Guidance for Industry

EVALUATING CLINICAL STUDIES OF ANTIMICROBIALS IN THE DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

DRAFT GUIDANCE - NOT FOR IMPLEMENTATION

This draft guidance document will be presented for comment at the March 5 to 7, 1997, Advisory Committee Meeting, Division of Anti-Infective Drug Products. Draft released for comment on February 17, 1997.

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GUIDANCE FOR INDUSTRY[1] EVALUATING CLINICAL STUDIES OF ANTIMICROBIALS IN THE DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

I. INTRODUCTION

In November of 1992, the Infectious Disease Society of America (IDSA) published its "Guidelines for the Evaluation of Anti-Infective Drug Products" in the supplement of *Clinical Infectious Diseases (*formerly*, Reviews of Infectious Diseases).* That same month, the Food and Drug Administration's (FDA) Division of Anti-Infective Drug Products (the Division) issued a Points to Consider document on issues related to evaluating new drug applications (NDAs) for anti-infective drug products. These documents contain helpful information for designing clinical trial protocols for evaluating the safety and efficacy of new therapies. They also contain guidance on gaining approval for supplemental indications. However, neither of the documents explains in detail the elements the Agency considers important when evaluating clinical studies. The purpose of this draft guidance is to provide investigators, academia, and industry with insight on those elements (often referred to as *evaluablility criteria)* considered important during the evaluation of clinical studies for anti-infective drug products.

The guidance document first describes general issues to consider when designing the protocol. It then reviews important criteria for the indications identified in the Points to Consider document along with other emergent indications. Not all of the indications have been included in this iteration because they have not yet been completed. Upon their completion, however, the remaining subsections will be incorporated in revisions of the guidance.

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[1] This guidance has been prepared by the Division of Anti-Infective Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. Although this guidance does not create or confer any rights for or on any person and does not operate to bind FDA or the industry, it does represent the Agency's current thinking on the criteria for evaluating clinical studies of anti-infective drug products. For additional copies of this guidance, contact the Drug Information Branch, Division of Communications management, HFD-210, CDER, FDA, 5600 Fishers Lane, Rockville, MD, 20857 (Phone: 301-827-4573). An electronic version of this guidance is also available as of February 19, 1997, via Internet using the World Wide Web (www). To access the document on the www, connect to the CDER Home Page at http://www.fda.gov/cder/guidance.htm and go to the "Regulatory Guidance" section.

II. GENERAL CONSIDERATIONS FOR CLINICAL TRIALS

A number of issues that apply to all clinical studies should be addressed and incorporated into the overall protocol design. Examples include preclinical issues, such as chemistry, toxicology/pharmacology, in-vitro microbiology; and clinical issues, such as pharmacokinetics, protocol design, implementation, compliance, and efficacy and safety outcome. It would be difficult, for example, to ask a sponsor to analyze patient outcome based on a specific entry pathogen colony count or to evaluate the impact of a drug on coagulation if the laboratory tests that would have made this analysis possible had not been addressed in the protocol and had not been carried out. And, although it is desirable to have clear and specific evaluability criteria for each infectious disease indication, it may not be possible to apply the criteria literally to each and every possible study scenario because of differences among drugs, drug classes, disease states, and patient populations. A post-treatment throat culture done 4 days after therapy may be appropriate for most drugs, but it would not be appropriate for a drug with a 48-hour half life. Failure to address these kinds of critical issues in the study protocol could result in a flawed clinical trial.

To provide investigators, academia, and industry additional insight into the Agency's current thinking, this guidance reviews some of the preclinical and clinical issues that play key roles in the drug development process and in the Division's evaluation of study results.

III. PRECLINICAL ISSUES

A. Pharmacology/Toxicology in Preclinical Studies

Results of animal studies should be considered when selecting dosage regimens to be tested. They also should be considered when determining what organ systems might be at risk for toxicity and what basic, as well as specialized, safety monitoring should be undertaken. Preclinical toxicology tests should identify the toxicologic profile, e.g., the complete spectrum of toxicities that a drug can elicit.

In most circumstances, acute and subacute toxicity studies should be completed in rodent and nonrodent mammalian species. The routes of drug administration in the animal studies should mimic the intended clinical route(s), and the durations of animal testing should be equal to or exceed the durations in 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 guidelines.

Chronic and carcinogenicity studies generally do not need to be done because anti-

infective drugs are used for short-term therapeutic durations except in special circumstances. Special studies (e.g., photo co-carcinogenicity, arthropathy) should be performed on an as-needed basis. ADME studies in the animal species should be performed to identify those pharmacokinetic parameters similar to humans and to verify the applicability of the animal species used in the toxicity tests.

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 looked for 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, neurotoxicity, hyperplasias, bleeding), monitoring should be carried out during the clinical study to detect such potential toxicities.

Certain potential toxicities cannot be investigated ethically in humans. Therefore such 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.

For many community-acquired infections, it is assumed that the conditions are usually self-limited and nonfatal. Therefore, drugs tested in the treatment of these infections should have a wide therapeutic margin and no permanent toxicities; drug-induced animal toxicities should be transient and have shown reversibility. For some nosocomial infections, a narrower therapeutic margin may be acceptable if no safer alternatives are available. Nevertheless, permanent toxicities to any organ or tissue should be avoided, or at least minimized, and should be discussed with the Division during the earliest phases of drug development.

Dose selection should be made in consultation with the Division (e.g., reviewing pharmacologist and clinical reviewer) and should be based on the doses shown to have an acceptable safety profile in animals. If warranted, due to an emergent infection or no effective therapy, agreement may be reached to test higher doses with acceptance of an underlying higher risk to the patient.

B. Microbiological Aspects of Preclinical Studies

Before an anti-infective drug is used in humans, it should be tested in vitro and in animals. 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 for the following purposes: (1) to demonstrate anti-infective

activity against target microorganisms in vitro; (2) to examine culture conditions that might affect the assessment of antimicrobial activity; (3) to determine interactions (synergistic, additive, and antagonistic) with other anti-infective agents; (4) to provide information on mechanisms of action and on the potential for the development of resistance; and (5) to develop interpretation criteria and quality control ranges for in-vitro susceptibility testing.

Studies in animals are designed to accomplish the following goals: (1) to provide preliminary information useful in selection of dosage schedules for humans; (2) to determine potential antimicrobial efficacy in general and in specific infections; and (3) to evaluate the potential efficacy of drugs that cannot be adequately evaluated using in-vitro methods.

In general, the preclinical microbiology program should be designed to learn about the drug's anti-infective activity in vitro and in animals, including the following parameters. (Further guidance can be obtained from the Microbiology section in the Division of Anti-Infective Drug Products.)

1. Mechanism of Action

If known, information on the mechanism(s) of action of a new therapeutic agent should be reported. This provides insight regarding the development of resistance through alterations in the drug's target sight(s).

2. 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, community, teaching, and federal 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 have been collected for assessments of 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 guidance on the potential clinical efficacy of the drug.

3. Susceptibility Testing Systems

Where feasible, susceptibility testing breakpoints are incorporated into dosage form labeling when standardized susceptibility testing methods are available or proposed for a particular antimicrobial drug. The susceptibility testing methods are standardized prior to clinical trials of the drug. The methods are standardized with respect to the size of the inoculum, 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. When the methods have been standardized, the tentative breakpoints are 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 impact on the activity of the 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 demand 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 are based on statistical analyses of the central tendencies of replicate susceptibility testing measurements using specific well-characterized bacterial isolates. Tentative QC limits may be adjusted to accommodate a perceived need to move most clinical susceptibility testing results away from false susceptible readings.

4. 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(s) of resistance and the method(s) by which this resistance might be transferred to other microorganisms should be included in the submission if known. When the mechanism of resistance is known, resistant organisms should be studied to determine if they possess the resistance determinants as well as

susceptible organisms to determine the lack of the resistance determinants. If the resistant organisms do not contain the known mechanism of resistance, the form of resistance should be characterized. The ability of resistant isolates to transfer resistance to other microorganisms should be characterized.

Information on whether the anti-infective agent can induce the production of enzymes or other methods of resistance should be included in the submission if known. 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.

If the mechanism of resistance is not known, it is suggested that efforts be made to assess the resistance mechanisms to better understand the increase in resistance rates and clinical failures.

5. Synergistic, Additive, Antagonistic, and Indifferent Effects

The effects of drug interaction can be determined by a variety of techniques. One method 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.

6. 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.

7. 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 animal models. Animal models may be used to identify which diseases in humans may be most suitable for clinical trials of a new anti-infective drug. These models can be employed in an exploration of the advantages or 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 for studies of infective endocarditis, meningitis, pneumonia, peritonitis, and pyelonephritis as well as infections in the neutropenic host.

C. Chemistry

Issues of importance in the chemistry that are pertinent to the clinical study conduct and evaluation include stability of a compound under various storage conditions, stability over time, purity of the compound including any possible toxic impurities or breakdown products.

IV. CLINICAL ISSUES

A. Pharmacokinetics

Pharmacokinetics (absorption, distribution, metabolism, and excretion) and biopharmaceutics (dissolution, bioavailability including drug-product by food interactions) information should be available for anti-infective drugs and drug products prior to beginning phase 3 clinical studies. For example, an oral drug product should not be administered to patients with meals before the effect of food on the bioavailability is known.

In the clinical study of anti-infective drug products, dose selection, dose regimen, and duration of therapy should take into account the pharmacokinetics, pharmacodynamic, and biopharmaceutic properties of the drug/drug product, as well as consideration of the disease state or other patient characteristics that may alter these properties. Pharmacodynamics include relating drug concentrations at the site of action to the in-vitro susceptibility of the target microorganisms (bacteria). Clearance, effective concentration range, and extent of availability are necessary pharmacokinetic parameters to 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 may 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 to guide dose interval selection. Half-life determines the time needed for drug concentrations in plasma to achieve steady-state or to decay from steady-state after a change in dosage regimen. However, alterations in half-life should be carefully interpreted since it 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.

Half-life is also important in considering the time intervals for evaluating treatment outcome after drug therapy, that is, the test-of-cure visit. For drugs with short half-lives (e.g., one hour), the time interval for plasma drug concentrations to decrease to clinically insignificant values after the last dose can be 5 to 6 hours. For drugs with longer half-lives, this time interval can extend to a period of weeks. Therefore, a test-of-cure visit at 5 to 9 days for urinary tract infections, is appropriate for a beta-lactam or quinolone with a short half-life. However, a test-of-cure visit at 5 to 9 days for urinary tract infections, is not appropriate for a drug with a 72-hour half-life. These kinds of issues should be discussed with the Division and addressed at the time of protocol design and implementation.

B. Study Design and Implementation

The protocol design should be based on sound scientific rationale. The protocol should be submitted to the Division for consideration before patient enrollment begins. Studies should be double-blinded whenever possible and evaluator-blinded at minimum, to prevent inadvertent introduction of evaluator bias. A block randomization code should be used in all comparative studies, and the code should remain unbroken throughout the conduct of the study and the analysis of the study results.

In most clinical studies both male and female adult patients are enrolled with their age ranges specified. Studies should also be conducted in which geriatric and pediatric patients are invited to participate, if it is anticipated that the drug to be tested will be used after approval in these age groups. Any questions about enrolling population subgroups, such as pediatric patients, pregnant or lactating patients, or patients with renal failure should be discussed with the Division at the time of protocol design and implementation. In general, exclusion of a population subgroup should be guided by concerns of potential adverse drug reactions to the patient (or fetus) because of the drug under study. This concern, however, should be weighed carefully against the need to evaluate and gain therapeutic information on the antimicrobial drug in these same subgroups.

Patients enrolled in the study should have the disease intended for study. The specific criteria that determine whether the patient meets the inclusion criteria and is therefore evaluable for the disease under study are specified in the sections on individual indications. As specified in the Points to Consider document, patients can be evaluated for their

clinical response to treatment, or they may be evaluated for clinical and microbiological response to treatment. The circumstances under which these evaluations are appropriate are specified in the Points to Consider document (which the reader should consult). It is assumed that patients have a complete history and physical examination at entry, both to confirm the diagnosis under study and to exclude other diagnoses.

Conversely, exclusion criteria generally are designed (1) to exclude patients who do not have the disease under study, (2) to exclude patients whose disease has progressed to a stage where drug intervention may be too late or inadequate to assess activity, (3) to protect patients from a potentially unacceptable risk of adverse event, or (4) to 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 conditions, and situation make it unlikely that their participation should yield information on the drug efficacy and safety. Otherwise, the risk of participation in the study may not result in benefit either for the patients or the study outcome.

Patients may 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 in a *clinical only* study. Patients who have received antimicrobial therapy for the same condition within 24 hours prior to enrollment in a *clinically and microbiologically evaluable* study should be excluded unless the pathogen can be isolated before initiating the study drugs. (See Points to Consider.)

- 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.

- Female patients who are pregnant or lactating. Alternatively, clinical protocols intended to study this population should be discussed with the Division before implementation. For example, patients in the second and third trimester have been involved in clinical trials of certain topical products.

- 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 an additional antimicrobial agent.

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

Finally, an investigator should maintain a patient log and list all patients screened who were enrolled and who were excluded. The reasons for exclusion should be noted.

The selection of the drug, dosage regimen and dosage duration should be based on information gleaned from preclinical testing, clinical pharmacokinetics, microbiology, and the disease under study.

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 protocols where the study involves conversion from intravenous therapy to oral therapy, a complete clinical (including radiological) and microbiological evaluation should be repeated before the patient is switched from intravenous to oral therapy. The results of the tests and findings should be documented.

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 later to document whether the value returns to normal.

Documentation of patient data in the case report form (CRF) and supporting documents

(e.g., laboratory print-outs, x-ray reports, pathology reports) should be completed and verified.

C. Microbiology Issues in Study Design

1. Laboratory Expertise

To qualify for participation in clinical trials, the microbiologists should be experienced in routine microbiology procedures as well as in recovering anaerobic and fastidious organisms, susceptibility testing, storage, and retrieval. The laboratory should be certified by the College of American Pathologists or a similar organization and should be licensed by the Health Care Financing Administration as a high-complexity facility. It should participate in a recognized inspection and quality-control or proficiency program. Alternatively, the laboratory may be recognized as having demonstrated expertise in the field under study (e.g., the clinical research laboratory of a principal investigator). The qualifications of the laboratory should be provided to FDA before clinical trials are initiated.

2. Standard Guidelines 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(s) 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. Defining an acceptable interval for transport is essential.

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, for assessing the amounts of growth of potential pathogens.

4. Identification of Microorganisms and Parasites to the Species Level

In general, identification to the species level should be standard. Procedures such as those outlined in the *Manual of Clinical Microbiology, Clinical Microbiology Procedures Handbook,* or those used with licensed commercial kits would be appropriate for the identification of isolates that are likely to be the cause of infection.

5. Serological Diagnosis and Direct Immunologic or Molecular Detection Procedures

A variety of procedures have been developed, but each procedure should be validated and verified as 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 will be acceptable as diagnostic alternative if the agent (e.g. *Legionalla* or *Mycoplasma)* is not isolated

from primary specimens.

6. Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing (AST) procedures should be standardized and should include routine testing of appropriate quality-control strains. Clinical strains (recovered during clinical trials) that are considered pathogenic should be frozen (at -70^{o} C) and saved by the clinical investigator. In selected circumstances (e.g., when the patient fails to respond clinically to treatment and/or the presumed pathogen is not eradicated), these microorganisms may be forwarded to the sponsor or to a reference facility for confirmatory speciation, repeat AST, and characterization of the mechanism of resistance when appropriate. It may be appropriate for a systematic prospective sample of all strains to be retested by the sponsor or by a reference laboratory. Primary AST procedures in the clinical centers should include both dilution and disk diffusion tests.

7. 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. Commercial systems using limited screening dilutions or breakpoint concentrations, rather than full twofold dilution series, are not acceptable.

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. In clinical trials, more than one anaerobic species from polymicrobial infections should be tested only when the clinical investigator determines that the research value substantiates the need for the individual patient. 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 CSF, 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. Quality-control 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 guidelines such as the following:

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

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

- 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.

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

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

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

- Analysis of any subset of organisms demonstrating potentially unique mechanism of resistance.

12. Emergence of Resistance

The emergence of resistance should be monitored by means of full species identification, antimicrobial susceptibility testing, and characterization of the mechanism of resistance of any isolate that appears to represent the same species as the original pathogen. Any apparent change in zone diameter or MIC should be confirmed by retesting of the second strain in parallel with the original isolate. The appearance of a new potential pathogen (with clinical signs of new infection) should also prompt full species identification and antimicrobial susceptibility testing. In general, a fourfold or greater increase in MIC or an equivalent decrease in zone diameter (e.g. more than 3-6 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 mechanism(s) 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 necessary to differentiate 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

Pharmacokinetics 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, if possible, according to the pharmacodynamic/ pharmacokinetic 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.

D. Efficacy Evaluation and Outcome

For an FDA reviewer to be able to perform an appropriate evaluation of efficacy results, the reviewer should have available for checking, validating, auditing, and 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).

The purpose of the review is 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 that the results provide information on the drug's efficacy and safety.

In all indications, the use of other antimicrobial therapy in the preceding few days or week (approximately), during the study and through the test of cure evaluation period should be documented.

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. By evaluating this information, ideally while blinded to drug therapy, the reviewer (as the applicant during their analysis) can independently conclude whether or not the patient responded to therapy.

The criteria considered important for evaluating the individual indications are not the same for each indication. For example, there is a focus on the culture results for indication 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 evaluation of clinical signs and symptoms. The specific minimum evaluability criteria are presented in the body of this document.

E. Definitions and Explanations of Commonly Used Terms

The following represents a list of terms commonly used during drug evaluation in which the clinical definition or connotation of the term may differ, be broader or stricter, compared to the regulatory definitions. To ensure uniformity and designate conventions, the terms are used to mean the following:

1. Documentation

As used in this document, the term *documentation* refers to recording the actual clinical, microbiological, radiological, laboratory and other findings for each patient for each visit in the patient case record form and subsequently transferring them to the case report tabulation (CRT) or database. For example, the signs and symptoms of disease that allowed the clinician to arrive at the diagnosis of a particular disease should be recorded in the case record form. Likewise, the signs and symptoms recorded at each evaluation visit should be recorded. A statement that the patient is *improved* or *cured* is insufficient.

2. Clinical Outcome

A judgment regarding the patient's response to therapy based on a comparison of the patient's baseline signs and symptoms and other nonmicrobiological criteria (e.g., may include radiology) to the patient's evaluation at the test-of-cure visit. These are classified as cure or failure. In some indications, a category of improvement is also used at the test of cure.

a. Cure

The term to describe clinical outcome in an evaluable patient who has resolution of all entry clinical signs at symptoms at the test-of-cure visit.

In practical terms, however, there are indications where there may be a clinical sign or symptom observed at the test-of-cure visit that is physiologic, represents a postinfectious stigmana, or represents the underlying disease and does not indicate active infection. Recognition of such a finding and its clinical implication is important to the proper classification of outcome. For example, while discharge (usually curdy white) is characteristic of vulvovaginal candidiasis, a mild physiological discharge at follow-up should be recognized as normal, and the patient classified as cure. In skin infections, change in skin color (erythema) is of the four cardinal symptoms of infection, yet a postinflammatory discoloration may be seen after therapy even when the infection is resolved. In acute exacerbation of chronic bronchitis, treatment is aimed at resolving the acute process but clearly does not succeed in reversing the underlying chronic bronchitis. These are some of the routine situations encountered; other examples may be added.

b. Failure

The term describes the clinical outcome in an evaluable patient who has either persistence, incomplete resolution, or worsening of entry signs and symptoms, who has emergence of new signs or symptoms of the disease, and/or who has been treated with additional antimicrobial therapy for the disease under study. Thus, patients who have some degree of *improvement* in their signs and symptoms but still need change in therapy or additional management would be classified as a failure.

Patients may be considered failures because they fail to respond to an adequate course of therapy (efficacy failure). However, patients may also fail to respond to therapy because they had to discontinue the drug due to

an adverse event and did not receive an adequate course of therapy (adverse event failure). An analysis and summary of patients who discontinued drug therapy because of an adverse event should be included in the safety section of the study report and in the ISS.

c. Improvement

This category may be used for determining whether the patient should continue on the current drug treatment arm or should be switched. It may be used to classify an interim evaluation (e.g., the on therapy visit), but should not be used as a test-of-cure outcome, except in rare cases. If it is used, a quantitative definition (e.g., present/absent or 0-3 scoring system) should be provided and justified.

d. Relapse

This term has been used in cases where a patient has an initial amelioration in the clinical picture, a favorable response to therapy, followed by worsening or reappearance of some signs or symptoms either later during treatment or once off therapy. Sometimes, it is even further characterized as early relapse or late relapse. For regulatory purposes, if a patient has worsening or reappearance of signs and symptoms before or at the test-of-cure visit, the patient should be considered a clinical failure. If a patient has these findings after the test-of-cure visit, the patient should be considered a clinical cure.

Confusion arises when there is no standardized time frame for applying this definition, resulting in the situation where one person's failure becomes another person's relapse. This is further confounded if the failures are counted with the failures and the relapse is forgotten in favor of the initial improvement response. This has the effect of arbitrarily resulting in inconsistent efficacy rates.

3. Microbiological Outcome

The assessment of microbiological outcome is based on results of the culture (in most cases) or serology (rarely, when culture is not feasible). Although a long list of outcomes has evolved over time, it should be recognized that the key question is whether the drug under study can eradicate the pathogen causing the disease under study. The other factors under consideration may be whether the use of the drug causes resistance to develop in bacteria or whether the drug makes the patient susceptible to other, new pathogens. The use of other categories should not

obscure the fundamental question: "Can the drug eradicate the pathogen or will the pathogen persist?"

a. Eradication

- Documented Eradication

The absence of the original pathogen from the post-treatment test-of-cure culture of specimen from the original site of infection.

- Presumed Eradication

In diseases where the complete resolution of signs and symptoms is associated with cessation of cultureable material (e.g., sputum) or where the procedure is too aggressive to justify repeating it in well patients (e.g., tympanocentesis) the bacteriological outcome is presumed to be eradication.

For purposes of final analysis, the two eradication categories may be pooled.

b. Persistence

- Documented Persistence

The presence of the original pathogen in the post-treatment test-of-cure culture specimen from the original site or organ of infection.

- Presumed Persistence:

In patients who are judged to be clinical failures, and a culture is not possible or it not done, it is presumed that there is persistence of the pathogen.

For purposes of final analysis, the two persistence categories should be pooled.

c. Superinfection

Isolation of a pathogen other than the original pathogen from a specimen taken while the patient is on therapy in a patient who has signs and symptoms of infection.

d. Recurrence

Isolation of the original pathogen from a culture taken after the test-of-cure visit. Note: Isolation of the original pathogen before the test-of-cure visit is considered persistence.

e. Reinfection

Isolation of a new pathogen from a post-treatment culture in a patient with signs and symptoms of infection.

f. Colonization

Isolation of an organism from a patient who has no signs or symptoms of infection.

4. Therapeutic Outcome

This category has also been called global outcome, overall outcome, overall success, etc. It is an evaluation that takes into consideration both the clinical outcome and the microbiological outcome of the patient.

a. Therapeutic Cure

A patient who is judged to be both a clinical cure and a microbiological eradication.

b. Therapeutic Failure

A patient who is judged to be either a clinical failure or a microbiological failure or both. (This means that if one evaluation is a failure and the other is missing, the patient is a therapeutic failure.)

Clearly, if there is a 100% concordance, the clinical, microbiological and therapeutic outcome rates may be the same. In most clinical studies, some degree of discordance in clinical and microbiological outcome is identified. It is expected that a small discordance may be found because of false negative or false positive laboratory results. However, a high discordance in clinical and microbiological outcome would need to be explained. Clearly, the higher the discordance in results, the lower the therapeutic cure rate.

5. Carrying Forward Failures

This is the concept that patients who are at any point during the course of the study considered to have failed drug therapy are considered as failures for the test-of-cure evaluation.

6. Test-of-Cure Visit

For purposes of evaluating anti-infective drug products, the concept of test-of-cure visit is defined as that time point at which the regulatory assessment is made of whether the drug had the effect it is intended to have or purports to have as stated in the proposed labeling. For decades now, it has been accepted that (for most short-acting drugs) the test of cure visit is 3 to 7 days after uncomplicated gonorrhea therapy, 4 to 8 days after streptococcal pharyngitis therapy, 5 to 9 days after UTI therapy, and 4 weeks after vulvovaginal candidiasis therapy. The timing of these visits for all other indications is presented under the sections for individual diseases.

F. Safety Evaluation and Outcome

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

The challenge in safety evaluation 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 needed or appropriate to fully 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), 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.

The evaluation of safety is fully characterized in the document *Guideline for the Format*

and Content of the Clinical and Statistical Sections of New Drug Applications.

G. Statistical Considerations in the Design, Conduct, and Evaluation of Clinical Trials of Anti-infective Drug Products

All trials that are to be submitted to support proposed claims should be adequate, well designed, and properly monitored. All data should be quality-controlled, checked, and entered into a computerized database. The issues that should be considered during the analysis of the data are presented below. It is assumed that these analyses will be performed by trained, competent statistical and data management personnel. The statistical evaluation tools should be appropriate for the questions to be asked, the design to be used, and the type of data that will be generated.

1. Study Design Considerations

    a. The study design should help control potential sources of bias (e.g., blinding, choice of controls, randomization plan, patient screening and selection criteria, strata, and covariates).

    b. The study should answer question(s) posed to support proposed claims such as therapeutic equivalency or superiority, population(s) of inference, dosage and duration, properly chosen endpoint(s), accepted definitions of cure, improvement, and failure.

    c. The patient sample size should be sufficiently large to support overall claims as well as to address questions of safety and efficacy by subsets, including adequacy, equivalency cutoff criteria, superiority criteria for representative numbers of male and female patients, the elderly, and other elements to support inferences to the general population of use.

    d. The design should be such that it is easy to monitor data quality (e.g., quality assurance/quality control procedures, safety monitoring, and testing).

2. Data Analysis Considerations

    a. The proposed statistical analysis plan should satisfy the conditions listed above.

    b. ITT populations should be defined, as well as how these will be used to test for robustness of conclusions.

c. Provisions should be made for an integrated safety evaluation.

d. Provisions should be made to handle early losses, competing risks, and differential losses among centers and treatment arms.

e. If interim looks are planned, a discussion should be provided of what will be gained; early stopping rules and penalties for interim looks should be given. (Interim looks in an equivalency trial make no sense and should be avoided.)

f. If multiple endpoints are measured, it should be determined how they will be evaluated (i.e., if the claim is that a *win* occurs if any endpoint wins, a test level adjustment for multiple comparisons should be made, but, if a *win* occurs only if all endpoints win, no adjustment in significance level is warranted.

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

a. The individuals and groups responsible for QA/QC should be identified and information on when QA/QC is done presented.

b. The procedures for resolving problems and questions should be established.

c. Data management staff and statistical reviewers should be aware of QA/QC procedures.

4. Considerations for Data Management and Presentation and Presentation of Results

a. Plans should be made at the protocol development stage for developing a computerized database.

b. If multiple CROs are used, they should use same data formats, nomenclature, etc. If foreign data are submitted, the same formats, nomenclature, and reporting units should be used

c. Data from one trial should be easily merged with data from another to allow subset analyses based on gender, age, race and, when appropriate, other subgroups. Efficacy and safety summaries should be easily consolidated and rapidly and correctly made.

V. INDIVIDUAL INDICATIONS SUBSECTIONS

The individual indications presented in the Points to Consider Document are discussed in detail below. A number of the subsections have not yet been completed. Once they are completed, they will be included as the document is updated.

The subsections are organized in the following fashion.

Indication(s)___: Individual Indication(s)

A. Regulatory synonyms, disease conditions subsumed under the indication
B. Study Considerations
C. Inclusion Criteria including the population studied and the diagnostic evaluability criteria
D. Exclusion Criteria
E. Drug(s) Studied and Dosing Rgimens
F. Evaluation Visits
    1. Entry/Pre-Therapy
    2. On-Therapy
    3. End-of-Therapy
    4. Post-Therapy/Test-of-Cure
    5. Late Post-Therapy

G. Outcome Categories
    1. Clinical Efficacy
    2. Microbiological Efficacy
    3. Safety Evaluation
    4. Statistical Issues

Indications 1 & 2: Uncomplicated Urinary Tract Infections Complicated Urinary Tract Infections and Pyelonephritis

Study Considerations: Refer to the Points to Consider document, pages 29-31, and the 1992 IDSA Guidelines, pages S216-S227. The Points to Consider document discusses two broad categories of labeling for anti-infective drugs in the treatment of infections of the urinary tract (UTI):

1. Uncomplicated Urinary Tract Infections
2. Complicated Urinary Tract Infections and Pyelonephritis

The IDSA Guidelines, in contrast, list 5 categories under "Entry criteria for studies of UTI":

1. Acute uncomplicated UTI in women
2. Acute uncomplicated pyelonephritis
3. Complicated UTI and UTI in men
4. Asymptomatic bacteriuria
5. Recurrent UTI (antimicrobial prophylaxis)

This document on UTI evaluability criteria will focus on uncomplicated urinary tract infections, pyelonephritis, and complicated urinary tract infections.

Uncomplicated Urinary Tract Infections

A. Disease Definition

A clinical syndrome in women characterized by dysuria, frequency, and/or urgency in combination with pyuria and bacteriuria. There is no known underlying renal or urologic dysfunction or obstruction.

B. Synonyms

Terms include *acute uncomplicated UTI, cystitis, acute cystitis,* and *dysuria-frequency syndrome*.

C. Inclusion Criteria

1. Non-pregnant adult females

2. Clinical signs and symptoms of a UTI (e.g., dysuria, frequency, urgency, supra-pubic pain) with onset of symptoms $\leq$ 72 hours prior to study entry.

3. One positive pre-treatment clean-catch mid-stream urine culture within 48 hours of enrollment in the study, defined as $\geq 10^5$ CFU/mL

4. In-vitro susceptibility testing of the uropathogen to both test and control drug

D. Exclusion Criteria

See General Considerations.

1. Males

2. Women who are pregnant,[2] nursing, or not using a medically accepted, effective method of birth control

3. Three or more episodes of acute uncomplicated UTI in the past 12 months

4. Patients with evidence of factors predisposing to the development of urinary tract infections, including calculi, stricture, primary renal disease (e.g., polycystic renal disease), or neurogenic bladder

5. Patients with the onset of symptoms 96 hours or more prior to entry

6. Patients with a temperature $\geq 101^0$ F, flank pain, chills, or any other manifestations suggestive of upper urinary tract infection

7. Patients with known or suspected hypersensitivity to the test or control drug

8. Patients who received treatment with other antimicrobials within 48 hours prior to entry

E. Drug Selection, Dosage, Route of Administration, and Duration of Therapy

Treatment duration may range from single-dose therapy to 3 to 10 days, depending on the drug regimen. Choice of appropriate comparator agents should be discussed with the Division in advance.

F. Evaluation Visits

[2] For companies that wish to enroll pregnant women in UTI trials, the Division recommends prior discussion of the protocol.

1. Pre-Therapy
2. On-Therapy
3. Post-Therapy Assessments

Table: EVALUATION VISITS

	VISIT			
ASSESSMENT/ OBSERVATION	**1 Baseline Day 0***	**1A[a] On-therapy**	**2 5-9 Days Post-therapy**	**3 4-6 Week Post-Therapy**
Inclusion/Exclusion	✓			
Informed Consent	✓			
Medical History	✓			
Physical Examination	✓		✓	✓
Vital Signs	✓	✓	✓	✓
Clinical Evaluation	✓	✓	✓	✓
Pregnancy Test[b]	✓			
Bacteriology Quantitative Urine Culture and Susceptibility	✓	✓	✓	✓
Urinalysis	✓	✓	✓	✓
Hematology	✓		✓	
Chemistry	✓		✓	
Adverse Events	✓	✓	✓	✓

* Visit days are recorded throughout this report as shown above; Day 0 = Day of first dosing.

[a] Visit 1A is an optional visit. Either a telephone contact or a visit is conducted at this time.

[b] A serum pregnancy test should be performed on all females of child-bearing potential.

G. Outcomes

Outcome at 5-9 Days Post-Therapy

1 . Microbiologic

a. Eradication: A urine culture, taken within the 5- to 9-day post-therapy window, shows that all uropathogens found at entry at $\geq 10^5$ CFU/mL are reduced to $< 10^4$ CFU/mL.

b. Persistence: A urine culture, taken any time after the completion of therapy, grows $\geq 10^4$ CFU/mL of the original uropathogen.

c. Superinfection: A urine culture grows $\geq 10^5$ CFU/mL of a uropathogen other than the baseline pathogen during the course of active therapy.

d. New Infection: A pathogen, other than the original microorganism found at baseline at a level $\geq 10^5$ CFU/ml, is present at a level $\geq 10^5$ CFU/mL anytime after treatment is finished.

2. Clinical

a. Cure: All pre-therapy signs and symptoms subside.

b. Improvement: Most, but not all, pre-therapy signs and symptoms subside.

c. Failure: No apparent response to therapy; continuation or worsening of most/all pre-therapy signs and symptoms.

Outcomes at 4-6 Weeks Post-Therapy

1. Microbiologic

a. Long-term, Sustained Eradication: A urine culture, taken within the 4 to 6 week post-therapy window, shows that all uropathogens, found at entry at $\geq 10^5$ CFU/ml, are still reduced to $< 10^4$ CFU/ml.

b. Persistence: A urine culture, taken any time after the completion of therapy, grows $\geq 10^4$ CFU/ml of the original uropathogen. These patients are carried forward from the 5- to 9-day post-therapy visit.

c. Superinfection: A urine culture grows $\geq 10^5$ CFU/ml of a uropathogen

other than the baseline pathogen during the course of active therapy with symptoms of infection as previously stated.

d. Recurrence: A urine culture grows $\geq 10^4$ CFU/ml of the original uropathogen taken anytime after documented eradication at the 5- to 9-day post-treatment visit, up to and including the 4- to 6-week post-therapy visit.

e. New Infection: A pathogen, other than the original microorganism found at baseline at a level $\geq 10^5$ CFU/ml, is present at a level $\geq 10^5$ CFU/ml anytime after treatment is finished.

2. Clinical

a. Sustained Cure: All pre-therapy signs and symptoms show no evidence of resurgence at the follow-up visit 4 to 6 weeks after the last dose of drug.

b. Failure: Patients carried forward from the 5- to 9-day post-therapy visit.

c. Relapse: Signs and symptoms, absent at the 5- to 9-day post-therapy visit, re-appear at the 4- to 6-week post-therapy visit.

Complicated Urinary Tract Infections

(Reserved)

Pyelonephritis

A. Disease Definition:

A systemic ascending urinary tract infection clinically manifested by fever, chills, flank pain, nausea, and/or vomiting. There may be associated bacteremia. Symptoms of lower urinary tract infection may or may not be present.

B. Study Considerations:

The Division recognizes that pyelonephritis can be either an uncomplicated or complicated clinical disease. Complicated UTIs are those that occur in the setting of catheterization or functional or anatomical abnormalities of the urinary tract. The Division suggests that pyelonephritis be studied with complicated urinary tract infections as dosing for pyelonephritis and complicated UTIs is

routinely similar. If there is not a sufficient number of patients with pyelonephritis successfully treated with the investigative agent (minimum: 30 patients/arm/study), then the listing may not include pyelonephritis.

C. Inclusion Criteria

1. Clinical signs and symptoms of an ascending UTI manifested by all three: fever, chills, and flank pain. In addition, patients may also have costo-vertebral angle tenderness, nausea, and/or vomiting.

2. One positive pre-treatment clean catch midstream urine culture defined as $\geq 10^5$ CFU/mL.

3. In-vitro susceptibility testing of the uropathogen to both test and control drug.

D. Exclusion Criteria

1. Women who are pregnant, nursing, or not using a medically accepted effective method of birth control.

2. Patients with known or suspected hypersensitivity to either the test or control drug.

3. Patients who received treatment with other antimicrobials within 48 hours prior to entry.

E. Drug Selection, Dosage, Route of Administration, and Duration

Treatment duration may range from 7 to 14 days, depending on the drug regimen. Choice of appropriate comparator agents should be discussed with the Division in advance.

F. Evaluation Visits

See table on Evaluation visits above.

G. Outcome Categories

See above for Uncomplicated Urinary Tract Infections.

Indications 3 & 4: Uncomplicated Skin and Superficial Skin Structure Infections and Complicated Skin and Soft Tissue Infections

A. Disease Entity Definition

Because of the vast array of skin and skin structure infections possible, it would be very difficult to study each individually. Additionally, because broad categories of skin and skin structure infections tend to share common pathogens (e.g., superficial skin infections, impetigo, erysipelas, cellulitis and simple abscesses are all predominantly caused by either *Streptococcus pyogenes* or *Staphylococcus aureus*) and similar responses to similar antimicrobial therapy, this cluster of diseases has been studies under the umbrella of skin and soft tissue infections and more recently in two broad categories: Uncomplicated skin and superficial skin structure infections and complicated skin and soft tissue infections.

The uncomplicated category includes such clinical entities as simple abscesses, impetiginous lesions, furuncles, and cellulitis. Infections that can be treated by surgical incision alone, such as cases of isolated (meaning, one solitary area of infection) furunculosis or folliculitis, should not be included in the clinical trials.

The complicated category includes infections either involving deeper soft tissue or requiring significant surgical intervention, such as infected ulcers, burns, and major abscesses (or a significant underlying disease state that complicates the response to treatment). Superficial infections or abscesses in an anatomical site, such as the rectal area, where the risk of anaerobic or gram-negative pathogen involvement is higher should be considered complicated infections.

There are clinical situations where it may be difficult to categorize the infection into one of these broad categories. Additionally, there are clinical situations that fall outside these categories: the treatment of active infections in burn patients or the prophylaxis against infections in this same group. Infections that occur infrequently (e.g., necrotizing fasciitis), are complicated by an underlying condition that may impair proper evaluation of the anti-infective agent's effect (e.g., a secondarily infected atopic dermatitis or eczema), are complicated by an immune deficiency in the patient (e.g., the development of ecthyma gangrenosum in neutropenic patients), or involving infections of prosthetic materials (e.g., catheter tunnel infections) should not be included in the primary clinical studies supporting the approval of the new agent. Though data about the efficacy of an agent in such situations is very valuable information, the rarity and/or the complicating factors involved would make proper evaluation of the study agent difficult.

Lesions that are superficial should be of an extensive enough nature that antimicrobial therapy is warranted.

Breakdown of Disease Entities: The sponsor should make an effort to include a wide array of disease entities when studying either uncomplicated or complicated skin and skin structure infections. Thus, in order to adequately evaluate the efficacy of an agent against uncomplicated skin infections, the sponsor should enroll a comparable number of patients with impetiginous

lesions, simple abscesses, and cellulitis. For complicated skin infections, a similar mix of infected ulcers, complicated or extensive abscesses and deeper soft tissue infections should be included. The two categories (uncomplicated and complicated) should be studied separately because of the different pathogens and pathophysiology involved. In the event that a sponsor does not have an adequate profile of disease entities studied, the product package insert may reflect this by only stating which disease entities were actually studied in adequate numbers.

B. Study Considerations

Refer to Points to Consider, pages 31- 34. and the IDSA guidelines, pages S148 - S154.

Several comments applicable to the study of skin and skin structure infections are:

1. This is a microbiologically driven indication, and all efforts should be made to ensure a good yield on pre-therapy cultures. There are conditions where the percentage of patients with growth of pathogen on pre-therapy cultures is low, such as seen in cellulitis, but other conditions usually have high percentages of positive pre-therapy cultures.

2. For uncomplicated skin and skin structure infections, the two most commonly seen pathogens are *Staphylococcus aureus* and *Streptococcus pyogenes.* In fact, this indication traditionally has only included these two pathogens, since other organisms are not uniformly agreed upon by academia to be pathogens in this indication, but rather seen as colonizers or contaminants. If a sponsor proposes the addition of another organism in this indication (uncomplicated skin and skin structure infections), they should provide a scientific rationale as to why they see this organism as being a true pathogen in these infections.

3. For complicated skin and skin structure infections, the possible pathogens are numerous and dependent on the clinical situation, the location of the lesion/infection, and past medical history of the individual patient. Additionally, it is often difficult to separate a colonizer from a pathogen, since the same organism can be either one, dependent on the clinical setting. Thus, it is very important that microbiologic specimens are obtained properly, and that the methods used are described in detail in the study protocol and report.

4. Another problem with complicated skin and skin structure infections is that there may not be any one organism which is found commonly. Thus, the organisms listed in this indication may be dependent on the overall study results and may reflect which organisms were found most commonly. Qualifying statements, such as " This organism was studied in less than 10 clinical cases," have been used previously when this indication has been granted, to alert the clinician that the

actual experience with a certain organism may not be extensive.

5. It is important to include an adequate mix of clinical conditions when studying either uncomplicated or complicated skin and skin structure infections. This should help in obtaining an adequate microbiologic profile with which to make a reasonable decision regarding approval or non-approval.

C. Inclusion Criteria

To be enrolled in a study evaluating skin and skin structure infections, the patient should have an infection consistent with one of the two categories presented above: either an uncomplicated skin and superficial skin structure infection or a complicated skin and skin structure infection. The patient enrollment should include both males and females. All patients should have a microbiologic specimen obtained prior to the initiation of therapy.

The sponsor should also elaborate upon the information that follows. This would allow the reviewer at the FDA to properly picture the patient's disease entity.

1. Anatomical site of infection
2. Extent of infection (length, width, etc.)
3. Superficial or deep involvement
4. Description of actual infected site: including erythema, swelling, tenderness, extension of redness, heat, etc.
5. Cause of infection (such as trauma, spontaneous, bite, etc.)
6. Underlying medical conditions (such as diabetes mellitus, etc.)
7. Previous medical/surgical therapy for the infection being studied.
8. Picture of the infected site (optional but potentially helpful)

D. Exclusion Criteria

Several points to consider include:

1. Infections that have a high cure rate after surgical incision alone (such as isolated furunculosis) or after aggressive local skin care (such as a minor skin infection) should not be enrolled.

2. Prior anti-infective use, even up to the day of patient enrollment, would exclude a patient, except if a culture is obtained showing the persistence of a pathogen. Because of the slow resolution of inflammation in many skin and skin structure infections (e.g., cellulitis) a clinical picture alone, without the positive culture, would be inadequate to enroll a patient on prior anti-infective therapy.

3. For complicated skin infections, medical conditions leading to difficulty in interpreting response (as may be the case in superinfected eczema where inflammation may be prominent for an extended period even after successful bacterial eradication) or where the response may be altered (e.g., as in immuno-compromised patients), should be taken into account and such patients excluded when applicable.

4. With skin and skin structure infections being both a clinically and microbiologically driven indication (i.e., efficacy for both is needed for drug approval), patients who do not have an initial culture should be excluded. However, a negative culture would not discontinue a patient, with that patient still followed for clinical efficacy.

E. Drug Dosing and Regimens

1. Investigational Agent:

Please see General Comments section for details. In clinical settings where the activity of the antimicrobial agent can be affected by environmental factors, studies should be done to evaluate this. For example, an agent which is less active in an acidic environment (as seen with aminoglycosides) may need to be given at a higher dose when treating an abscess.

2. Comparator Agent:

Due to the multiple presentations of these infections and, thus, the use of multiple treatment regimens in clinical practice, there is the potential problem that a clinical trial may have no one comparator agent used frequently enough to compare with the investigational agent. In light of this, the sponsor should clearly specify the comparator (or give one or two appropriate options) to be used in the trial.

It is also appropriate to compare agents administered via different routes of administration. For example, an investigational topical agent could be compared to an approved *first-line* oral agent, or an investigational oral agent could be compared to an

approved *first-line* intravenous agent. In all such cases the sponsor should first discuss the study design with the FDA so as to resolve such issues as blinding.

3. Adjunctive Therapy:

With both uncomplicated and complicated skin and skin structure infections, adjunctive therapy is commonly used. Included among these are: daily dressing changes, use of topical solutions including antimicrobial agents such as Betadine, daily debridement, etc. Because these are considered to be "standards of therapy", the disqualification of patients who receive adjunctive therapy may lead to major enrollment problems. Thus, the sponsor should clearly specify which adjunctive therapies are to be allowed and which would potentially disqualify a patient. With proper blinding and randomization both the investigational agent arm and the comparator arm should have comparable use of these adjunctive therapies.

4. Minimum Duration of Therapy:

The length of therapy needed may vary from condition to condition, with complicated skin structure infections most likely needing longer courses. The course of therapy chosen should be based on appropriate preclinical data and discussed with the agency prior to study initiation.

5. Switch in Therapy:

The sponsor should decide prior to study initiation the criteria necessary to allow a switch from an intravenous agent to an oral agent. This is usually based upon the afebrile period prior to the switch (e.g., 24 or 48 hours of the patient being afebrile would allow for the switch to be made) and also upon certain clinical criteria (e.g., extent of erythema, formation of granulation tissue, etc.) These criteria should be discussed with the FDA prior to study initiation. Prior to switching, a full assessment (including obtainment of cultures) of the patient should be done.

F. Evaluation Visits

1. Pre-Therapy

Microbiologic Tests: At the time of enrollment, all patients (regardless of the disease type) should have appropriate cultures obtained. Several caveats to consider:

a. For superficial skin infections, open impetigo, and open superficial wound infections, a swab from the base of the lesion, after vigorous debridement of an infected area, sent for aerobic culture only should suffice. However,

in cases where such a lesion is in an anatomical site where anaerobes are potential pathogens (e.g., rectal area lesions or when a foul-smelling discharge from a postoperative wound is present), anaerobic cultures should be obtained as well. Antimicrobial susceptibility testing should be done on potential pathogens isolated.

b. For cellulitis and erysipelas, a leading edge needle aspiration culture should be obtained and sent for aerobic culture and antimicrobial susceptibility testing. In addition, two sets of aerobic blood cultures should be obtained as well.

c. For complicated skin and skin structure infections, deep cultures (such as from a biopsy, needle aspiration, surgically obtained specimens or fluids/pus) of an area contiguous to the infected burn, ulcer, wound, etc. should be obtained. Swabs are not acceptable. Specimens should be sent for aerobic, anaerobic, mycobacterial and fungal cultures, as the clinical picture indicates. For anaerobic cultures, proper anaerobic transport methods should be followed. In addition, two sets of blood cultures (both aerobic and anaerobic) should be obtained prior to study drug initiation. Antimicrobial susceptibility should be performed on the isolated pathogens.

d. Only microorganisms accepted as pathogens should be considered as valid when determining the microbiologic evaluability of a patient. Patients who grow only transient or resident skin flora on the pre-therapy culture should be found to be microbiologically unevaluable. A list of accepted pathogens should be created by the sponsor prior to study initiation, and should be discussed with the FDA. This is especially important in complicated skin and skin structure infections where the potential number of pathogens is great.

In all cases, gram stains of the specimen are helpful and should be encouraged. This is of special importance in cases where prior anti-infective therapy was initiated.

Safety studies: Please refer to the General Comments section for full details.

Prior anti-infective therapy: As noted previously, prior anti-infective use, even up to the day of patient enrollment, would be acceptable if a culture is obtained showing the persistence of a pathogen. Because of the slow resolution of inflammation in many skin and skin structure infections (such as cellulitis) a clinical picture alone, without the positive culture, would be inadequate to enroll a patient on prior anti-infective therapy.

2. On-Therapy

Assessments During Therapy: Please refer to the General Comments section for more details. It should be noted that the number and timing of assessments during therapy may vary depending upon the study drug and the diagnoses (be it uncomplicated or complicated). Additionally, interventions, such as daily debridements, dressing changes, etc., are allowed if the study protocol clearly defines their limits. Such interventions should be considered the standard of care by the academic community and should not be done so as to only help the efficacy rate of the study drug. There are situations in which an intervention should be considered a sign of a clinical failure, and these should be discussed with the FDA and spelled out in the study protocol. An example of this would be an unplanned incision and drainage (I&D) of an abscess several days after therapy had been started.

In situations where an intravenous agent may be transitioned to an oral agent, the sponsor should discuss which criteria may be needed to qualify a patient for such a switch with the FDA prior to study initiation. Commonly used criteria are a period of apyrexia and appearance of the skin infection. As had been stated before, a full assessment (including attainment of microbiologic specimens for culture and Gram stain) should be performed prior to the transition being made.

3. End-of-Therapy

Medication Related Questions: Please refer to the General Comments section for more details. In regard to the study medication, several important points to consider are:

a. Patients should receive between 80-120% of the proposed duration of therapy.

b. Prolonged Medication Use: There may commonly be situations where patients receive a course of therapy longer than the protocol specifies. In general, patients who receive greater than 120% of the protocol specified course should be found unevaluable. However, if an extension of therapy (meaning greater than 120% of the intended course) is found to be a common occurrence, the sponsor may be asked to recommend a longer course (and additional studies).

c. Daily dressing changes with the application of antimicrobials, such as Betadine, can be allowed if specified in the study protocol and the patients properly randomized.

4. Post-Therapy

Timing: The timing of the test-of-cure visit (the visit whose assessments should be used to evaluate the clinical and microbiological response) should be at least 7 days after the tissue levels of the study drug have gone lower than the MICs of the expected pathogens. Thus, for most anti-infectives, an appropriate window for the test-of-cure follow-up visit would be 7 to 14 days after completion of therapy. For such agents where tissue levels remain elevated for days after completion of therapy, a window of 14 to 21 days would be more appropriate. Please refer to the General Comments section for more details.

Assessments: All clinical assessments performed at the pre-therapy and on-therapy visits should be done at the follow-up visits. As much information as possible is needed in these infections, as had been noted before. In cases where a case report form or tabulation only allows the investigator to state if a patient was cured/improved/not cured and does not leave room for reporting clinical assessments the FDA retains the right to find all such patients as unevaluable.

Appropriate microbiologic specimens should be obtained in all patients at the follow-up visits, if there is a focus to culture. In situations where the skin infection has healed to the extent that microbiologic specimens can not be obtained, such patients should be seen as *presumed eradications*. The specimens obtained should be cultured the same way as done at the pre-therapy visit. An important aspect to follow in all follow-up cultures is the development of resistance to the study drug. Thus, if a pathogen is isolated on a follow-up culture(s), antimicrobial susceptibility testing should be done.

The need for safety studies, and the type of safety studies needed, should depend upon the study drug and should be discussed with the FDA prior to study initiation.

G. Outcome Categories

1. Evaluability:

With demonstration of both clinical and microbiologic efficacy needed for an investigational drug to be approved for the treatment of either complicated or uncomplicated skin and skin structure infections, all patients should have a pre-therapy culture(s) obtained. However, with a percentage of pre-treatment cultures inevitably showing no growth of pathogen, patients can be found to be either clinically and microbiologically evaluable or clinically evaluable alone.

2. Clinically Evaluable

The following criteria should be met:

- No violations of inclusion/exclusion criteria

- Pre-treatment culture obtained

- An adequate description of the patient's infected area/lesion has been provided (as has been described before)

- Adequate length of therapy i.e., 80-120% of the protocol specified course (usually in days, not doses) or at least 2 full days of therapy for patients deemed to be failing while on therapy

- No use of concomitant antimicrobial therapy

- Adequate follow-up visit (at or after the timing for the test-of-cure visit), with a full description of the infected area provided in the patient's record, and a culture obtained (if an appropriate site to culture is available)

3. Clinically and Microbiologically Evaluable

- Clinically evaluable, as described above

- Growth of pathogens on an adequate pre-treatment culture, and antimicrobial susceptibility testing

- Adequate follow-up visit, with repeat culture and antimicrobial susceptibility testing (if an appropriate site to culture is available).

4. Efficacy Outcome

A separate clinical and microbiologic evaluation should be done on each patient. The options for a response should be either cured (or eradicated for microbiologic response) or not cured (or not eradicated), with all unevaluable patients considered unevaluable.

5. Clinical Response

Evaluable patients who at the test-of-cure visit (or at a later date if they failed to come to this visit) have the following, should be considered cured:

Total resolution of all signs and symptoms of the infection, or Improvement of the above to such an extent that no further antimicrobial therapy is necessary.

6. Microbiologic Response

This should be done both on a patient level and a pathogen level. Patients who at the test-of-cure visit (or a later date if they failed to come to this visit) have the following should be considered as having had their pathogen eradicated:

- No growth of either the pre-treatment pathogen or of a new potential pathogen on a post-therapy culture **or**

- A post-therapy culture was not obtained due to lack of culturable material, secondary to an adequate clinical response

All clinical failures should have a repeat culture and antimicrobial susceptibility testing done, especially in an age where resistance development is not uncommon.

7. Clinical and Microbiologic Response Resolution

In the vast majority of cases the clinical and microbiologic cure rates should be consistent, with an explanation provided for cases where they are not. Two such situations are:

a. Clinical Cure/Microbiologic Not Cure

In such situations, one should consider whether the repeat positive culture is showing the growth of a true pathogen or of a colonizer/contaminant. In a large number of skin and skin structure infections (such as in burns), the most common pathogens are also common skin flora, which makes evaluation of culture results difficult at times.

b. Clinical Not Cured/Microbiologic Cure

In complicated skin and skin structure infections, either underlying medical conditions or a large inflammatory component to the underlying process (such as seen in decubitus ulcer) may make it difficult to adequately evaluated the patient clinically. In such cases, a longer post-treatment follow-up period should be considered. However, in no situation should a microbiologic response alone be viewed as proof of clinical efficacy.

8. Therapeutic Response

This refers to a combined overall efficacy response, where patients who have been deemed as both clinically cured and microbiologically eradicated are called overall cures. All other combinations of results are seen as failures. The the majority of cases should have the same response both clinically and microbiologically, and an effort should be made to explain discrepancies. Please refer to the General Comments section for more details

concerning the use of *therapeutic response*.

9. Safety Outcome:

Please refer to the General Comments section for full details.

Indication 5 & 6: Community-Acquired Pneumonia and Nosocomial Pneumonia

A. Regulatory Synonyms

Before these categories were identified in the Points to Consider document, these disease entities were included under the indication *lower respiratory tract infections* with specific information on whether pneumonia or bronchitis were included.

Because there is extensive overlap of the evaluability for nosocomial and community-acquired pneumonia, the two indications are discussed together. Wherever appropriate distinctions between the two entities should be identified in detail.

B. Study Considerations

Refer to Points to Consider, pages 35 - 37 and the 1992 IDSA Guidelines pages S80-/86.

Various combinations of clinical, radiographic, and laboratory criteria are used by clinicians and academicians to diagnose pneumonia. For the purposes of the evaluation of clinical trials, there should be supportive evidence in each of these categories. The clinical entity of *pneumonia* may manifest in a variety of ways given the spectrum of organisms and host conditions to be considered. It was proposed in the IDSA Guidelines that because there is a blurring between community- and hospital-acquired pneumonia, it is reasonable to select patients as trial candidates on the basis of the clinical picture.

The six categories outlined in the IDSA Guidelines for inclusion criteria for enrollment and/or stratification of patients who are febrile and have radiographic evidence of pulmonary infiltrates are: Atypical pneumonia, viral pneumonia, acute bacterial pneumonia, aspiration pneumonia, ventilator-associated pneumonia, and pneumonia in an immuno-compromised and/or neutropenic host.

Though the health care environment is rapidly changing, for the most part, cases of atypical pneumonia and viral pneumonia may still be community-acquired (and treated) while those of aspiration pneumonia and ventilator-associated pneumonia may be nosocomial infections. The entity *acute bacterial pneumonia* could be acquired and treated in either setting, but many of these patients may be hospitalized for at least part of their treatment course, thereby adding more challenges to the design, conduct, and evaluation of a clinical trial.

The criteria in this document are general so that they can encompass most of the IDSA-proposed categories listed above. However, since the etiologies, clinical manifestations, and

diagnostic methods in immuno-compromised and/or neutropenic hosts may be markedly different, this set of guidelines is not intended to necessarily encompass this category.

C. Inclusion Criteria

The criteria to establish the diagnosis of infectious pneumonia in *adults* based on the clinical, radiographic, and microbiologic criteria are listed below:

1. Clinical Findings

New onset of a clinical picture compatible with bacterial pneumonia with at least two of the following signs and symptoms:

- Cough
- The production of purulent sputum or a change in the character of sputum
- Auscultatory findings on pulmonary exam of rates and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony)
- Dyspnea, tachypnea, or hypoxemia, particularly if any or all of these are progressive in nature
- Organism consistent with a respiratory pathogen isolated from blood culture(s)

and at least one of the following:

- Fever, defined as body temperature >38^{o} C (100.4^{o} F) taken orally; >38.5^{o} C (101.2^{o} F) tympanically; or >39^{o} C (102.2^{o} F) rectally
- An elevated total peripheral white blood cell count (WBC) > 10,000/mm^{3}, or > 15% immature neutrophils (bands), regardless of total peripheral white count, or leukopenia with total WBC < 4500/mm^{3}

To establish diagnosis of infectious pneumonia for *pediatric* patients, the same diagnostic criteria can be used, but since there might be lack of sputum specimen in pediatric patients, blood cultures or serology can be substituted.

2. Radiographic Findings

Within 48 hours of institution of therapy, the chest radiograph should show the presence

of a new or progressive infiltrate(s), consolidation, cavitation, or pleural effusion in conjunction with the clinical and microbiological findings necessary to establish the diagnosis (see the Clinical Findings section above and the Microbiologic Section below).

The state of hydration of the patient at the time of the initial radiograph should be taken into consideration. Repeat films after hydration or diuresis are acceptable provided they are taken within the above time frame.

3. Microbiologic Criteria

Within 24 hours prior to, or at the time of enrollment, all patients should have had a Gram stain, culture and susceptibility testing of respiratory secretions obtained by any of the following means: Deep expectoration, nasotracheal aspiration, intubation with endotracheal auctioning, bronchoscopy with endobronchial lavage or protected-brush sampling, transtracheal aspiration, percutaneous lung or pleural fluid aspiration.

Blood culture and susceptibility testing should be done in all hospitalized and pediatric patients.

Isolation by culture is preferred for the diagnosis of pneumonia due to *Mycoplasma pneumoniae, Legionella pneumophila,* or *Chlamydia pneumoniae.* The alternate diagnostic test may be used to establish infection with one of these pathogens. However, due to rapid advances in technology, this should be discussed with the Division prior to initiation of the study. However, in general, the use of antibody titer information would necessitate a single diagnostic antibody titer, (IgM), or a fourfold increase in paired serum samples (IgG) for the pathogen under study.

Microscopic examination of the Gram stained respiratory secretions should show presence of microorganisms, $\geq$ 25 polymorphonuclear cells and $\leq$ 10 squamous epithelial cells per field at 100X magnification (low-power, 10X objective).

Because in evaluation of nosocomial pneumonia, there does not seem to be a consensus in the literature on the criteria for interpretation of culture and Gram stain results of specimens obtained from mechanically ventilated patients, the assessment of the Gram stain and culture data should be based on criteria established and discussed with the Division *a priori.*

D. Exclusion Criteria

In addition to general exclusion criteria applicable to other trials, patients enrolled in pneumonia trials should be excluded for the following reasons:

1 Patients with known bronchial obstruction or a history of post-obstructive pneumonia. (This does not exclude patients who have chronic obstructive pulmonary disease.)

2. Patients with primary lung cancer or another malignancy metastatic to the lungs should be excluded.

3. Unless the study is specifically designed for such a patient population, patients with cystic fibrosis, AIDS, or those with known or suspected active tuberculosis should be excluded.

E. Drug and Dosing Regimens

Generally recognized minimum criteria that could be applied to the duration of therapy necessary for evaluation of a clinical response are that the patient receive at least 80% of the intended regimen for at least 48-72 hours (in the absence of an adverse event or other extenuating circumstances necessitating drug discontinuation) before the clinical assessment of failure can be made and at least 5 days of therapy with $\geq$ 80 % compliance for an assessment of a favorable clinical outcome.

Depending on the specific agent and indication under study, the duration of therapy may be variable and somewhat arbitrary. But, 5-10 days of therapy is advocated for common bacterial pneumonias treated with outpatient regimens, and 10-14 days of therapy is customary for bacterial pneumonias treated on an inpatient basis (allowing for the parenteral to oral transition of therapy). However, there are certain recognizable exceptions to these time-frames. Pneumonias due to *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* are typically treated on an outpatient-basis for 10-14 days. Legionnaire's disease, which may be a community-acquired or nosocomial pneumonia but frequently causes hospitalization, is typically treated with a 14- to 21-day course.

F. Evaluation Visits

1. Pre-Therapy

Patients should have documentation of their pre-therapy evaluation including results of the physical examination, the chest x-ray, laboratory tests including gram stain and culture and susceptibility testing. Depending on the particular protocol, a baseline oxygen saturation reading by pulse oximeter or an arterial blood gas may be used as well.

2. On-therapy

Outpatients and hospitalized patients should have clinical assessments, captured in the case

report form. If clinical conditions warranted daily assessments, the results of these should be captured in the case report forms. The frequency of assessments should be based on the indication studied (e.g., community-acquired pneumonia that necessitated hospitalization vs. nosocomial pneumonia in a ventilated patient in the intensive care unit).

The laboratory assessments to be made during the course of the study can be individualized somewhat for the agent and indication under study. However, some general principles are the following:

a. Repeated cultures and susceptibility testing of respiratory tract secretions, if obtainable, should be performed at 48 to 72 hours after initiation of therapy.

b. Blood cultures and susceptibility testing should be repeated 48 to 72 hours if initially positive or the patient is failing to respond to treatment.

c.. The collection of specimens using semi-invasive techniques (e.g., collection of pleural fluid, transtracheal aspiration, bronchoscopy) should be repeated only if the clinical response is suboptimal.

d. The hematologic, renal, serum chemistry laboratories should be repeated within 3 to 5 days of initiation of therapy, and at least every 5 to 7 days during therapy.

At any time while on therapy a patient may be withdrawn from the study if, in the opinion of the investigator, continuing therapy would jeopardize the patient's health or safety. However, the criteria for early drug discontinuation/withdrawal and how such patients should be handled should be defined *a priori.*

Datapoints at Visits of Clinical Interest

1. Temperature
2. Peripheral white cell count (WBC)
3. Respiratory rate(not a valid parameter if patient is on a ventilator)
4. Sputum quality
5. Sputum production
6. Severity of cough
7. Pleuritic chest pain
8. Rigors (if present either initially or after therapy initiated)
9. Oxygenation
10. Chest radiograph appearance

These signs, symptoms, & laboratory datapoints should be captured at each visit, especially, if they were present at entry.

3. End-of-Therapy

An end-of-therapy assessment visit is not needed to be evaluable. The IDSA Guidelines recommend follow-up cultures, serum chemistry lab testing, and chest radiography be performed within 72 hours of completion of therapy. Studies done within this window of time could be considered to be end of therapy or done to fulfill the goals of the short-term follow-up visit, but are not sufficiently removed from the course of therapy to be used for the assessment of clinical efficacy for the purposes of the drug approval process.

Unfavorable clinical responses can be assessed at any point, and can be considered to be therapeutic failures if the patient received at least the minimum amount of therapy needed for determination of efficacy. In most instances, for the assessment of clinical efficacy there should be early (short-term) and late (long-term) follow-up visits.

The timing of the short- and long-term follow-up visits proposed for the assessment of clinical efficacy should be based upon the half-life of the drugs and the natural history of the disease entity under study. Protocols employing drugs with very long half-lives, abbreviated courses of therapy, different durations of therapy between study drug and comparator agent, or any combination thereof, should be reviewed with the Division prior to study initiation.

4. Post-Therapy

The investigator's assessment at each visit as well as that of the applicant's assessment at each visit are important. If the applicant's assessment differs from the investigator's, an explanation for the difference should be provided to assist the Agency's medical officer in assessing the case.

5. Test of Cure

For a favorable outcome to be considered the overall assessment of clinical efficacy, that visit should be at least 7 days or the time equivalent to five half-lives of the test agent post an adequate course of therapy. (Whichever is longer -- See General Considerations section.) In other words, in cases with favorable clinical outcomes with only one post-therapy visit, to be evaluable (as a test-of-cure visit) that visit should be at least 7 days or five study drug half-lives after an adequate (as defined in the protocol) course of therapy.

G. Outcome

See Definitions within the section General Considerations for Clinical Trials

1. Clinically and Microbiologically Evaluable

For a patient who has adequate clinical data to be considered both *clinically and microbiologically evaluable*, the Gram stain data on the respiratory secretions should be as outlined above and the culture data should corroborate with the morphotypes present on the Gram stain.

Alternatively, in patients with adequate clinical data, blood cultures showing a respiratory pathogen could be used to substantiate the microbiologic evaluability.

2. Clinically Evaluable

Patients who have adequate clinical data, but incomplete or inadequate microbiologic data, should be considered to be clinically evaluable only. The clinical outcome is paramount in the assessment of the overall efficacy of the therapy, but in most instances this does not negate the need for sufficient pathogen data to garner approval for specific a organism under this indication.

3. Statistical Considerations

See General Considerations.

Indications 7 & 8: Acute Bacterial Exacerbation of Chronic Bronchitis and Secondary Bacterial Infection of Acute Bronchitis

A. Regulatory Synonyms

Synonyms that have been used in past years include *lower respiratory tract infection*, which could include bronchitis as well as pneumonia; more recently, the Points to Consider document provides four categories for infections of the lower respiratory tract, including two for bronchitis: Acute exacerbation of chronic bronchitis (AECB), secondary bacterial infection of acute bronchitis (SBIAB). The IDSA Guidelines provides the diagnostic category AECB.

B. Study Considerations

Because of confusion of how much lumping or splitting of diagnoses under the heading *bronchitis* should occur, a discussion of the spectrum of disease (summarized from major textbooks on adult and pediatric infectious diseases), and role of bacteria, is warranted.

Bronchitis is an inflammatory condition of the tracheobronchial tree. Acute bronchitis is generally an infectious process. In children, it is fairly common during the early years and is due to viruses (adenovirus, influenza virus, parainfluenza virus, respiratory syncytial virus, rhinovirus, enterovirus) or *Mycoplasma pneumoniae. Streptococcus pneumoniae* or *Hemophilus influenzae* are exceedingly rare. Signs and symptoms of URI and fever often precede bronchitis manifestations such as cough and sputum production. In adults, the same disease may be recognized, with *Chlamydia pneumoniae* as an added pathogen.

Chronic bronchitis is usually defined as a condition characterized by cough and sputum production for > 2 consecutive years and for most days in a consecutive 3-month period. The underlying problem is typically exposure to irritants, most commonly cigarette smoking, with resulting obstructive pulmonary disease and emphysema. Acute exacerbation of this chronic process is characterized by increased coughing, sputum and respiratory distress. These symptoms may be due to viral infection in 25-50% of patients. The role of bacterial infection in exacerbation of chronic bronchitis is unclear since patients may have *S. pneumoniae, H. influenzae,* or *Moraxella catarrhalis* isolated from sputum cultures between episodes of acute illness. *S. pneumoniae, H. influenzae,* and *M. catarrhalis* are generally accepted as the most frequent bacterial causes of acute exacerbation of chronic bronchitis; less common isolates are *M. pneumoniae* and *C. pneumoniae.* While the role of bacteria in the pathogenesis of the acute process and the role of antimicrobial agents in the management of the acute process continue to be investigated, there is evidence that antimicrobials have clinical benefit. Some patients who show complete clinical response may continue to harbor the pathogen as a colonizer in the respiratory secretions (making outcome assessment a challenge). Chronic

bronchitis is poorly defined in pediatric patients and usually overlaps with asthmatic bronchitis, in that both are characterized by persistent cough and wheezing. An infectious etiology may be postulated.

Refer to Points to Consider, pages 37 - 39, and the IDSA guidelines, pages S77 - S80.

C. Inclusion Criteria

For practical purposes, AECB is a disease of adults who have a documented history of chronic bronchitis and they should be enrolled in these studies. SBIAB, where an underlying chronic pulmonary pathology is not present, may be diagnosed at any age.

To be clinically evaluable for this indication, patients should have a *clinical* diagnosis of AECB based on history, physical examination and radiographic examination.

1. The patients should have a history of chronic bronchitis, characterized by cough and sputum production for > 2 consecutive years and most days in a consecutive 3-month period. The acute process should be characterized by increased cough, sputum production and dyspnea. Fever may be present. Documentation of both the chronic process and the acute exacerbation can be made on the basis of history, physical examination and/or pulmonary function studies (FVC, FEV 1, TLC, peak flow, ABGs).

2. Physical examination should be performed, and any abnormal findings documented, especially those pertinent to the respiratory tract. The presence of purulent sputum, defined as $\geq$ 25 WBC per field and $\leq$ 10 squamous epithelial cells at 100x magnification (low power, 10x objective), should be documented.

3. Radiographic documentation should include a chest X-ray which serves to exclude pneumonia.

The clinical diagnosis of SBIAB should be based on a recent history of respiratory tract illness, characterized by recent-onset of cough, sputum production, fever or other evidence of infection.

To be microbiologically evaluable for this indication, patients should have a *microbiological* diagnosis of AECB or SBIAB based on isolating a pathogen from a sputum sample. For adequate evaluation, it is important that the patient receive proper instruction on providing a sputum and not a saliva sample and the clinical laboratory evaluate the adequacy of the specimen.

To be evaluable for microbiological assessment, documentation should include gram stain examination of the specimen, quantitation of WBCs and oral epithelial cells, isolation of a pathogen on culture and results of susceptibility testing. The sputum specimen is considered 50

adequate when it contains ≤ 10 squamous epithelial cells and ≥ 25 WBC per field at 100x magnification (low power, 10x objective).

D. Exclusion Criteria

Patients with cystic fibrosis, tuberculosis, bronchiectasis, or pulmonary malignancies should be excluded. In addition, patients receiving systemic steroids in a dose of ≥10 mg per day of prednisone (or the equivalent) should be excluded.

E. Drugs and Dosing Regimen

To be evaluable, the patient should receive ≥ 80% (or within 80-120%) of the prescribed dose amount and/or dosing regimen. Dosing should be documented as should compliance (diary or urine test for latter). Patients who received at least 72 hours of therapy and are not doing well may be classified as failures.

Test Drug: Lot number and other identifier should be provided (safety, not evaluability recommendation).

Control Drug: While any drug and dosing regimen approved by the FDA may be used, consideration should have been given to a regimen considered clinically relevant in the area where the study was conducted. For example, a beta-lactamase stable drug should be used in areas with a high incidence of beta-lactamase producing organism. A minimum target efficacy rate for that drug should be provided.

F. Evaluation Visits

1 . Entry/Pre-Therapy

To be evaluable, the patients should have an entry visit. The following information from the initial visit should be included in the patient record: date of visit, clinical signs and symptoms of present episode of bronchitis, including a qualitative and quantitative description of the sputum, past history of chronic bronchitis, use of concurrent medications such as steroids, bronchodilator, results of the clinical examination, radiologic examination (chest X-ray), sputum characterization and culture results, and laboratory test results. Hospital status (inpatient vs outpatient) should be documented.

The following patient pre-exacerbation information should also be recorded: cough frequency, sputum volume and characteristics, baseline supplemental oxygen use, recent history of antibiotic use, and history of allergies.

2. On-Therapy

To be evaluable, the patient should have an on-therapy visit either in the investigator's office or by phone. In clinical practice, physicians see patients approximately 3 to 5 days into therapy to evaluate the patient's response to therapy. If the patient is doing well, therapy is continued. If the patient is considered to be failing therapy, the drug is stopped and the patient is prescribed another antimicrobial; a sputum gram stain and culture should be obtained. If the patient is seen for the on therapy visit, findings from this visit (e.g., history, physical examination, laboratory test results) should be documented in the patient record. If the patient is contacted by telephone, documentation of specific questions asked and responses given should be included in the record. This visit is strongly recommended for good study conduct, but its absence should not serve as the only reason for exclusion from evaluability.

The IDSA Guidelines (Nov 1992) recommend a 3- to 5-day visit and weekly examinations thereafter until end of therapy, then clinical and microbiological assessment at 48 hours, 7 to 14 days and 21 to 28 days after the completion of therapy

3. End-of-Therapy

This visit is optional. In clinical practice, physicians may see patients near the completion of therapy to optimize patient care. If clinical examination and other tests are performed at this visit, they may be included in the case record. However, this visit should not be considered a test of cure visit.

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

This visit should occur approximately 1 to 2 weeks after the completion of therapy. The results of the clinical evaluation, including status of all presenting signs and symptoms as well as emergence of any new signs and symptoms of bronchitis or pneumonia should be documented. Radiographic examination is not necessary unless clinically indicated. The character of the sputum and results of repeat gram stain and culture should be documented.

No additional visits are routinely necessary.

G. Outcome

1 . Clinical Outcome

Clinical response is the primary determinant of efficacy for the indication of bronchitis.

a. Clinical Cure

Patient meets above evaluability criteria and has resolution of the acute signs and symptoms at the test of cure visit. For patients with chronic bronchitis, this should be interpreted as return to baseline condition (see IDSA Guidelines, Nov 1992, page S79). No antibiotics (other than per protocol) were given. The category of clinical improvement should be avoided for purposes of drug development. If it is unclear whether the patient meets either the cure or failure category, further follow-up should be planned. If the improved symptoms persist and additional antimicrobials are added, then the patient is failure. If the patient returns to baseline condition without additional antimicrobial therapy, the patient is classified as a cure.

b. Failure

Patient is considered a failure if there is persistence or worsening in the signs or symptoms of the acute process, or need for hospitalization (rehospitalization). Also, patients who receive additional antimicrobials or whose antimicrobial therapy is changed are considered failures. If a patient is classified as a failure at the on-therapy or end-of-therapy visit, this evaluation of failure should be carried forward into the final visit outcome. That is, for the purpose of calculating outcome rates -- once a failure, always a failure.

Note: No distinction is thus made between failure and relapse.

2. Microbiological Outcome

A microbiological evaluation is not appropriate if a baseline pathogen is not identified.

a. Presumed eradication

In the absence of a repeat sputum culture, a patient should be considered a presumed eradication if the definition of clinical cure is met. In a patient with SBIAB, eradication should be presumed when there is no more sputum production.

b. Eradication

The absence of the entry pathogen from a repeat sputum culture performed 1- to 2-weeks post-therapy in a patient with chronic bronchitis.

c. Presumed Persistence

In a patient who is classified as a clinical failure, as defined above, it should be

presumed that there is persistence of the original pathogen.

d. Persistence

Presence of the original pathogen on repeat culture of the sputum done on therapy or at the 2- to 4-weeks (1-2 weeks) post-therapy evaluation.

e. Superinfection

Isolation of a new pathogen on therapy in a symptomatic patient.

Indication 9: Acute Otitis Media

A. Regulatory Synonyms

Synonyms include *acute bacterial otitis media*, *acute suppurative otitis media*, *acute purulent otitis media*, *otitis media*. This entity has also been mistakenly called *otitis media with effusion*; the latter should be reserved for patients who are asymptomatic and have an isolated middle ear effusion identified by physical exam

Acute otitis media is defined as inflammation of the middle ear, manifested by localized signs or symptoms such as ear pain, hearing loss, nonspecific symptoms like lethargy, fever, irritability, nausea and vomiting, and characterized on otoscopic examination by inflammatory changes in the tympanic membrane.

B. Study Considerations

Refer to Points to Consider, pages 39 - 40, and the IDSA guidelines, pages S69 - S73.

C. Inclusion Criteria

Usually male and female pediatric patients are enrolled. Although less common, the disease may also be studied in adult patients. To be clinically evaluable, patients should have a *clinical* diagnosis of otitis media based on history, physical examination, pneumatic otoscopy and tympanometry. The localizing signs and symptoms referable to each ear should be recorded.

The otoscopic findings considered most consistent with bacterial acute otitis media and which should be documented include:

1. Swollen, bulging tympanic membrane which may be erythematous

   Because hyperemia may be present in a febrile or crying child, a red tympanic membrane alone is not adequate for the diagnosis of otitis media.

2. Loss of the light reflex

3. Abnormal tympanic membrane mobility on pneumatic otoscopy due to the presence of pus or fluid behind the membrane and edema of the membrane.

Documentation of these signs is of particular importance in the *clinical-only* study (See Points to Consider, where a microbiologic diagnosis is not available to distinguish patients with acute

otitis media due to bacterial etiology from those with simple hyperemia, viral otitis media, otitis media with effusion.

Thickening of the tympanic membrane indicates a chronic process and should be noted.

Other signs or symptoms which may be present in patients with acute otitis media and help confirm the diagnosis include one or more of the following:

- earpain
- earache
- ear fullness
- discharge from external canal (perforation)
- decreased hearing
- fever
- vomiting
- diarrhea
- fussiness
- not eating, etc.
- anorexia

Infants and younger children often present with nonlocalizing symptoms, older ones can usually articulate symptoms referable to the ear. Naturally, otitis externa needs to be distinguished from otitis media.

To be microbiologically evaluable, the patient should have a *microbiological* diagnosis of bacterial otitis media based on a specimen typically obtained by tympanocentesis.

Because of the invasiveness of a tympanocentesis, the Points to Consider document distinguishes between studies in which patients are clinically evaluable, meaning all evaluation is based on clinicallotoscopic evaluations and clinically and microbiologically evaluable, which means that a bacterial pathogen is isolated at baseline.

To be evaluable for microbiological assessment, documentation should include:

- ear sampled (right and/or left)
- bacterial organism isolated
- the isolate's in-vitro susceptibility testing to both the study and control drugs.

Furthermore, it is recommended that tympanocentesis be performed in any patient who is judged to be failing therapy. The obtained fluid should be cultured and the isolate(s) should be tested for development of antimicrobial resistance against the test drug. However, absence of such a follow-up culture should not be considered a reason for considering a patient unevaluable.

In the 1990s, the three most common bacterial pathogens are *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis.* Other infrequently isolated pathogens are *Streptococcus pyogenes, Staphylococcus aureus* and *Pseudomonas aeruginosa.*

D. Exclusion Criteria

See General Considerations

Patients with perforated eardrums need not be excluded from study but the presence of the perforation should be recorded. Patients with recurrent episodes or chronic episodes need not be excluded but should be enrolled with planned subset analyses.

E. Drugs and Dosing Regimen

To be evaluable, the patient should receive $\geq$ 80% (within 80-120%) of the prescribed dose amount and/or dosing regimen. Dosing should be documented as should compliance (diary or urine test for latter). A patient who received at least 72 hours of therapy and is not doing well may be classified as a failure.

Test Drug: Lot number and other identifier should be provided (safety, not evaluability recommendation).

Control Drug: While any drug and dosing regimen approved by the FDA may be used, consideration should have been given to a regimen considered clinically relevant in the area where the study was conducted. For example, a beta-lactamase stable drug should be used in areas with a high incidence of beta-lactamase producing organism. A minimum target efficacy rate for that drug should be provided.

F. Evaluation Visits

1. Entry

To be evaluable, the patient should have been examined at entry. Documentation from that examination should include date of visit, signs and symptoms identified, physical examination including pneumatic otoscopy and tympanometry results for each ear, tympanocentesis (if done) and submission of middle ear fluid for culture and susceptibility testing, and laboratory tests. Medical history should include number of episodes of acute otitis media in the past 12 months and patients with recurrent otitis media (> 3 episodes in 6 months) should be evaluated separately from patients without frequent episodes..

2. On-Therapy

In clinical practice, physicians see patients approximately 3 to 5 days into therapy to evaluate the patient's response to therapy. If the patient is doing well, therapy is continued. If the patient is considered to be failing therapy, the drug is stopped and the patient is prescribed another antimicrobial. If the patient is assessed at the on-therapy visit, findings from this visit (e.g., history, physical examination, laboratory test results) should be documented in the patient record (CRF). If the patient is contacted by telephone, documentation of specific questions asked and responses given should be included in the record. This visit is strongly recommended for good study conduct, but its absence should not serve as the only reason for exclusion from evaluability.

IDSA recommends observations at 3 to 5 days after initiating therapy, and at least 2 and 4 to 6 week later.

3. End-of-Therapy

In clinical practice, physicians may see patients near the completion of therapy to optimize patient care. If clinical examination and other tests are performed at this visit, they may be included in the case record. However, this visit should not be considered a test of cure visit.

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

This visit should occur approximately 1 to 2 weeks after the completion of therapy. The results of the clinical evaluation, including status of all presenting signs and symptoms as well as emergence of any new signs and symptoms of acute otitis media should be documented.

5 . Late Post-Therapy

Patients may be seen 30, 60, and 90 days after completing therapy if they have persistence of a middle ear effusion. While these follow-up visits are important in patient care, the absence of these visits in the CRF would not make the patients unevaluable.

G. Outcome

1. Clinical Outcome

It should be noted that the clinical assessment of disease outcome in otitis media is based on the patient, not on the ear. Thus, a patient who starts with right otitis media and in the middle of therapy develops left otitis media is not considered to have a new infection. A patient who is entered for right otitis and at the test of cure visit has left otitis media is not called a cure. For systemically absorbed drug, it is assumed that drug is distributed to

both ears. Thus both ears should benefit from a full treatment regimen.

a. Clinical Cure

Patient meets above evaluability criteria and has resolution of signs and symptoms at the test of cure visit, including resolution of edema and erythema, return of the light reflex and mobility. No effusion is present. No antibiotics (other than per protocol) were given.

b. Clinical Improvement

Alternatively, this category can be called *cure with effusion*. Patient has an otoscopic examination demonstrating resolution of signs and symptoms but persistence of an effusion.

c. Clinical Failure

The patient is considered a failure if there is no improvement in signs and symptoms or if there is incomplete resolution of these. Also, patients who receive additional antimicrobials between entry and the 1- to 2-week visit or whose antimicrobial therapy is changed during this time are considered clinical failures. If a patient is classified as a failure at the on-therapy or end-of-therapy visit, this evaluation of failure should be carried forward into the final visit outcome. That is, for the purpose of calculating outcome rates--once a failure, always a failure.

2. Microbiological Outcome

For purposes of evaluability and outcome assessment, if a patient has the same pathogen isolated from both ears, that patient is considered to have one pathogen (e.g., *S.pneumoniae* isolated from the left and the right ear).

If a patient has one pathogen isolated from the right ear and a different pathogen isolated from the left ear, the patient is considered to have two pathogens.

For outcome analysis, if a patient has a pathogen isolated from one ear at entry, and has that pathogen isolated only from the contralateral ear on follow up, that patient is considered to have persistence.

a. Presumed Eradication

In most patients, the microbiological eradication should be presumed based on a favorable clinical response on therapy and through the 1- to 2-week follow up

examination; i.e. a patient who is judged to be a clinical cure or a patient who is judged to be a clinical cure with only an effusion is a presumed microbiological eradication.

b. Documented Eradication

Patients who have a repeat tympanocentesis at 1 to 2 weeks post-therapy and have no organism isolated from the culture would be considered a documented eradication.

c. Documented Persistence

A patient who continues to have the original pathogen isolated from a culture obtained by tympanocentesis is considered a documented persistence.

d. Presumed Persistence

A patient who is judged to be a clinical failure and has no concurrent tympanocentesis performed to evaluate the status of the pathogen is presumed to have persistence of the pathogen. A patient who receives additional antimicrobial therapy before 1-to 2-week follow up visit is considered a presumed persistence.

Indication 10: Acute Sinusitis

A. Regulatory Synonyms

Synonyms include *acute maxillary sinusitis*, *acute bacterial sinusitis*, *acute community-acquired sinusitis*. In early approvals, this condition may have been included under *upper respiratory tract infections* or infections of the ear, nose and throat.

Acute sinusitis is an infection of one or more of the paranasal sinuses.

> NOTE: Ethmoid and maxillary sinuses are present at birth, spenoid and frontal develop by 6 years but change over time. It is considered that postpubertal patients have same disease condition as adults.

The pathogenesis of sinus infection is undoubtedly similar to that of otitis media. Both the middle ear, with its extension, the eustachian tube, and the paranasal sinuses are normally sterile, but their contiguous areas (nasopharynx and nose) have a dynamic microbial flora. Is this reason to consider extrapolating efficacy of drug from one site to other? Is penetration and activity in these sites comparable?

B. Study Considerations

Refer to Points to Consider, pages 40 - 41, and the IDSA guidelines, pages S73 - S77.

C. Inclusion Criteria

Male and female patients of any age may be enrolled; adult patients should be studied (or analyzed) separately from pediatric patients.

To be clinically evaluable, patients should have a *clinical* diagnosis of acute sinusitis based on history, physical examination and radiographic examination. It is assumed that in most patients this means acute maxillary sinusitis, although involvement of other sinuses may be present.

For the diagnosis of acute sinusitis, a history of signs and symptoms lasting for longer than 7 days, but less than 28 days should be solicited. These should include facial pain/ pressure/ tightness typically over the maxillary sinuses, a purulent nasal discharge and cough. Other complaints may be headache, nasal obstruction, bad breath, change in perception of smell, toothache, tearing, periorbital swelling. In children, otitis media may be present concurrently.

Patients with an underlying history of allergic rhinitis should be identified so that they may be analyzed separately.

Physical examination findings should be recorded. This examination should document clinical evidence of paranasal sinus involvement such as tenderness or pain on percussion over the sinuses, the presence of a purulent nasal or post nasal discharge. The examination may also be able to demonstrate opacity of sinuses, and discharge originating from the sinus, inflamed and swollen sinus mucosa, fever.

Radiographic documentation should include either roentgenography (e.g., basal and Caldwell, lateral and Waters) and/or CT or ultrasound examination of the affected sinuses and should comment about sinus abnormalities such as mucosal thickening, air-fluid levels or sinus opacity.

Patients with chronic sinusitis--generally defined as 3 or more episodes of sinusitis in the preceding 12 months or as symptoms lasting greater than 28 days--may be excluded. If they are included in clinical studies, they should be stratified and analyzed separately.

The microbiological diagnosis of acute sinusitis is based on isolating a bacterial pathogen from a specimen obtained by direct sinus aspiration at base line. Specimens obtained by sinus endoscopy are considered to be contaminated by the nasopharyngeal flora.

To be evaluable for microbiological assessment, documentation should include gram stain examination with WBC and bacterial morphotype semiquantitation, quantitative bacterial cultures, and antimicrobial susceptibility testing. The pathogens should be susceptible to the study and control drugs.

If the sample is obtained by direct sinus aspiration, isolation of the common pathogens *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* is considered significant (i.e. etiological agent) only in counts $\geq 10^4$.

If the sample is obtained by sinus endoscopy, *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* are considered pathogens in counts $\geq 10^4$.

In the 1990s, the three most common bacterial pathogens are *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis.* Some reports state that *S. pneumonaie* and *H. influenzae* comprise 50% of the bacterial pathogens in adults while *M. catarrhalis* in addition to *S. pneumonaie* and *H. influenzae* comprise two-thirds of the bacterial pathogens in children. The Points to Consider document suggests that 25, 25, and 15 evaluable isolates, respectively, be available for an assessment of outcome in this disease. Other infrequently isolated pathogens are *Streptococcus pyogenes, Staphylococcus aureus* and *Pseudomonas aeruginosa.* Anaerobes are seen in a small percentage of cases, usually ones associated with dental disease.

D. Exclusion Criteria

See General Considerations

E. Drugs and Dosing Regimen

To be evaluable, the patient should receive within 80-120% of the prescribed dose amount and/or dosing regimen. Dosing should be documented as should compliance (diary or urine test for latter). If a patient received 72 hours of therapy and is not doing well, the patient may be classified as a failure.

Test Drug: Lot number and other identifier should be provided (safety, not evaluability recommendation).

Control Drug: While any drug and dosing regimen approved by the FDA may be used, consideration should have been given to a regimen considered clinically relevant in the area where the study was conducted. For example, a beta-lactamase stable drug should be used in areas with a high incidence of beta-lactamase producing organism. A minimum target efficacy rate for that drug should be provided.

F. Evaluation Visits

1. Entry

To be evaluable for analysis, the patient should have been seen at entry. The following information from the initial visit should be included in the patient record: date of visit, clinical signs and symptoms of present episode of sinusitis, relevant past history of sinusitis episodes or respiratory allergies, results of the clinical examination including ears, nose, throat and teeth, radiologic examination (X-ray or CT or ultrasound), quantitative sinus aspirate culture and antimicrobial susceptibility testing (if done) and laboratory test results.

2. On-Therapy

In clinical practice, physicians see patients approximately 3 to 5 days into therapy to evaluate the patient's response to therapy. If the patient is doing well, therapy is continued. If the patient is considered to be failing therapy, the drug is stopped and the patient is prescribed another antimicrobial. If the patient is seen for the on therapy visit, findings from this visit (e.g., history, physical examination, laboratory test results) should be documented in the patient record. If the patient is contacted by telephone, documentation of specific questions asked and responses given should be included in the record. This visit is strongly recommended for good study conduct, but its absence should not serve as the only reason for exclusion from evaluability.

IDSA recommends a 2-3 day and 5-7 day on-treatment visit, then weekly or biweekly until resolution of symptoms..., also recommentd is a repeat sinus aspiration for microbiological assessment in all clinical nonresponders at 72 hours.

3. End-of-Therapy

In clinical practice, physicians may see patients near the completion of therapy to optimize patient care. If clinical examination and other tests are performed at this visit, they may be included in the case record. However, this visit should not be considered a test of cure visit.

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

This visit should occur approximately 1 to 2 weeks after the completion of therapy. The results of the clinical evaluation, including status of all presenting signs and symptoms as well as emergence of any new signs and symptoms of sinusitis should be documented. Results of radiographic examination should be documented. If a sinus aspiration is performed, the results of the culture and antimicrobial susceptibility testing should be documented.

5. Late Post-Therapy

Additional visits are not necessary with the exception of patients who are not seen at the test-of-cure visit or who may have a response of improvement at the test-of-cure visit.

G. Outcome

1. Clinical Outcome

a. Clinical Cure

Patient meets above evaluability criteria and has resolution of signs and symptoms at the test-of-cure visit, and at least improvement in the radiographic appearance of the sinuses. No antibiotics (other than per protocol) were given.

b. Clinical Failure

Patient is considered a failure if there is persistence of one or more signs or symptoms of sinusitis (including the appearance of the new ones). Also, patients who receive additional antimicrobials or whose antimicrobial therapy is changed are considered failures. If a patient is classified as a failure at the on-therapy or end-of-therapy visit, this evaluation of failure should be carried forward into the final visit outcome. That is, for the purpose of calculating outcome rates--once a failure, always a failure.

2. Microbiological

The specimen for microbial evaluation for this disease should be obtained through a direct sinus aspiration. It is recognized that patients may elect not to undergo this procedure at follow up visits; therefore, the microbiologic outcome may be presumed, based on clinical findings, as defined below.

A microbiological evaluation is not possible if a baseline pathogen is not identified.

a. Presumed Eradication

In the absence of a repeat sinus aspiration, a patient should be considered a presumed eradication if the definition of clinical cure is met.

b. Documented Eradication

The absence of the entry pathogen from a repeat sinus aspiration at 1 to 2 weeks post-therapy.

c. Presumed Persistence

In a patient who is classified as a clinical failure, as defined above, it should be presumed that there is persistence of the original pathogen.

d. Persistence

Presence of the original pathogen of culture in a sinus aspiration taken 1 to 2 weeks post therapy.

Indication 11: Streptococcal Pharyngitis

(Reserved)

Indication 12: Bacterial Meningitis

(Reserved)

Indication 13: Uncomplicated Gonococcal Urethritis/Cervicitis (Proctitis, Pharyngitis)

A. Regulatory Synonyms

This indication has been granted either as *gonorrhea*, *uncomplicated gonorrhea* or *acute uncomplicated gonorrhea*. A search of the PDR for labeling of approved products revealed that in many labels, the actual site of the infection (endocervical/cervical, urethral, rectal, pharyngeal) is specified, and there are labels in which the gender (male, female) is specifically mentioned. In addition, for most beta-lactam-type antimicrobials, the labeling specifies whether approval is granted for beta-lactamase positive isolates as well as beta-lactamase negative isolates.

Uncomplicated gonorrhea is a sexually-transmitted disease caused by *Neisseria gonorrhoeae.* The disease involves mucosal sites such as the urethra, rectum and pharynx in the male, and the urethra, cervix, (endocervix), rectum and pharynx in the female.

NOTE: Pelvic inflammatory disease in the female, gonococcal arthritis, neonatal gonorrhea involving the eye, etc., are separate entities not covered in this section.

The primary efficacy endpoint is site-specific (i.e., urethral, endocervical, rectal, pharyngeal) eradication of *Neisseria gonorrhoeae.*

B. Study Considerations:

Refer to Points to Consider, pages 43 - 44, and the IDSA guidelines, pages S123 - S130.

1. Protocol

The protocol design should have been discussed with the Division prior to implementation. Some issues that should be addressed include:

a. Because of the public health significance of this indication, consideration should be given to enrollment of pregnant women to study the effectiveness of a drug for the treatment of gonorrhea.

b. Because many patients with gonorrhea may have other STDs concurrently (e.g. chlamydia, syphilis) it is customary and expected in clinical practice to perform cultures (or rapid diagnostic tests) and treat for these infections concurrently with another agent, usually a 7-day course of doxycycline. However, for purposes of clinical studies of single-dose gonorrhea therapy,

these patients may be excluded or, if retained in the study, treatment of these other STDs should be started after the post-treatment culture specimens to assess the eradication of *Neisseria gonorrhoeae* have been taken.

2. Labeling: It is the current practice to label drug products approved for the treatment of gonorrhea with the following information:

   a. Site of infection: urethral, cervical/endocervical, rectal and pharyngeal.

   b. Gender: cervical involvement is synonymous with female patients and urethritis implies men; for rectal or pharyngeal approval, the gender of the patients in whom approval is granted is specified.

   c. Organism: For beta-lactam drugs, the labeling specifies whether beta-lactamase positive *N. gonorrhoeae*, beta-lactamase negative isolates or both were studied and garnered approval.

C. Inclusion Criteria

Postpubertal, usually adult male and female patients are enrolled.

The primary efficacy parameter in this indication is the eradication of the pathogen, *Neisseria gonorrhoeae,* from the specific site of infection, therefore, the microbiological criteria are listed first.

To be microbiologically evaluable, the patients should have a microbiological diagnosis of gonorrhea based on the isolation of the organism from the infected site. Documentation should include the site cultured, isolation of *N. gonorrhoeae,* beta-lactamase status (when applicable) and susceptibility to both the study and control drugs. However, even if the susceptibility is unknown or the isolate is resistant to the study drug(s), in this indication, the eradication rate for all isolates without regard to susceptibility results should be performed (analyzed).

A gram stain of the culture specimen may be used as preliminary evidence to enroll patients in the study; however, a confirmatory culture should be done to consider a patient evaluable.

As a general rule, the urethra should be cultured in all men, urethra and rectum in all female patients. Depending on the history of sexual exposure, the rectum in males or the pharynx in either gender should be cultured. All sites cultured at the entry visit should be recultured at the post-treatment visit.

For the reasons of patient management and public health issues stated earlier, results of

chlamydia and syphilis testing are important, but their absence is not a reason to classify a patient as unevaluable for the purposes of the study.

To be clinically evaluable, patients should have a clinical diagnosis of gonorrhea that is based on history and physical exam including genital, rectal and oral examination. For purposes of clinical evaluation, the investigator should record the signs and symptoms present at entry, or should state that the patient was asymptomatic at entry.

1. In men, characteristic symptoms of acute urethritis are mucoid or purulent urethral discharge and dysuria (generally without urgency or frequency).

2. In women, symptoms may include vaginal discharge, intermenstrual spotting and bleeding, urethral discharge, or dysuria (generally without urgency or frequency).

3. However, many women and some men have asymptomatic infections with *N. gonorrhoeae.*

4. Gonococcal proctitis may be asymptomatic. If symptomatic, the patient has pruritus, tenesmus, purulent discharge and/or rectal bleeding.

5. Gonococcal pharyngitis is usually asymptomatic, but in symptomatic patients, erythema and exudate may be observed.

D. Exclusion Criteria

See General Considerations

Patients with complicated or systemic gonococcal infections such as pelvic inflammatory disease, arthritis, endocarditis, should be excluded.

Patients with other symptomatic STDs may be excluded because they may confound clinical evaluation.

E. Drugs and Dosing Regimen

The drug and dose taken should be documented. Although a minimum target efficacy rate (pathogen eradication) of 95% for ureteral and endocervical gonorrhea, and a 90% target efficacy rate for rectal and pharyngeal gonorrhea has been established, controlled clinical trials are nevertheless desirable to assess safety and efficacy of the product.

Test Drug: Lot number and other identifier should be provided (safety, not evaluability recommendation).

Control Drug: Any drug and dose approved by the FDA for uncomplicated gonorrhea that has a 95% microbiological efficacy.

F. Evaluation Visits:

There are only two visits in the evaluation of this disease entity.

1. Entry

Documentation should include date of visit, signs and symptoms identified, physical examination including genital examination, gram stain (if done), culture, and antimicrobial susceptibility testing, laboratory testing.

2. Post-Therapy (Test-of-Cure)

This visit should occur approximately 3 to 7 days after drug administration. (Drugs with long half-lives should have later follow-up; this issue should have been addressed at the time of the protocol discussion with the Division). Patients should have documentation of the date of the visit, site(s) cultured, culture and antimicrobial susceptibility testing results, any reexposure history, use of other antimicrobials, clinical symptoms or signs.

G. Outcome

Microbiological outcome by site of infection (e.g., urethritis, cervicitis, proctitis, pharyngitis) is the primary efficacy endpoint. In this indication, an eradication rate of 95% for urethral and cervical (90% for rectal and pharyngeal) gonorrhea should be demonstrated for all baseline pathogens for approval to supported. Clinical outcome is important to assess resolution of clinical signs and symptoms because these are the evidence of disease which patients can identify.

While the isolation of a pathogen resistant to the study drug is typically a reason for considering a patient nonevaluable in other infectious disease studies, these patients should be included in the efficacy population in gonorrhea studies because of the public health implications of failing to eradicate *N. gonorrhoeae* in a patient.

1. Primary Efficacy End Point

a. Microbiological Outcome/by Site

I. Eradication: Absence of the pathogen from the site-specific 3-7 day post therapy culture.

ii. Persistence: Presence of the pathogen in site-specific 3-7 days post

therapy culture.

2. Other Efficacy Endpoints

a. Microbiological Outcome/by Patient

I. Eradication: Absence of the pathogen from all the 3-7 day post-therapy cultures.

ii. Persistence: Presence of the pathogen in any culture form any site at 3-7 days post therapy.

b. Clinical Outcome/by Patient

I. Asymptomatic: A patient who is asymptomatic at entry and asymptomatic at follow-up (and meets all other evaluability criteria).

ii. Clinical Cure: Patient meets above evaluability criteria and has resolution of signs and symptoms at all infected sites at the test of cure visit. No other antimicrobial (other than per protocol) were given.

iii. Clinical Failure: Patient who meets evaluability criteria and has persistence of signs and symptoms or *N. gonorrhoeae* at one or more sites of infection, or the appearance of any new signs or symptoms. Also, patients who receive additional antimicrobials are considered failures.

3. Clinical Outcome/by Site

Clinical results from the urethra, endocervix, rectum or pharynx:

a. Asymptomatic: A patient who is asymptomatic at entry and asymptomatic at follow-up (and meets all other evaluability criteria, including a positive culture at the site).

b. Clinical Cure: Patient meets above evaluability criteria and has resolution of signs and symptoms at the specified site at the test of cure visit. No other antimicrobial (other than per protocol) were given.

c. Clinical Failure: Patient who meets evaluability criteria and has persistence

of signs and symptoms or *N. gonorrhoeae* at the specified site of infection, or the appearance of any new signs or symptoms. Also, patients who receive additional antimicrobials are considered failures.

Indication 14: Non-gonococcal Urethritis/Cervicitis

(Reserved)

Indication 15: Acute Prostatitis

(Reserved)

Indication 16: Endocarditis

(Reserved)

Indication 17: Uncomplicated Intra-abdominal Infections

(Reserved)

Indication 18: Complicated Intra-abdominal Infections

(Reserved)

Indication 19: Gynecologic Infections (except STD, PID)

(Reserved)

Indication 20: Pelvic Inflammatory Disease

(Reserved)

Indication 21: Bacterial Vaginosis

(Reserved)

Indication 22: Osteomyelitis (acute and chronic)

(Reserved)

Indication 23: Acute Bacterial Arthritis

(Reserved)

Indication 24: Empiric Therapy in Febrile Neutropenic Patients

(Reserved)

Indication 25: *Helicobacter Pylori*

Primary Objective: *H. pylori* eradication 4 weeks after the end of treatment
Secondary Objective: Peptic ulcer healing 4 weeks after the end of treatment

A. Disease Definition[3]

The presence of *H. pylori* is determined in patients with an active duodenal ulcer defined as a single defect in the gastrointestinal mucosa that penetrates the muscularis mucosa.[4] This distinguishes ulcers from superficial erosions that do not extend through the muscularis mucosa. Peptic ulcers generally occur in the stomach, pylorus, or duodenal bulb. Endoscopy confirms the diagnosis. Screening for *H. pylori* can be done with urea breath tests, serologic tests, and approved urease tests (for the purpose of study inclusion). Cut-off points (i.e., threshold values which distinguish positive from negative results) for all non-approved urea breath tests (UBTS) at the pre-treatment and post-treatment time points should be discussed with the Division prior to unblinding. The cut-off point for the post-treatment assessment may be lower than the pre-treatment assessment to maximize sensitivity post-treatment:

B. Study Considerations

1. Factorial Design

Strict factorial designs[5] are rarely used when multiple agent regimens are evaluated. However, if a triple therapy regimen is evaluated, appropriate dual therapy controls need to be included. Appropriate factorial designs should be discussed with the Division.

2. Blinding

a. Double dummy placebos should be used to maintain blinding in comparative studies.

b. The patient should be blinded to treatment and results of *H. pylori*

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[3] To date, the Division of Anti-Infective Drug Products has considered treatment indications for duodenal ulcers only. The Division may consider gastric ulcers in the future as an indication for treatment. If sponsors would like a claim for the treatment of gastric ulcers due to *H. pylori,* the Division should be contacted in advance.

[4] Patients with ulcers > 2 cm should be excluded. If not, they should be analyzed separately.

[5] Strict factorial designs indicate that each component of a regimen contributes to the overall claim (21 CFR 300.50).

endoscopic tests.

c. The endoscopist should be blinded to treatment, clinical information, and results of all *H. pylori* endoscopic tests.

d. The microbiologist should be blinded to treatment, clinical information, endoscopic information, and all *H. pylori* endoscopic tests other than culture.

e. The pathologist should be blinded to treatment, clinical information, endoscopic information, and results of all *H. pylori* diagnostic information other than histology.

f. The investigator that performs the urease testing should be blinded to treatment, clinical information, endoscopic information, and all other *H. pylori* diagnostic information.

g. The investigator that performs the urea breath test should be blinded to treatment, clinical information, endoscopic information, and all other *H. pylori* diagnostic information.

h. Ideally, the reviewer should be blinded to treatment.

C. Minimal Inclusion Criteria

1. *H. pylori* diagnosed by a non-invasive test (UBT or serology)

2. History of duodenal ulcers (endoscopically confirmed) within the past 2 years

3. Age greater than 16

4. Ulcer size $\geq$ 3 mm and $\leq$ 2 cm in diameter

D. Minimal Exclusion Criteria

1. Zollinger-Ellison Syndrome

2. Allergy to study medications

3. Pregnancy (depending on specific agents studied)

4. NSAID use

5. More than one ulcer[6]

E. Dosage Administration and Duration of Therapy

Minimum of 7 days and maximum of 28 depending on the regimen.[7]

F. Evaluation Visits

1. Pre-Study Visit (within one week of beginning treatment)

- Upper endoscopy
- H. pylori Testing (See Tables 1 and 2.)
- History
- PE
- Laboratory Testing

2. Post Study Visit (≤ 28 days following the end of treatment)

- Upper endoscopy
- H. pylori Testing (See Tables 1 and 2.)
- Safety Evaluations
- PE
- Laboratory Testing
- Adverse Reaction Evaluation

G. Data Analysis

1. Primary Efficacy Analyses

H. pylori eradication at ≥ 4 weeks following the end of treatment (or > 8 weeks following the beginning of treatment)

- Modified intent-to-treat (MITT) analysis
- Per-protocol (Evaluable) analysis

2. Secondary Efficacy Analyses

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[6] Patients with more than one ulcer should be excluded from trials. If not, they should be analyzed separately.

[7] For projected treatment durations outside this scope, the sponsor should contact the Division to discuss clinical trials issues in advance.

Ulcer healing at ≥ 4 weeks following the end of treatment (or ≥ 8 weeks following the beginning of treatment)

- Modified intent-to-treat analysis
- Per-protocol (Evaluable) analysis

H. General Evaluability Criteria

The following descriptions outline how selected patients should be treated for each analysis (per-protocol or modified intent-to-treat). The MITT population for both *H. pylori* eradication and ulcer healing analyses include all patients who have a duodenal ulcer and *H. pylori* infection prestudy (See Tables I and Table 2.) The MITT population differs from a true ITT population, which would include all patients randomized regardless of the *H. pylori* status pre-treatment. The per-protocol population for the *H. pylori* eradication analysis differs from that used for the ulcer healing analysis (as described below).

1. Definition of primary (eradication) analyses

a. Modified intent-to-treat eradication analysis

i. Non-Evaluable Patients

- Negative *H. pylori* status pre-treatment (See Table 1 and Table 2.)
- Missing or not-assessable *H. pylori* status pre-treatment (See Table 1 and Table 2.)
- Ulcer status as defined in the study protocol should dictate what is considered evaluable

ii. Evaluable Failures

- Patients with a positive *H. pylori* status at ≥ 4 weeks from the end of treatment (or ≥ 8 weeks from the beginning of treatment)
- All dropouts
- Missing *H. pylori* data or not-assessable *H. pylori* status post-treatment (See Table 1 and Table 2.)
- Follow-up visit < 4 weeks following the end of treatment

iii. Evaluable Successes

Patients with a negative *H. pylori* status at ≥ 4 weeks from the end of treatment (or ≥ 8 weeks from the beginning of treatment) among those patients in the MITT population (See Table 1 and Table 2)

b. Per-protocol (evaluable) eradication analysis

i. Non-Evaluable Patients

- Negative *H. pylori* status pre-treatment (see Table 1 and Table 2)
- Missing or not-assessable *H. pylori* status pre-treatment (see Table 1 and Table 2)
- Missing *H. pylori* data or not-assessable *H. pylori* status post-treatment (see Table I and Table 2)
- Ulcer status as defined in the study protocol should dictate what is considered evaluable
- Less than 80% compliance for any study medication
- Dropouts (without follow-up endoscopy performed) unrelated to study medication or progression of disease
- Follow-up visit < 4 weeks following the end of treatment and *H. pylori* status negative post-treatment
- Use of antibiotics known to be effective against *H. pylori* in vitro before (within 28 days), during, or following treatment
- Use of anti-secretory agents before (within 14 days), during, or following treatment

ii. Evaluable Failures

- Patients with a positive *H. pylori* status at $\geq$ 4 weeks from the end of treatment (or $\geq$ 8 weeks from the beginning of treatment)
- Dropouts during the treatment period where the reason for dropout is related to study medication or progression of disease
- Dropouts during the post-treatment period (who do not have endoscopy performed at the time of withdrawal) whose reason for withdrawal is related to study medication or presumed progression of disease
- Follow-up visit < 4 weeks following the end of treatment with a positive *H. pylori* status at withdrawal

iii. Evaluable Successes

Patients with a negative *H. pylori* status at $\geq$ 4 weeks from the end of treatment (or $\geq$ 8 weeks from the beginning of treatment) among those patients in the per-protocol population (See Table 1 and Table 2.)

2. Definition of secondary (ulcer healing) analyses

a. Modified intent-to-treat ulcer healing analysis

i. Non-Evaluable Patients

- Negative *H. pylori* status pre-treatment (See Table 1 and Table 2)
- Missing or not-assessable *H. pylori* status pre-treatment (See Table 1 and Table 2)
- Healed ulcer prestudy

ii. Evaluable Failures

- Patients with an unhealed ulcer at $\geq$ 4 weeks from the end of treatment (or $\geq$ 8 weeks from the beginning of treatment)
- All dropouts
- Follow-up visit < 4 weeks following the end of treatment
- Use of anti-secretory agents following treatment

iii. Evaluable Successes

Patients with a healed ulcer at $\geq$ 4 weeks from the end of treatment (or $\geq$ 8 weeks from the beginning of treatment) who are in the MITT population.

b. Per-protocol (evaluable) ulcer healing analysis

i. Non-Evaluable Patients

- Negative *H. pylori* status pre-treatment (See Table 1 and Table 2)
- Missing or not-assessable *H. pylori* status pre-treatment (See Table 1 and Table 2)
- Healed ulcer prestudy
- Less than 80% compliance for any study medication
- Dropouts during the treatment period unrelated to study medication or progression of disease
- Dropouts during the post-treatment period who are not assessed for ulcer healing at the time of withdrawal and whose reason for withdrawal is unrelated to study medication or presumed progression of disease
- Use of anti-secretory agents following treatment

ii. Evaluable Failures

- Patients with an unhealed ulcer at ≥ 4 weeks from the end of treatment (or ≥ 8 weeks from the beginning of treatment)
- Dropouts during the treatment period related to study medication or presumed progression of disease
- Dropouts during the post-treatment period who are not assessed for ulcer healing at the time of withdrawal and whose reason for withdrawal is related to study medication or presumed progression of disease
- Use of anti-secretory agents before (within 2 weeks), during or after treatment

iii. Evaluable Successes

Patients with a healed ulcer at ≥ 4 weeks from the end of treatment (or ≥ 8 weeks from the beginning of treatment) who are in the per protocol population for ulcer healing.

Note: The ulcer healing and eradication per protocol populations may differ in number because patients who drop out during the post-treatment period and are found to be persistently infected should be evaluable failures in the per-protocol eradication analysis but unevaluable in the per-protocol ulcer healing analysis.

To ensure expedited review of applications, sponsors should include patient disposition data as shown on Figure 1.

I. Microbiological Considerations

All patients should be cultured pre- and post-treatment. Patients whose post-treatment cultures are positive should also have susceptibility tests performed. The data should be analyzed to determine the levels of pretreatment resistance, the emergence of *H. pylori* resistance on therapy and the bacteriological efficacy among patients with resistant strains prestudy. At a minimum, at least 65% of the evaluable patients should have pretreatment susceptibility results and post-treatment culture results. For patients that have failed therapy, resistance assessment is particularly important and at minimum, at least 50% of the patients that fail therapy should have both pretreatment and post-treatment susceptibility test results. In addition, open labeled re-treatment may help address the impact of failed therapy and susceptibility testing should be performed if possible. For those patients that had negative culture results, but *H. pylori* present by other testing methodologies (histology, urease, or urea breath test), the results should be

reported in the microbiology section of the new drug application. If the patient is retreated with a different antimicrobial regimen, susceptibility tests results to the original and subsequent antimicrobial agent should be reported if possible.

1. Laboratory Expertise

To qualify for participation in clinical trials, the microbiologists should be experienced in *H. pylori* culturing, susceptibility testing, storage, and retrieval. The laboratory should be certified by the College of American Pathologists or a similar organization and should be licensed by the Health Care Financing Administration as a high-complexity facility. Such laboratories should participate in a recognized inspection and quality-control or proficiency program. However, the most important factor is the experience of the microbiologists performing the tests. The qualifications of the laboratory should be reviewed with and approved by the FDA before clinical trials are initiated.

2. Standard Guidelines

Each study protocol should outline specific clinical and microbiological procedures for diagnosis and follow-up. All protocols used during the clinical trials (specimen collection, transport, primary isolation, identification, susceptibility testing, quality control, mechanisms of resistance, molecular typing, and pharmacokinetic protocols) should be submitted in as much detail as possible.

Protocols should designate how long before administration of the study drug a specimen should be collected. Prior therapy should be noted, particularly in regard to the study medication having been given previously and possibly being responsible for pretherapy resistance to the study medication. Additionally, prior therapy may distort the evaluation of clinical efficacy and obscure the detection of valid pathogens.

3. Specimen Collection and Transport

Two gastric mucosal biopsy specimens (one antrum and one fundus) should be collected from the patient for culture and susceptibility testing.

The biopsy specimens should be transported in a manner that avoids desiccation and long exposure to ambient air. If there is less than four hours from collection of the biopsy specimen to processing in the laboratory, biopsies may be transported in semi-solid transport medium (e.g., Stuart's medium) or liquid medium (broth, 20% glucose solution, isotonic saline solution). If processing by the laboratory is over four hours from the time of collection, the biopsy specimens should be frozen in a medium such as *Brucella* or Cysteine broth with 15-25% glycerol as soon as possible and maintained at -70^{o} C or below (e.g., dry ice, liquid nitrogen) and shipped by overnight carrier.

4. Isolation of *H. pylori* from Biopsy Specimens

Both non-selective (blood agar medium) and selective media (such as Skirrow's) should be utilized for primarily isolation of *H. pylori.* There is some evidence that fresh sheep blood (less than two weeks old) may inhibit growth of *H. pylori*, but it is also very important that fresh media be used in the isolation of *H. pylori.* Horse blood has not been shown to be inhibitory to *H. pylori* growth. The quality control for each lot of media (selective and non-selective) could be incubation of plates inoculated with an *H. pylori* strain, an *E. coli* strain, as well as uninoculated plates.

The biopsy specimens should be homogenized (in a small volume of sterile saline for no more than 10 - 20 seconds), ground or rubbed onto both selective and non-selective media. Incubation should be at 37^{o} C in a microaerophilic atmosphere with a high relative humidity with daily inspection after the second day. Negative cultures should be held for 10 days.

5. Identification of *H. pylori*

H. pylori identified as helical shaped gram negative rods that are oxidase positive, catalase positive, and urease positive. A modified gram stain techniques should be used because *H. pylori* stains too lightly with safranin. Kinyoun or carbofushin stains are possible alternates for safranin.

6. Antimicrobial Susceptibility Testing

The current recommendations are to use the agar dilution MIC (minimum inhibitory concentration) methodology as the reference method. The range of dilutions tested should yield on-scale (rather than off-scale) end points. MIC_{50} and MIC_{90} values should be calculated for the pretreatment isolates. Quality control strains should be tested in parallel with the clinical isolates. All *H. pylori* strains collected during the clinical trials should be stored frozen in a suitable medium such as *Brucella or* Cysteine broth with 15-25 % glycerol.

Studies are ongoing to standardize the agar dilution MIC methodology for use with H. *pylori.* When the studies are completed, this document will be updated with the appropriate information. At this time, use of the disk diffusion and the E-test methodologies are not acceptable. It is highly recommended that the FDA Microbiology Officer reviewing *H. pylori* submissions be contacted prior to the initiation of any study for the latest information regarding establishment of the standardized method.

7. Quality-Control Standards

For antimicrobial agents used in *H. pylori* treatment regimens that have quality control ranges as indicated in Table 3, M7-A3[1] and Table 4, M11-A3[2] of the NCCLS documents, the quality control strains should be tested in parallel to the clinical isolates using the agar dilution technology. An *H. pylori* quality control strain and appropriate ranges will be added to this document when the QC portion of the standardization studies is completed. It is highly recommended that the FDA Microbiology Officer reviewing *H. pylori* submissions be contacted prior to the initiation of any study for the latest information regarding establishment of the standardized method.

8. Pharmacokinetic Data

Pharmacokinetic data at the site of infection (mucus, antrum, and fundus) for the treatment regimen in question should be determined. Data form pharmacology studies should also be considered when defining breakpoints.

9. Mechanisms of Action

Information on the mechanism of action of the therapeutic agents against *H. pylori* should be included if known.

10. Mechanisms of Resistance

Information on the mechanisms of resistance for *H. pylori* should be included in the submission if known. For those treatment regimens for which the mechanism of resistance is known, some of the *H. pylori* isolates known to be resistant should be studied to determine if they possess the resistance mechanism and a few susceptible strains should be tested to show the lack of that resistance mechanism. If the mechanism of resistance is not known, it is suggested that efforts be made to assess the resistance mechanisms in order to better understand the spread of resistance and clinical failure.

11. Emergence of Resistance

In general, a fourfold or greater increase in MIC 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. If possible, molecular techniques should be used to distinguish a resistant variant of the original isolated from a superinfecting strain. Routine use of these methods is not be recommended in clinical trials. However, such typing procedures should be available for application to selected pertinent isolates such as via reference laboratories.

12. Storage of the isolates

It is extremely important to freeze (at -70°C) and save the *H. pylori* isolates from the clinical trials. This should provide for the possibility of retesting the isolates if necessary. A very heavy suspension (or a block of agar with heavy growth) of the *H. pylori* isolate should be placed into a suitable medium, such as *Brucella* or Cysteine broth with 15 -25 % glycerol and frozen at -70°C or stored in liquid nitrogen.

J. Statistical Considerations

Adequate representation of gender and age distribution should be used. Multicenter trials are recommended in *H. pylori* trials.

1. Establishment of an efficacy threshold

The Division suggests that *H. pylori* eradication using a modified intent-to-treat analysis should be considered primary. The Division traditionally has recommended the use of approved active controls for the study of new anti-infective drug products. However, approved regimens for *H. pylori* have not existed until recently. An alternative to active controlled studies is to use a threshold approach. This approach would define a minimal standard for the percentage of patients eradicated of *H. pylori*. However, many factors should be considered in setting this threshold limit. For example; *H. pylori* eradication rates, safety/tolerability levels, rate of emerging resistance, and compliance should all be different when multiple agent regimens are used. All of this

information may be needed to choose the appropriate threshold level for specific treatments.

As seen in Table 3 the recommended sample size needed to obtain a specific 95% confidence interval lower limit (using a two-sided test) decreases dramatically as the hypothesized mean cure rate increases from 5 % to 15 % compared to the lower limit of the 95% confidence interval. These calculations assume the power and type I error are fixed. Note that *H. pylori* eradication is the only factor considered in this table; all other factors are ignored.

The Division recommends that *H. pylori* regimens should include enough patients to achieve a lower 95% confidence limit of 60%. This assumes 80% power and a type I error of 5%. Using this approach the minimum number of patients recommended in a study would be 178 if the expected mean cure rate is 70% and the lower 95% confidence limit is 60%. This standard is more strict as compared to previous recommendations by the Division (Draft Division Review Criteria) suggesting that mean cure rates of 60% (using a modified intent-to-treat analysis) would be considered effective. Nevertheless, even the current threshold recommendation (a lower limit 95% confidence interval of 60%) may be considered too low for future applications given the presence or absence of other treatment-specific factors: rate of emerging resistance, efficacy among patients with resistant *H. pylori* strains prestudy, and safety/tolerability issues.

In addition to threshold recommendations, sponsors are reminded that multi-therapy regimens need to include factorial designs which may demonstrate the contribution of each component to the overall effect. Factorials designs should be discussed with the Division at the IND stage.

2. Active Controls

If an active-controlled study design is used to establish the effectiveness of a new *H. pylori* regimen, the following considerations should be taken into account. To be considered a successful trial under this design, the results should demonstrate that the new *H. pylori* regimen is statistically and clinically superior or equivalent in efficacy to an approved H. *pylori* regimen. The suggested analytical approach is estimation via two-sided 95% confidence intervals of the treatment difference (test minus control) in success rates. In this approach, the confidence interval should include zero, and the lower limit of the confidence interval should not exceed the clinically specified boundary for establishing

efficacy equivalence. These boundaries vary depending on the treatment success rates observed in the trial as follows:

The observed success rate for the better of the two agents is:	The lower bound of the C.I. (in absolute value) should not exceed:
$\geq$ 90%	10%
$\geq$ 80% and < 90%	15%
<80%	20 % (note)

Table 1. Diagnostic Status Based on 3 Endoscopic *H. pylori* Tests

	H. pylori Tests*			Patient *H. pylori* Status †	
	Cult	Hist	Urease	Pre-therapy	Post-therapy
Three Tests Available					
	+	+	+	Evaluable	Persistence§
	+	+	-	Evaluable	Persistence
	+	-	+	Evaluable	Persistence
	+	-	-	Evaluable	Persistence
	-	+	+	Evaluable	Persistence
	-	-	+	Not Evaluable	Persistence
	-	+	-	Not Evaluable	Persistence
	-	-	-	Not Evaluable	Eradicated
Two Tests Available					
	+	+	N/A	Evaluable	Persistence
	+	-	N/A	Evaluable	Persistence
	-	+	N/A	Not Evaluable	Persistence
	-	-	N/A	Not Evaluable	Eradicated
	+	N/A	+	Evaluable	Persistence
	+	N/A	-	Evaluable	Persistence
	-	N/A	+	Not Evaluable	Persistence
	-	N/A	-	Not Evaluable	Eradicated
	N/A	+	+	Evaluable	Persistence
	N/A	+	-	Not Evaluable	Persistence
	N/A	-	+	Not Evaluable	Persistence
	N/A	-	-	Not Evaluable	Eradicated
One Test Available					
	+	N/A	N/A	Evaluable	Persistence
	-	N/A	N/A	Not Evaluable	Not Evaluable
	N/A	N/A	+	Not Evaluable	Persistence
	N/A	N/A	-	Not Evaluable	Not Evaluable
	N/A	+	N/A	Not Evaluable	Persistence
	N/A	-	N/A	Not Evaluable	Not Evaluable

* N/A Indicates not available or missing result.

† Note, the "pre-therapy" and "post-therapy" columns relate to *H. pylori* status and not to individual patients. Patients are either considered "Evaluable" or Not Evaluable" for the prestudy assessment. When incongruent tests preclude an accurate *H. pylori* status assessment, these patients are considered "Not Evaluable" prestudy and are not included in either the MITT (Modified Intent-to-Treat) analysis or per protocol analysis. Patients are classified into the following categories for the post-therapy visit: "Persistence", "Not evaluable", or "Eradicated." A "Not evaluable" assessment post-therapy indicates that the patient should be considered with "Persistence" for the MITT analysis and "Not Evaluable" for the per protocol analysis.

§ Persistence is considered synonymous with infected.

Table 2. Diagnostic *H. pylori* Status Based on 3 Endoscopic Tests and Urea Breath Test

	H. pylori Tests*				Patient *H. pylori* Status †	
	UBT§	Cult	Hist	Urease	Pre-therapy	Post-therapy
Three Tests Available +/- UBT						
	NA	+	+	+	Evaluable	Persistence¶
	+	+	+	+	Evaluable	Persistence
	-	+	+	+	Evaluable	Persistence
	NA	+	+	-	Evaluable	Persistence
	+	+	+	-	Evaluable	Persistence
	-	+	+	-	Evaluable	Persistence
	NA	+	-	+	Evaluable	Persistence
	+	+	-	+	Evaluable	Persistence
	-	+	-	+	Evaluable	Persistence
	NA	+	-	-	Evaluable	Persistence
	+	+	-	-	Evaluable	Persistence
	-	+	-	-	Evaluable	Persistence
	NA	-	+	+	Evaluable	Persistence
	+	-	+	+	Evaluable	Persistence
	-	-	+	+	Not Evaluable	Persistence
	NA	-	-	+	Not Evaluable	Persistence
	+	-	-	+	Not Evaluable	Persistence
	-	-	-	+	Not Evaluable	Persistence
	NA	-	+	-	Not Evaluable	Persistence
	+	-	+	-	Not Evaluable	Persistence
	-	-	+	-	Not Evaluable	Persistence
	NA	-	-	-	Not Evaluable	Eradicated
	+	-	-	-	Not Evaluable	Not Evaluable
	-	-	-	-	Not Evaluable	Eradicated

* N/A Indicates not available or missing result.

† Note, the "pre-therapy" and "post-therapy" columns relate to *H. pylori* status and not to individual patients. Patients are either considered "Evaluable" or Not Evaluable" for the prestudy assessment. When incongruent tests preclude an accurate *H. pylori* status assessment, these patients are considered "Not Evaluable" prestudy and are not included in either the MITT (Modified Intent-to-Treat) analysis or per protocol analysis. Patients are classified into the following categories for the post-therapy visit: "Persistence", "Not evaluable", or "Eradicated." A "Not evaluable" assessment post-therapy indicates that the patient should be considered with "Persistence" for the MITT analysis and "Not Evaluable" for the per protocol analysis.

§ UBT = urea breath test.

¶ Persistence is considered synonymous with infected.

Table 2 (Cont.). Patient *H. pylori* Status Based on Endoscopic Tests and Urea Breath Test

	H. pylori Tests*				Patient *H. pylori* Status †	
	UBT§	Cult	Hist	Urease	Pre-therapy	Post-therapy
Two Tests Available +/- UBT						
	NA	+	+	N/A	Evaluable	Persistence¶
	+	+	+	N/A	Evaluable	Persistence
	-	+	+	N/A	Evaluable	Persistence
	NA	+	-	N/A	Evaluable	Persistence
	+	+	-	N/A	Evaluable	Persistence
	-	+	-	N/A	Evaluable	Persistence
	NA	-	+	N/A	Not Evaluable	Persistence
	+	-	+	N/A	Evaluable	Persistence
	-	-	+	N/A	Not Evaluable	Persistence
	NA	-	-	N/A	Not Evaluable	Eradicated
	+	-	-	N/A	Not Evaluable	Not Evaluable
	-	-	-	N/A	Not Evaluable	Eradicated
	NA	+	N/A	+	Evaluable	Persistence
	+	+	N/A	+	Evaluable	Persistence
	-	+	N/A	+	Evaluable	Persistence
	NA	+	N/A	-	Evaluable	Persistence
	+	+	N/A	-	Evaluable	Persistence
	-	+	N/A	-	Evaluable	Persistence
	NA	-	N/A	+	Not Evaluable	Persistence
	+	-	N/A	+	Evaluable	Persistence
	-	-	N/A	+	Not Evaluable	Persistence
	NA	-	N/A	-	Not Evaluable	Eradicated
	+	-	N/A	-	Not Evaluable	Not Evaluable
	-	-	N/A	-	Not Evaluable	Eradicated
	NA	N/A	+	+	Evaluable	Persistence
	+	N/A	+	+	Evaluable	Persistence
	-	N/A	+	+	Evaluable	Persistence
	NA	N/A	+	-	Not Evaluable	Persistence
	+	N/A	+	-	Evaluable	Persistence
	-	N/A	+	-	Not Evaluable	Persistence
	NA	N/A	-	+	Not Evaluable	Persistence
	+	N/A	-	+	Evaluable	Persistence
	-	N/A	-	+	Not Evaluable	Persistence
	NA	N/A	-	-	Not Evaluable	Eradicated
	+	N/A	-	-	Not Evaluable	Not Evaluable
	-	N/A	-	-	Not Evaluable	Eradicated

* N/A Indicates not available or missing result.

† Note, the "pre-therapy" and "post-therapy" columns relate to *H. pylori* status and not to individual patients. Patients are either considered "Evaluable" or Not Evaluable" for the prestudy assessment. When incongruent tests preclude an accurate *H. pylori* status assessment, these patients are considered "Not Evaluable" prestudy and are not included in either the MITT (Modified Intent-to-Treat) analysis or per protocol analysis. Patients are classified into the following categories for the post-therapy visit: "Persistence", "Not evaluable", or "Eradicated." A "Not evaluable" assessment post-therapy indicates that the patient should be considered with "Persistence" for the MITT analysis and "Not Evaluable" for the per protocol analysis.

§ UBT = urea breath test.

¶ Persistence is considered synonymous with infected.

Table 2 (Cont.). Patient *H. pylori* Status Based on Endoscopic Tests and Urea Breath Test

	H. pylori Tests*				Patient *H. pylori* Status †	
	UBT§	Cult	Hist	Urease	Pre-therapy	Post-therapy
One Test Available +/- UBT						
	NA	+	N/A	N/A	Evaluable	Persistence¶
+	+	N/A	N/A	Evaluable	Persistence	
	-	+	N/A	N/A	Evaluable	Persistence
	NA	-	N/A	N/A	Not Evaluable	Not Evaluable
	+	-	N/A	N/A	Not Evaluable	Not Evaluable
	-	-	N/A	N/A	Not Evaluable	Not Evaluable
	NA	N/A	N/A	+	Not Evaluable	Persistence
	+	N/A	N/A	+	Evaluable	Persistence
	-	N/A	N/A	+	Not Evaluable	Persistence
	NA	N/A	N/A	-	Not Evaluable	Not Evaluable
	+	N/A	N/A	-	Not Evaluable	Persistence
	-	N/A	N/A	-	Not Evaluable	Not Evaluable
	NA	N/A	+	N/A	Not Evaluable	Persistence
	+	N/A	+	N/A	Evaluable	Persistence
	-	N/A	+	N/A	Not Evaluable	Persistence
	NA	N/A	-	N/A	Not Evaluable	Not Evaluable
	+	N/A	-	N/A	Not Evaluable	Not Evaluable
	-	N/A	-	N/A	Not Evaluable	Eradicated

* N/A Indicates not available or missing result.

† Note, the "pre-therapy" and "post-therapy" columns relate to *H. pylori* status and not to individual patients. Patients are either considered "Evaluable" or Not Evaluable" for the prestudy assessment. When incongruent tests preclude an accurate *H. pylori* status assessment, these patients are considered "Not Evaluable" prestudy and are not included in either the MITT (Modified Intent-to-Treat) analysis or per protocol analysis. Patients are classified into the following categories for the post-therapy visit: "Persistence", "Not evaluable", or "Eradicated." A "Not evaluable" assessment post-therapy indicates that the patient should be considered with "Persistence" for the MITT analysis and "Not Evaluable" for the per protocol analysis.

§ UBT = urea breath test.

¶ Persistence is considered synonymous with infected.

Table 3. Relationship Between Lower Limit 95% Confidence Interval and Hypothesized Mean Eradication Rate to Sample Size*

Lower Limit 95% Confidence Interval	Hypothesized Mean Cure Rate	Sample Size
60	65	736
60	70	178
60	75	76
70	75	625
70	80	146
70	85	60
80	85	452
80	90	98
80	95	35

* Note: In these calculations the power is fixed at 80% and the type I error is fixed at 5% for a 2-sided test

Indication 26: Vaginal Candidiasis

A. Regulatory Synonyms

This indication has been called *candidal vaginitis, vaginal candidiasis, vaginitis due to Candida albicans, moniliasis, yeast vaginitis*.

Note: While the topical vaginal drug products were available by prescription only, the indication approved was vaginal candidiasis without regard to whether the patient was treated for an initial or a recurrent episode of vaginitis. Then, the Agency convened an Advisory Committee meeting during which the prescription to over-the-counter conversion of topical vaginal therapies was discussed. The Committee's recommendation was that women who have had a previous episode of vaginal candidiasis diagnosed and treated by a physician could self-treat the disease if they had the disease again.

B. Study Considerations

(This is the text from the proposed revision of the Points to Consider document, addition of Item 27. Vulvovaginal Candidiasis). Please refer to IDSA Guidelines pages S115 - S122.

The Division recommends that two statistically adequate and well-controlled multicenter trials establishing equivalence or superiority to an approved product (7 day regimen that is approved for Rx or OTC) is suggested. In this infection, an evaluable patient should be expected to be clinically and mycologically evaluable. Entry criteria should include signs and symptoms attributable to *Candida* infection of the vagina with or without extension to the vulva. These include local edema, erythema, irritation, itching and burning. The discharge associated with *Candida* is usually described as white and curdy in appearance; a KOH preparation of the discharge should reveal yeast forms and a culture should be positive for *Candida.* Special testing should be performed to identify the isolates to the species level (e.g., *Candida albicans, C. tropicalis, C. globrata).* In-vivo susceptibility testing using standardized methods should be performed and minimum inhibitory concentrations (MICs) should be determined. Other pathogens commonly associated with vulvovaginitis (e.g. *Trichomonas vaginalis, Chlamydia trachomatis, N. gonorrheoeae,* bacterial vaginosis and *Herpes simplex* virus) should be ruled out. It should also be expected that the antimicrobial drug product exhibits acceptable in vitro activity against *Candida*.

Each study should use a currently-approved seven day regimen as the control agent, to assure that there is no "biocreep" as dose regimens get shortened from the standard seven days to shorter durations. This recommendation is particularly important when the drug product under discussion is intended for the OTC market, where consumers may not have the benefit of a physician-patient

interface to assist them in deciding the correct treatment regimen for them. Therefore, the overall anticipated benefit to the patient should be comparable, regardless of the formulation selected.

Each study should contain a minimum of 100 patients evaluable for the analysis of efficacy and safety. The majority, if not all, of these patients should have "recurrent" (recurrence should be documented as the number of episodes of candidiasis diagnosed and or treated in the preceding 12 months) vaginitis because the intent of over-the-counter therapies for vaginal candidiasis is patients who have had previous episodes of the disease and can therefore make the determination that they have the same condition again and can therefore self-treat with appropriate anti-candidal treatment.

C. Inclusion Criteria

Female patients, usually postmenarchal and adult with the diagnosis of vaginal candidiasis basedon the criteria listed below and free of other vaginal or pelvic infection as delineated under exclusion criteria.

As in other infectious diseases, diagnosis uses the correlation among clinical findings, microscopic examination (i.e., KOH examination), and vaginal discharge culture.

To be clinically evaluable, patients should have a clinical diagnosis of vaginal candidiasis based on history and physical exam (including vaginal exam). Signs and symptoms should include itching, burning, irritation, edema, erythema, excoriation of the vaginal and/or vulvar sites.

> *As for other indications, the applicant should have determined and justified before protocol implementation both how many of these signs and symptoms should be present, and what rating scale they wish to use to grade severity (e.g., mild, moderate, severe). Clearly, this is hard to quantitate in rigid terms.*

Furthermore, it is expected that the patient may have a vaginal discharge which is usually described as white, curdy (creamy, cottage cheese-like), adherent to epithelium.

The patient's record should also reflect the history of preceding vaginal infections, specifically the number of *Candida* infections. Patients with $\geq$ 4 episodes of vulvovaginal candidiasis in the preceding 12 months are considered to have recurrent vaginitis.

To be microbiologically evaluable, patients should have a microbiological diagnosis of vaginal candidiasis based on examination of a KOH preparation and a culture of the vaginal discharge/fluid/secretions. To obtain appropriate specimen for culture, wipe excessive amounts of discharge and obtain secretions from mucosal membrane of the vaginal vault with a sterile swab. Obtain a second swab for the KOH preparation. The KOH preparation should reveal the presence of yeast forms and the culture should be positive for *Candida*. Susceptibility testing should be

performed and the MIC_{90} should be determined for all clinical isolates.

Most cases of vaginal candidiasis are caused by *Candida albicans*. It is estimated, however, that about 10-20% of cases are due to other species, including *Candida tropicalis, Candida glabrata* (formerly *Torulopsis*), etc. At present, the Division has not stipulated *Candida* speciation and has not recommended susceptibility testing. However, since *Candida* species other than *albicans* are generally resistant to treatment, the Division recommends *Candida* speciation and antimicrobial susceptibility testing.

D. Exclusion Criteria

Patients with other infectious causes of vaginitis such as bacterial vaginosis, *Trichomonas vaginalis, Chlamydia trachomatis, N. gonorrhoeae* should be excluded because the presence of these infections confounds clinical assessment of outcome. Patients with anti-candidal therapy within 7 days of study should be excluded. Also see General Considerations.

E. Drugs and Dosing Regimen

To be evaluable, the patient should receive $\geq$ 80% of the prescribed dose amount and/or dosing regimen. Dosing should be documented as should compliance (e.g, in patient diary)

Test Drug: Lot number and other identifier should be provided (safety, not evaluability recommendation).

Control Drug: For the purposes of obtaining drug approval for a regimen (particularly a shortened course) to treat vaginal candidiasis, the Division has specified that the control regimen should be one of the currently-approved 7-day OTC regimens of clotrimazole or miconazole (cream or insert). The purpose of this is to prevent biocreep in comparing 7 to 3 day, then 3 to 1 day. Regardless, control regimens which yield acceptable cure rates should be selected.

F. Evaluation Visits

1. Entry

At entry, documentation should include date of visit, findings from the medical history, physical examination including speculum examination of the vagina, KOH, culture and susceptibility testing results and other laboratory results. Medical history documentation should specifically query the number of vaginal candidiasis episodes in the past 12 months.

2. On-therapy

This visit is usually not performed, and is certainly impractical for a 3 day or 1 day regimen.

3. First Post-treatment

This visit should occur approximately 7 days after the completion of therapy or 14 days after the beginning of therapy (if the regimen is less than 7 days). Some flexibility in determining the range of days should be allowed for weekends, holiday, or other special circumstances. At this visit, clinical history, vaginal examination of vaginal discharge culture and susceptibility testing and microscopic examination of KOH preparation should be repeated.

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

This visit should occur approximately 4 weeks after the completion of therapy. Some flexibility in determining the range of days should be allowed for weekends, holiday, or other special circumstances. At this visit, clinical history, vaginal examination, vaginal discharge culture and susceptibility testing, and microscopic examination of KOH preparation should be repeated.

G. Outcome

Post-treatment Visit One

This is an interim visit to evaluate patient continuing response to therapy. The following terms may be used to describe the patients condition at this visit.

1. Clinical Cure

Patient meets above availability criteria and has resolution of presenting signs and symptoms at the test of cure visit, including normal physical exam. No anti-candidal drug (other than per protocol) was given. No new signs or symptoms can appear. If a discharge is present, it should be minimal, physiologic and non-pathologic. This definition applies to first and to second post-treatment visits.

2. Clinical Improvement

This applies only to the first post-treatment visit, and represents a patient who has significant but incomplete resolution of signs and symptoms.

3. Clinical Failure

Patient is considered a failure if there is no improvement in signs and symptoms by the first post-treatment visit or if there is incomplete resolution of these by the second post-treatment visit. Also, patients who receive additional medication for the infection are considered failures. If a patient is classified as a failure at the first post-therapy visit, this evaluation of failure should be carried forward into the second post-treatment visit. That is, for the purpose of calculating outcome rates--once a failure, always a failure.

4. Mycological Cure

A patient who has a negative KOH and a negative culture for *Candida* is considered a mycological cure. No additional candida therapy can be given. In rare cases where KOH or culture are discordant, the results of the culture should determine the outcome. This definition applies to first and second post-treatment visits.

5. Mycological Improvement

This applies only to the first post-treatment visit and represents a patient who is symptom free and culture negative, but in whom yeast forms may be identified on KOH. That is, KOH does not distinguish viable and nonviable organisms.

6. Mycological Failure

Represents a patient who is culture positive at either post-treatment visit and/or KOH positive at the second post treatment visit. Also refers to a patient who received additional candida therapy.

Post-Treatment Visit Two

This represents the test of cure visit. Patient's clinical, mycological and therapeutic outcome should be classified according to the following definitions. Approval is based on the results of the therapeutic analysis.

1. Clinical Cure

Patient meets above availability criteria and has resolution of presenting signs and symptoms, including normal physical exam. No anti-candidal drug (other than per protocol) was given. No new signs or symptoms can appear. If a discharge is present, it should be minimal, physiologic and non-pathologic.

2. Clinical Failure

Patient is considered a failure if there is incomplete resolution of signs and symptoms of disease. This includes patients classified as a failure at the first post-therapy visit. Patients who receive additional anti-candidal medication for the infection are considered failures.

3. Mycological Cure

A patient who has a negative KOH examination and a negative culture for *Candida* is considered a mycological cure. No additional candida therapy can be given.

4. Mycological Failure

A patient who is culture positive or KOH positive. Also refers to a patient who received additional therapy for candida.

An overall assessment of the patient represents the outcome taking into consideration both the clinical and the mycological outcome. The relationship of the two follow-up visits, clinical and mycological and derived therapeutic outcomes is presented below:

FIRST VISIT	**SECOND VISIT**		
	CLINICAL	MYCOLOGIC	THERAPEUTIC
See *comment*	cure	cure	cure
below	failure	cure(*)	failure
	cure(*)	failure	failure
	failure	failure	failure

(*) if this evaluation is missing, the patient is still considered a therapeutic failure
Comment: If the patient is seen at the first post-treatment visit and is judged to be either a clinical or a mycologic failure, then that failure shall be brought forth to the second (TOC) visit.

Indication 27: Lyme Disease

(Reserved)

Indication 28. *Clostridium Difficile* Colitis

(Reserved)

VI. REFERENCES

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