric, adult, geriatric), or gender.

The analyses should include not only listing of the adverse events reported, but should provide

adverse event groupings by organ system or by adverse event syndrome. For example, individual terms such as *loose stool, unformed stool, liquid stool, diarrhea,* and *bloody diarrhea* should be recognized as being related, and an overall incidence of such events should be reported. Similarly, the various components of an anaphylactic reaction, or allergic reaction should be recognized and the diagnostic interpretation made. (See also the Agency's *Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Application.)*

Developing an antimicrobial drug for the treatment of several infections should usually constitute an acceptable clinical safety database, unless there are unusual safety concerns for a specific product. Thus, if an applicant chooses to develop a drug product for the treatment of only one or two infections, the applicant is strongly encouraged to discuss with the division the adequacy of the clinical safety database the proposed studies should provide. (See also *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions*.)

XV. EVALUATING EFFICACY

FDA has issued general guidance on the numbers and types of studies that should be conducted to demonstrate effectiveness (See FDA's guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,* May, 1998). The companion guidances on specific indications discuss the numbers and types of studies that should be conducted to demonstrate effectiveness of antimicrobial drug products. These recommendations are based on a number of factors including whether the effectiveness of the product has been demonstrated in a closely related indication, the natural history of the disease, and for some particularly serious indications, ethical considerations associated with conducting two trials once the effectiveness of the drug has been demonstrated in one trial. In addition, the companion guidances recognize that corroborating evidence of effectiveness may be obtained from other sources (e.g., pharmacokinetic/pharmacodynamic studies of a drug).

To be able to perform an appropriate evaluation of efficacy results, the FDA reviewer should have available for checking, validating, auditing, and, if necessary, analyzing all of the inclusion criteria, exclusion criteria, diagnostic criteria, drug dosing, and compliance information, results of history, physical examination, radiographic and laboratory tests from all study visits, investigator assessments, company study reports, tablets and drafts, data sets and the integrated summary of efficacy (ISE) and integrated summary of safety (ISS). Appropriate safety and effectiveness data (by gender, age, and racial subgroups) should be presented according to 21 CFR 314.50.

The purpose of such a review is not to validate and examine all the raw data and perform all the analyses specified in the protocol, but to make an independent assessment that the clinical

protocol was implemented correctly, that the requested data were collected and documented, that the analyses were appropriate and accurate, and that the results provide information on the drug's efficacy and safety.

The information considered important for evaluating the individual indications is not the same for each indication. For example, there is a focus on the culture results for indications such as gonorrhea or *Chlamydia,* and patients who may be missing a clinical evaluation may still be assessable for efficacy outcome (these diseases may be asymptomatic). In contrast, other indications rely heavily on the use of clinical signs and symptoms. The criteria that should be used are presented either in this document or in the companion guidances on individual indications.

Of paramount importance to valid analysis of trial data is to be able to delineate clearly and prospectively the primary effectiveness parameters, the specific population for both intent-to-treat and subsequent analyses, and the statistical analysis plan. These prospective criteria should be followed in post-study analyses, unless there are special circumstances dictating deviation. Such circumstances should be scientifically defensible and clearly explained in the NDA.

XVI. ADEQUATE CLINICAL TRIALS

The adequacy of a clinical study requires appropriate trial design, which is addressed in various sections of this document as well as the individual indication companion documents, good conduct and appropriate monitoring to ensure that there is strict adherence to the study protocol and that missing data are minimized. Prospectively defined data analysis plans that include procedures for handling missing information and well described statistical methodology are important in the assessment of the study results and provide the basis for making valid inferences regarding safety and efficacy.

XVII. WELL-CONTROLLED CLINICAL TRIALS

FDA's implementing regulations describe five categories of clinical trials that can be classified as adequate and well controlled (21 CFR 314.126). Placebo-controlled trials are seldom used in clinical trials of antimicrobial drug products because it is ethically unacceptable not to treat infected patients when effective therapy is available. Therefore, active-controlled studies usually are used to establish effectiveness of a new antimicrobial drug product, using comparator agents already approved for those indications in the United States. (See also Section VIII.H.2. on comparator agents.) With the increasing effectiveness of antimicrobial drug products in many infections, high cure rates make it nearly impossible or impractical for a new antimicrobial drug product to demonstrate statistical or clinically relevant superiority to an approved comparator

agent. The Agency has granted unrestricted (i.e., no caveats or limitations regarding the breadth of the specific claim) effectiveness claims for new antimicrobial drug products when those new products demonstrate statistical and clinical equivalence to a product already approved for treatment of the same infection. In such cases, patient numbers for studies should be readily obtainable, effectiveness end points should be fairly well established, and studies should be completed in a reasonable time frame.

XVIII. FOREIGN STUDIES

Sections 312.120 and 314.106 of Title 21 of the Code of Federal Regulations govern the acceptability of foreign data as the sole basis for U.S. marketing approval, as a partial basis for U.S. marketing approval, or as noncritical (supportive) data for an IND or NDA.

The Agency accepts clinical trials, including multicenter trials, wherever they are conducted, as critical data for marketing authorization if they characterize drug activity and safety for the U.S. population in a clinically relevant and statistically valid manner.

Applicants should be cognizant of special concerns about the relevance of some foreign infectious disease data to the American population because of known differences in microorganism susceptibility patterns in various parts of the world and known differences in pathogenic etiologies for various infections in various parts of the world. Should an applicant choose to submit foreign clinical or in-vitro data critical to the approval of a new drug application, it is the responsibility of the applicant to demonstrate that these data are clinically and microbiologically relevant to the U.S. population. Applicants are encouraged to discuss with the division how the applicant can meet its responsibility to establish the relevance of the critical foreign data to the U.S. population in a specific situation. This discussion should take place well in advance of reaching a corporate decision that a foreign study will provide critical data for the U.S. NDA.

Likewise, applicants should be aware of the regulatory requirement for the availability of source documentation for FDA inspection should the necessity for such arise (21 CFR 312.62 and 312.68). This requirement is applicable to both domestic and foreign data submitted in the NDA.

XIX. MULTICENTER TRIALS

Multicenter trials are often used to garner requisite clinical data in a more expeditious manner. Likewise, well-performed multicenter trials can provide a corroborative undergirding of data by demonstrating similar outcomes from different investigators in different geographic and clinical settings. In some cases in the past, data from many multicenter trials previously submitted to a

reviewing division have raised concerns. This is because outcomes reported from centers with large numbers of enrolled patients differed substantially from centers with small numbers of enrolled patients. Analyses of treatment by center versus by investigator raised questions about data reproducibility and consistency across and within centers. Although the reviewing division is interested in receiving data from different, appropriate clinical treatment environments (large institutions, small institutions, primary care environments, tertiary care environments, group practices, solo practices), individual study integrity should not be sacrificed to a large-scale, shotgun approach to patient enrollment for the sake of speed.

The Agency is not setting a minimum number of evaluable patients required per study to consider a site or study valid. However, critical multicenter trials should be evaluated closely and critically to establish that the data are not compromised by treatment by center or by investigator interactions. However, for certain infections (e.g., uncomplicated urinary tract infections, pharyngitis, uncomplicated skin and skin structure infections, gonorrhea), where large per-center enrollment could be expected, a minimum of 10 evaluable patients per arm should be a goal for investigators participating in multicenter trials.

Unless specified otherwise in guidance on the specific indication, multicenter trials to produce critical data for an NDA should be conducted by a minimum of three investigators located in different geographic areas. In general, no individual study site should be allowed to enroll more than 40 percent of the total patients enrolled for a specific multicenter trial. As mentioned above, concerns about potential bias created by treatment, by center, or by investigator interaction should be evaluated and adequately addressed.

XX. STATISTICAL CONSIDERATIONS

Clinical trials submitted to support proposed claims should be adequate and well-controlled (21 CFR 314.126). Issues regarding study design, data quality, and data analysis are presented below.

A. Study Design Considerations

The study design should support the proposed claim(s). The protocol should specify clearly the study objective, the patient population, study drug dosage and duration, the primary endpoint, and key planned analyses.

The protocol should be well designed and followed rigorously, and data collection should be complete and in compliance with the protocol. Planned analyses should be described in the protocol to avoid giving the appearance at the time of data analysis of choosing approaches to produce a significant result. Departures from the protocol make it difficult

to interpret the resulting data. For this reason, a formal plan for monitoring study conduct and data quality should be implemented. Changes in the design and analysis plan prior to the unblinding of the trial should be documented in the protocol or in a separate analysis plan provided to the Agency. Changes to the design and analysis plan made without modification in the protocol, or made after examination of the study data, should be clearly identified as such.

1. Sample Size

The patient sample size should be sufficiently large to support overall claims, as well as to address questions of safety and efficacy for important subsets such as those formed by gender, age (e.g., pediatric, elderly), race and other special populations.

The method for calculating the sample size should be specified clearly in the protocol. At a minimum, the protocol should include a description of the specified level of the two-tailed type I error, power, and treatment difference (delta). If a dichotomous (cure/fail) outcome is the primary endpoint, the assumed rate should be provided. If a continuous outcome variable is used, the standard deviation should be provided. The basis for the choice of these assumptions should be discussed. Sample size should reflect whether the primary endpoint will be evaluated by a confidence interval or a test of significance.

The approach chosen for sample size calculation should take into account anticipated patient loss due to protocol violations, negative culture results, inability to begin study medication, loss to follow-up, and other missing results. Additionally, the need for multiple comparison adjustments should be identified and incorporated into the sample size calculations.

2. Study Blinding and Randomization

The method of blinding should be described in the protocol. Double-blind trial design should be used whenever possible.

The algorithm used for assigning patients to treatment should be described, particularly the method of stratification and blocking. The analysis plan should adequately reflect the restrictions on randomization imposed by the trial design. For this reason, the use of excessively complex randomization (e.g., adaptive randomization or dynamic balancing) schemes should be avoided unless the methods of analysis are well understood.

3. Inclusion/Exclusion Criteria

The choice of inclusion/exclusion criteria should closely mimic the intended patient population. Trials should be designed to maximize the patients with disease and minimize the number of randomized patients who will not be included in the study analysis. The performance characteristics of key culture and assay procedures should be well understood prior to their use in a clinical trial. (See companion guidances on the individual indications.)

4. Patient Follow-up

The study should be designed to obtain complete data on efficacy and safety parameters for all subjects randomized. Such outcome data should be obtained regardless of patient treatment status. Concomitant medications should be documented. The loss of patients to follow-up should be minimized and reasons for loss documented.

5. Interim Data Analysis

Interim data analysis should be reserved for situations where the primary endpoint involves mortality and irreversible morbidity and the early termination is for ethical considerations rather than statistical efficiency. In most studies, the complete sample size should be available to analyze safety and efficacy outcomes. If an interim analysis is planned, an appropriate statistical procedure (e.g., O'Brien-Fleming) should be specified in the protocol.

6. Issues in Similarity, or *Equivalence* Trial Design

The intent of clinical studies is to determine whether a drug is safe and effective. Because placebo controlled studies designed to show superiority are considered unethical, active controlled studies are designed to demonstrate that a new product is efficacious by demonstrating that it is similar or *equivalent* to an accepted control.

The evaluation of similarity or equivalence should be based on a two-sided confidence interval; 95% intervals, adjusted for multiplicity, have traditionally been considered acceptable for most situations. The sponsor should document that the control arm is active in the indication under review by comparing the efficacy in the control arm to historical results.

The *Points to Consider* document suggested rules for establishing statistical equivalence that could be used under certain circumstances for the purpose of sample size estimation. The historical application of these broad principles has been reviewed and indication specific approaches to the evaluation of clinical similarity are being developed (see companion guidances on specific indications for deltas that should be used in sample size computations). Ultimate drug approval will depend on many factors, including (a) historical cure rate using existing products, (b) degree of risk associated with treatment failure, (c) toxicity of the proposed treatment relative to the control, and (d) ease of use.

The lack of a *statistically significant* difference should not be used as evidence of similarity. Rather, the objective of an analysis for a similarity trial should be to demonstrate that the test treatment is adequately similar to the control using a confidence interval approach as discussed above.

B. Data Quality and Management Considerations

1. Data Validation, Quality Assurance, and Quality Control Practices

The study should be monitored in an ongoing fashion to ensure that the protocol is being administered correctly and complete data are being collected. At the time of submission, a description of quality assurance (QA) and quality control (QC) procedures should be provided. If an individual or group other than the sponsor has been responsible for such activities, such individuals and groups should be identified. Any procedures that could lead to discrepancies between source documentation and analysis databases should be described.

2. Data Management and Presentation of Results

For effective data management, plans should be made at the protocol development stage for developing a computerized database. Because it is often difficult to determine the source of computerized data from the labels contained on a submitted database, fully annotated case report forms should be submitted. That is, a complete codebook linking database variables and case report form fields should be provided. This codebook should clearly identify each variable submitted and a description of codes.

Databases submitted should allow primary NDA analyses to be recreated. Differences between the database used to prepare the NDA and databases submitted with the NDA should be avoided.

If multiple contract research organizations are used, they should use the same data formats, nomenclature, and reporting units. If foreign data are submitted, they should use the same terms as U.S. data. The same variable names should be used in databases so data from one trial can be easily merged with data from another to allow subset analyses based on gender, age, race and, when appropriate, other subgroups.

C. Data Analysis Considerations

The analysis of data from clinical trials is complicated if there has been poor compliance with the assigned drug regime and/or data are missing. These problems seriously compromise the interpretation of results and can weaken the ability of a trial to support approval. Therefore, the protocol should be designed to minimize noncompliance with the drug regime and missing data. To evaluate the treatment effect completely, submissions should include both intent-to-treat analyses and analyses of subsets that may exclude subjects due to noncompliance or missing data. The reports should also incorporate the various strategies for handling missing data. To evaluate safety, submissions also should contain analyses of all randomized patients who receive at least one dose of the study medication.

1. Intent-to-Treat and Subset Analyses

The intent-to-treat principle suggests that eligible, randomized patients should be evaluated with respect to outcome based on the original treatment assignment regardless of modifications to treatment occurring after randomization. The statistical analysis seeks to establish if the particular assignment received is predictive of outcome, and the study can be interpreted as a strategy trial where the initial assignment is only the beginning of the treatment strategy. However, many researchers seek to glean results from the clinical trial that would have been observed if all patients had been able to remain on their initial assignment. This leads to analyses of subsets that exclude patients with imperfect compliance or follow-up data. However, the validity of these analyses rests on the assumption that the two treatment groups, after excluding such patients, differ only by the treatment received. This assumption could be violated in many subtle ways. For example, differential toxicity related to severity of illness could lead to selection bias. Similarly, the subjects unable to comply with medication may be those most at risk of a negative outcome and their exclusion may bias the treatment comparison.

The best solution is to suggest endpoints and trial design that will make the two

analyses as similar as possible, except for those situations in which poor compliance is an important part of the evaluation of the treatment efficacy in practice. It is recommended that both intent-to-treat and these subset analyses always be specified clearly in the protocol and always be conducted. The results of the approaches should be logically consistent in the context of the trial. In situations where there are major discrepancies between the two approaches, an explanation of the difference should be provided. Because the goal is to demonstrate a good treatment effect with both types of analysis, there is no need for a multiple comparisons adjustment.

2. Study Populations

a. Analysis Population (Intent-to-Treat Population)

The analysis population may be a subset of all randomized patients, with exclusions determined by variables collected at baseline. The appropriate baseline-determined exclusions depend on the nature of the study and the indication sought. The analysis population is synonymous with the intent-to-treat population; this population has also been called the modified intent-to-treat population. The rules for patient exclusion should be explicitly described in the protocol. A careful review of the sensitivity and specificity of the particular procedure used for exclusion, and of the standard medical practice for the indication (i.e., the use of culture/assay results) should be conducted. In general, these exclusions should be based on information provided in the individual indication sections.

b. Subset Analyses

These populations are generally a subset of the analysis population, with further exclusions based on post-baseline variables. For each indication, there may be slightly different definitions regarding what constitutes an evaluable patient (see companion guidances on individual indications). The protocol should clearly define the criteria for determining the patients, where relevant.

c. Accounting for Patients in the Study Population

The submission should contain a detailed tabular summary that accounts for all patients randomized. In general, this should include the number of patients unambiguously evaluated with respect to the primary endpoint at

the end of protocol specified follow-up. Patients with unknown status should be further broken down by reason. The number of patients available for each type of primary analysis should be indicated. The precise tabulations will vary by specific indication and the nature of the trial. For example, deaths should be indicated corresponding to the way they are handled in the analysis. Entries at any given tabular level should be mutually exclusive.

The submitted tabulation serves as a guide to analyses that should be performed to address ambiguities that arise due to unforeseen situations. The primary study analyses should address the difficulties associated with treatment comparisons in the presence of the patterns seen in early losses to follow-up and lack of compliance.

Sample Table

This example is for illustrative purposes only. Specific tabulations will depend on the indication and the nature of the trial.

	Study Drug				**Control Drug**			
	Cure	Improve	Fail	Unknown	Cure	Improve	Fail	Unknown
All Patients Randomized								
Excluded from intent to treat population:								
Reason 1								
Reason 2								
Reason 3, etc.								
Intent to treat population								
Excluded from evaluable subset(s):								
Reason 1								
Reason 2								
Reason 3								
Reason 4, etc.								

3. Statistical Analysis in the Presence of Missing Data

The issue of missing data is a problem for any analysis performed. The intent-to-treat principle does not provide a mechanism for dealing with missing data due to study discontinuation or missed evaluations. Subset analyses may exclude patients

with missing data who would otherwise have been considered evaluable. Thus, for both intent-to-treat and any subset analyses, a method for dealing with missing data should be specified in the protocol. The primary intent-to-treat analysis should employ this specified method to include patients with missing data. If the primary subset analyses exclude patients with missing data, another subset analysis should be performed using the method for including patients with missing data.

Since all methods for handling missing data have weaknesses, the submission should contain additional analyses that adequately demonstrate that conclusions made from the study are independent of the particular statistical strategy used to incorporate the missing data (i.e., a sensitivity analysis should be conducted). That is, these analyses should ensure that the results of the protocol-specified method do not inappropriately favor the experimental arm due to unforeseen patterns in the missing data. For example, if missing data caused by treatment discontinuations due to toxicity are treated as treatment failures and the control arm has an excess of such treatment discontinuation, other analyses should be provided that demonstrate that the establishment of efficacy is not primarily due to the incorporation of missing data as treatment failures.

4. Multiplicity Adjustments

If the trial contains multiple tests of significance for any reason (e.g., three or more treatment arms, multiple primary endpoints, interim data analysis, model fitting, subgroup analyses), the analysis plan should include an adjustment to avoid inflation of the type I error. A particular adjustment approach should be specified in the protocol before examination of data. Simpler procedures (e.g., Bonferroni) are preferred due to ease of interpretation and availability of simultaneous confidence intervals. If no plan was specified in the protocol or if the proposed plan was not implemented, the overall type I error level of the trial will be difficult or even impossible to evaluate. Sample size calculations should incorporate the multiplicity adjustment.

5. Choice of Statistical Analysis

Analyses should be chosen that adequately reflect the design of the trial and have not made statistical assumptions, which, if untrue, may lead to an incorrect regulatory decision. Analyses that are sensitive to departures from the underlying assumptions, should be avoided. This will be especially true in situations where the study will be underpowered to investigate the assumptions underlying the primary method of analysis. A Mantel-Haenszel style estimate of the treatment

effect stratified by the design strata is recommended. Furthermore, any covariate adjustment used in the primary analyses should be pre-specified in the protocol, and the method for incorporation of the design strata should be clearly described. Any post-hoc covariate adjustment analyses that are not pre-specified in the protocol will be interpreted as exploratory data analysis.

XXI. LABELING AND PROMOTION

A. Indications and Usage

Section 201.57(c)(2) of Title 21 of the Code of Federal Regulations states that all indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in section 314.126(b). For the purpose of this paragraph, with respect to antimicrobial drug products, the term *indication* means *the treatment (and/or prevention) of infections at specified body sites due to specified, susceptible microorganisms*.

The definition of *indication* as applied to antimicrobial drug products has evolved over time. In the past, it assumed a broader interpretation, such as *lower respiratory tract infections* or *upper respiratory tract infections*. More recently, a more definitive interpretation, such as *community-acquired pneumonia* or *hospital-acquired pneumonia* has been applied. This recent change recognizes the different pathophysiologies of certain infectious diseases and the inability to extrapolate effectiveness in one disease to effectiveness in another disease when pathophysiology or microbiology differ. This change in perspective has been undertaken in an effort to fulfill the mission of the Agency to inform physicians in the labeling, as accurately as possible, about the established effectiveness of a product and to limit manufacturer promotion of products only to those indications for which adequate effectiveness and safety have been established.

In regard to microorganisms included in the INDICATIONS AND USAGE section, only those considered to be an etiologic agent (pathogen) in at least 10% of the evaluable cases of the specific infection studied with the investigative agent should be included in the product labeling if the efficacy or cure rate for these cases is clinically relevant and acceptable. The phrase *at least 10%* means *at least 10% of the evaluable cases meeting both clinical and microbiological evaluability criteria, or 10 total cases (as just defined), whichever is higher*. In addition to comprising at least 10% of evaluable cases or at least 10 evaluable cases (whichever is greater), the eradication rate of the particular pathogen should be considered adequate and clinically acceptable for that pathogen to be included in this section of the labeling.

Some situations support adding microorganisms to the INDICATIONS AND USAGE section of the product labeling with less than 10% of the cases, as defined in the preceding paragraph. In such situations, explicit labeling to inform the physician of the actual extent of data available should be included in the product labeling. Usually, these situations would include (1) pathogens generally accepted at the site of infection under investigation (however in numbers less than 10%) where the number of such infections studied in the clinical trials is consistent with the percentage of such infections due to these pathogens in the general population; (2) pathogens for which in-vitro activity is at least similar to that of other pathogens more substantially evaluated in the clinical trials; (3) pathogens for which the mechanism of resistance is similar to other pathogens more substantially evaluated in the clinical trials; and (4) pathogens for which there are no scientific data suggesting any differences in the management of the infection due to these pathogens or in the prognosis of patients with the infection due to these pathogens.

B. Qualifications in Labeling

The minimal scientific information for individual infections discussed subsequently in this document should usually be adequate to support an unrestricted listing in the INDICATIONS AND USAGE section of the final product labeling. Some situations, however, warrant a restricted label. For example, restricted labeling would be used if a product possessed a significantly improved safety profile or offered some significant advantage to the patient of physician, but did not meet the statistical or clinical equivalence requirements for an unrestricted listing. Such restrictions (e.g., limitations to the treatment of only certain levels of severity of infections, specifications of comparative cure/eradication rates, recommendations that a product not be first line therapy for a given infection, restrictions to treating certain subclasses of pathogens) should be prominently placed in the label, usually in the form of a NOTE placed in the INDICATIONS AND USAGE section.

Products that (1) are combinations of active drug substances, or that otherwise result in two or more active moieties at the site of infection; (2) are less safe or less effective than comparator agents; or (3) have not established their effectiveness against all major pathogens in an infection that is routinely treated empirically should usually be restricted. Such products should only claim effectiveness in the treatment of infections due to specific organisms (where appropriate) where there is a clear rationale for use of the combination or a clear expectation of effectiveness or safety that results, in certain circumstances, in a clinically relevant offsetting advantage. These restrictions should be highlighted in a NOTE that is prominently placed in the INDICATIONS AND USAGE section of the labeling.

Any attempt by an applicant to promote an antimicrobial drug product for specific infections other than those listed in the INDICATIONS AND USAGE section of the product labeling (either directly or by misleading or disinformative promotional practices) would not comply with section 502 of the FD&C Act and implementing regulations. Furthermore, any advertisement or promotional labeling for products will be considered false and misleading under the Act if it does not include the entire INDICATIONS AND USAGE section of the labeling when referring to the infections for which these products are approved. The NOTES and other added statements in the INDICATIONS AND USAGE section are considered integral parts of the approved indication and should not be deleted or edited. In advertising or promotional labeling, the NOTES and other added statements should not be spatially separated from the wording in the initial part of the INDICATIONS AND USAGE section so as to minimize their impact. Such information should be presented in advertising or promotional pieces in at least the same print size and with at least the same impact as any other information from this section of the labeling.

C. Labeling for the Microbiology Subsection

To provide the practicing physician with more complete data to characterize an antimicrobial drug product, the following format should be used in listing microorganisms in the *Microbiology* subsection of the CLINICAL PHARMACOLOGY section of the product labeling:

1. The following statement should generally precede a listing of those microorganisms found specifically in the INDICATIONS AND USAGE section of the product labeling:

   > *(Generic name of drug) has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section.*

   Microorganisms should be listed alphabetically in the following four categories: aerobic Gram-positive microorganisms, aerobic Gram-negative microorganisms, anaerobic microorganisms, and *other* microorganisms. This list is referred to as list #1 (#1).

2. The following statements should immediately follow the preceding list (#1):

   > *The following in-vitro data are available, but their clinical significance is unknown. (bolded and underlined)*

(Generic name of drug) exhibits in-vitro minimal inhibitory concentrations (MICs) of (clinically relevant susceptible breakpoint) or less against most (> 90%) strains of the following microorganisms; however, the safety and effectiveness of (generic name of drug) in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

To be included in this *in-vitro only* list (#2), the more easily obtained and tested microorganisms should have a minimum of at least 100 isolates of each individual microorganism (genera and species) tested. When feasible, it is expected that testing should be by both the diffusion and dilution techniques. It is suggested that the great majority (>75%) of these isolates should be from geographically representative, recent, typical clinical isolates obtained from patients (but not necessarily the specific patients in the NDA clinical trials) throughout the United States. More than one laboratory, using standardized in-vitro susceptibility methods, should be used in this testing process, and the mean MIC_{90} for the 100+ isolates should be equal to or less than the final clinical *susceptible* breakpoint for the investigational drug.

For more fastidious microorganisms or those with difficult growth/testing methodologies, testing of fewer numbers of isolates should suffice (e.g., 15 to 25). The requisite numbers should be discussed with the division on a case-by-case basis. As the sufficient number of specific isolates in these situations becomes established for a given microorganism, this information will be made public, most likely in updates of this document.

Ordinarily, only microorganisms should be listed that are recognized as significant (not anecdotal) pathogens at the body sites or in the infections for which clinical effectiveness for other pathogens has been established in adequate and well-controlled trials.

If clinical data exist that cast doubt on the potential effectiveness of the investigational compound to treat infections due to a given microorganism at a given body site or in a given indication at the dosing regimen approved for use with the drug product, the microorganism should not usually be included in this list (#2), even if the in-vitro microbiologic data are consistent with the suggestions in these paragraphs.

Note: Microorganism susceptibility patterns can differ significantly in various parts of the world. In situations where an applicant chooses to submit microbiologic

data derived from sources outside the United States, it is the responsibility of the applicant to demonstrate that the data are microbiologically relevant to the treatment of U.S. populations.

3. Microorganism susceptibility patterns can change with time. As part of its on-going, postapproval drug safety monitoring and reporting responsibilities, the sponsor should report to the division available information on the continued susceptibility of the listed microorganisms to the drug product, especially those microorganisms listed as having established clinical relevance. This documentation should be provided, at a minimum, in the annual report to the approved NDA. Any necessary changes in the drug product labeling should be submitted to the division in accordance with the supplemental application regulations (21 CFR 314.70).

4. The susceptibility testing information in the *Microbiology* subsection should include information on the following:

   - Dilution techniques
   - Diffusion techniques
   - References — NCCLS methodology[3]

   For details on *Microbiology* subsection labeling, contact the appropriate division.

In some circumstances, in-vitro data allow a comparison of the in-vitro antimicrobial activity of two compounds, but do not allow a comparison or imply potential clinical effectiveness of various compounds. This is especially true when the in-vitro data are presented out of context with the known human pharmacokinetic properties of the antimicrobial drug product and out of context with the drug product's clinical experience. Balanced promotional activities with clear delineation between in-vitro activity and clinical effectiveness should be the standard. Promotional materials dedicated only to in-vitro data, without equivalent, balanced reference to data on human pharmacokinetic properties of and clinical effectiveness of a given antimicrobial drug product, would be deemed misleading under most circumstances.

The following are some examples of inappropriate uses of in-vitro data in promotional materials:

---

[3] NCCLS (National Committee for Clinical Laboratory Standards).

- Comparisons should not be made between or among products based solely on in-vitro data that imply superiority, either directly or indirectly, and that do not portray equal, adjacent presentations of clinical effectiveness data that demonstrate no clinical difference between the products. Examples include MIC tables showing superiority of one product over others when all available clinical trial data show equal effectiveness, or MIC tables purporting or implying superiority in activity without the relevant human pharmacokinetic data requisite to interpret such MIC data as they apply to humans.

- Comparisons should not be made between or among products of MIC or *percent susceptible* figures selectively taken from various published or unpublished sources that are presented in such a format as to imply fairly balanced and scientifically rigorous data when, in fact, the data presented are biased through the selection process in favor of the applicant's product because they eliminate results unfavorable to the applicant's product.

- Comparisons should not be made of results between or among antimicrobial drug products from various in-vitro studies of unestablished clinical relevance that imply superiority, either directly or indirectly, because of the presence or absence of the particular characteristic or which are presented in a format that implies fair balance and scientific rigor when, in fact, the data are selective and biased in favor of the applicant's product. Examples of such studies include inoculum effect, post-antibiotic effect, time/kill kinetics, serum/tissue kill ratios, mechanisms of action, and resistance mechanisms.

In-vitro microbiology data should be made available in the final product labeling for use by individual physicians in comparing in-vitro antimicrobial activity of antimicrobial compounds. When taken together with published information on in-vitro antimicrobial activity and human drug pharmacokinetics, these data may be useful in managing individual patients. They should not be intended to imply effectiveness claims for the antimicrobial drug product. Clearly, the data should not be used as the basis for supposedly clinically relevant, comparative promotional statements.

REFERENCES

Agency Guidance for Industry

Clinical Evaluation of Anti-Infective Drugs (Systemic), FDA 1977.

Division of Anti-Infective Drugs Advisory Committee Meeting Transcripts, dated March 5, 1997.

E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions, March 1995.

E7 Studies in Support of Special Populations: Geriatrics, August 1994.

Environmental Assessment of Human Drug and Biologics Applications, July 1998.

FDA Policy Statement for the Development of New Stereoisomeric Drugs, May 1, 1992.

Food-Effect Bioavailability and Bioequivalence Studies, draft, December 30, 1997.

Format and Content of the Chemistry, Manufacturing, and Controls Section of an Application, February 1, 1987.

Format and Content of the Clinical and Statistical Sections of New Drug Application, July 1988.

Guideline for the Study of Drugs Likely to be Used in the Elderly, March 1990.

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998.

Population Pharmacokinetics, draft, September 18, 1997.

Providing Regulatory Submissions in Electronic Format — NDAs, draft, April 1998.

Studies in Support of Special Populations: Geriatrics, August 1994.

Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances, November 1, 1994.

Submission of Documentation for Sterilization Process Validation Applications for Human and Veterinary Drug Products, November 1, 1994

Submission of Documentation in Drug Applications for Container Closure Systems Used for the Packaging of Human Drugs and Biologics, July 15, 1997.

Submitting Documentation for the Manufacturing of and Controls for Drug Products, draft, February 1, 1987.

Other Sources

Infectious Disease Society of America (IDSA), *Guidelines for the Evaluation of Anti-Infective Drug Products,* suppl. *Clinical Infectious Diseases* (formerly *Reviews of Infectious Diseases),* vol. 15, Sup. 1, November 1992.

Isenberg, H. D., in *Clinical Microbiology Procedures Handbook,* American Society for Microbiology Press: Washington, D.C., 1992.

Murray, P. R., J. E. Baron, and M. A. Pfaller et al., in *Manual of Clinical Microbiology,* 6th ed., American Society for Microbiology Press: Washington, D.C., 1995.