CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

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

POINTS TO CONSIDER

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

CLINICAL DEVELOPMENT AND LABELING
OF ANTI-INFECTIVE DRUG PRODUCTS

NUMBER TWO

PREAMBLE

Changing or unclear interpretations of clinical trial data needed to demonstrate the effectiveness and safety of antimicrobial drug products have at times led to confusion and frustration on the part of both applicants and Division of Anti-Infective Drug Products reviewers. The Federal Food, Drug, and Cosmetic Act (FD&C Act) and the implementing regulations clearly state that adequate and well-controlled investigations (emphasis added) are necessary to demonstrate the safety and effectiveness of a given drug product. The intent of these regulations is to require safety and effectiveness data from well-performed, interpretable, independently corroborated studies as the basis for marketing a drug product in the United States. How to interpret this statutory requirement with respect to antimicrobial drug therapies, where there is no clear consensus on the boundaries of possible "indications", has, over time, resulted in confusion. The terms - "adequate", "well-controlled", and "indication" - have been interpreted variously by the Division over time. Manufacturers of new drug applications approved in the United States, also, have interpreted these terms variously and have taken, in some instances, wide liberties in the promotion of their antimicrobial drug products based on the semantics of approved labeling rather than the strength of the submitted scientific data.

This document is not intended to undergird a "cookbook" approach to antimicrobial drug development. Rather, it is a "Points to Consider" document for applicants and reviewers alike, which suggests minimal information appropriate for the clinical development of routine antimicrobial drug products and identifies issues common to many antimicrobial new drug applications that should be addressed. This document should not replace the exercise of good scientific judgment by applicants or reviewers at any point in the development or review process. Likewise it should not supplant appropriate scientific and technical advice available to the Division from Advisory Committees and other appropriate outside consultants. It should be considered complementary to other

guidance documents that suggest specifics of clinical trial design and administration.

All circumstances and contingencies surrounding the development of antimicrobial drug products, including all the possible desired infection claims and all the extenuating circumstances for certain diseases and compounds, cannot reasonably be addressed in a general "Points to Consider" document. Many antimicrobial drug product development programs should be discussed with the Agency so agreements can be reached on effectiveness criteria that could be used in the evaluation of a specific antimicrobial drug product in order to facilitate desired final product labeling. For example, applicants wishing to develop unique antimicrobial drug products (*e.g.*, one with dosing regimens that depart from established practices, one with unusual pharmacokinetic or pharmacodynamic properties, or one with evidence of sub-inhibitory antimicrobial drug concentrations at sites of infection) should discuss clinical development plans with the Division prior to the initiation of a capital-intensive development program, which is based on the assumption the information identified in this document is applicable in all situations. If an applicant is in doubt, discussion with the Division is highly encouraged. In every case, however, the appraisal of a desired labeling statement will take into account the entire NDA data package and will not be decided by viewing specific data in isolation.

Hopefully, this document will not be viewed as an onerous, obstreperous intrusion into antimicrobial drug product research, but rather as effort to help define good scientific methodology and good scientific discipline in these research efforts. It is hoped this document will be a vital communication vehicle between the Division, the pharmaceutical industry, the infectious disease academic community, and the public. As our collective knowledge of this class of drug products expands and as our collective perspective of the clinical trial process (GCP) involving these drug products further matures, the Division anticipates that this document will change to reflect that new knowledge and perspective. This document will hopefully afford all parties interested in the development of new antimicrobial drug products a mechanism by which both to apprise others and to become apprised themselves of this new knowledge and these new perspectives.

INTRODUCTION TO ISSUES

ADEQUATE CLINICAL TRIALS:

In an effort to introduce a more objective approach for interpreting "equivalence" or "superiority" of antimicrobial drug products, more rigorous statistical analyses and better database review procedures have been employed recently by the Division. These changes, along with the tightening of evaluability criteria and more definitive delineation of infections under investigation, have resulted in the need to enroll more patients in clinical trials of antimicrobial drug products. They have also placed a premium on monitoring these studies more effectively to maximize the number of evaluable patients in a given trial. This has incurred the ire of some applicants, who contend the Division is requiring more data today to establish the effectiveness of their new antimicrobial drug products than was required for "similar" products in the past.

Any discussion of the "adequacy" of a clinical study requires discussion of issues of clinical trial design and management, primary effectiveness variables and endpoints, evaluability criteria, and statistical analysis. Several of these issues are addressed in this document. Other issues, more appropriately, are addressed in greater detail in complementary documents on clinical trial design and management published by the FDA and others.

Recently most clinical trials of antimicrobial drug products have been randomized; yet, the masking ("blinding") of patients, clinicians, evaluators, and applicants has been varied at best. In addition, several open trial designs have also been accepted previously by the Division when pre-determined effectiveness standards have been achieved (*i.e.*, trials establishing effectiveness in treating gonococcal urethritis/cervicitis). Such trial designs have their limitations and their own inherent problems with potential bias introduction that must be recognized and addressed.

WELL-CONTROLLED CLINICAL TRIALS:

A "well-controlled clinical trial" has been more clearly and consistently defined, as the implementing regulations describe five categories of clinical trials that can be classified as "well-controlled". In clinical trials of antimicrobial drug products, we only occasionally have the luxury of placebo-controlled trials, because it is often felt to be ethically unacceptable not to treat infected patients when effective

therapy is available. Therefore, we have most often relied upon active-controlled studies to establish effectiveness of a new antimicrobial drug product, usually using comparator agents already approved for similar indications in the United States. (See comments on "Issues with Comparator Agents".) With the increasing effectiveness of antimicrobial drug products in many infections, high cure rates make it nearly impossible or impractical for a new antimicrobial drug product to demonstrate statistical or clinically-relevant superiority to an approved comparator agent. However, when patient numbers for studies can reasonably be obtained, effectiveness end points are fairly well established, and studies can be completed in a reasonable time frame, the Agency has granted "unrestricted" (*i.e.*, no caveats or limitations regarding the breadth of the specific claim) effectiveness claims for new antimicrobial drug products when those new products, in clinical trials, demonstrate statistical and clinical equivalence to a product already approved for treatment of the same infection. Most recently, the Division has used a "two-tailed 95% confidence interval around the difference in outcomes" approach to determine such statistical equivalence between two products.

Presently, the Division also has great interest in exploring the possibility of using alternate clinical trial designs to characterize the dose-response of a new antimicrobial drug product in treating a given infection and also using these data as pivotal data for evaluating the approvability of a new drug application. This issue is discussed further in the "1992 Addendum" at the conclusion of this document.

"INDICATION"

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

PERSPECTIVE ON ANTIMICROBIAL DRUG PRODUCT UNIQUENESS

Antimicrobial drug products do not usually exert their intended therapeutic effect directly on humans as do most other human drug products. Rather the human therapeutic effect is a by-product of the drug's ability to kill or inhibit the growth of microorganisms. Pharmacologic effects on humans are, usually, unintended adverse events. Antimicrobial drug products often also have standardized *in vitro* techniques that afford reproducible data on the amount of drug required to kill or inhibit the growth of certain microorganisms in an *in vitro* setting. Better techniques for assessing the pharmacokinetic properties of certain antimicrobial drug products in humans often afford reproducible knowledge of the rate and extent of drug present in various body tissues and fluids.

These *in vitro* data do not reproduce the exact conditions of drug/microbe interface in the human host. The human host normally does not present a constant level of antimicrobial exposure to the microorganism, and the *in vitro* methodology does not replicate the intrinsic defense mechanisms of the human host. Nonetheless, one can deduce useful knowledge from these types of *in vitro* and human pharmacokinetic data applied in concert. The amount and depth of human clinical data required to corroborate and confirm the *in vitro*/pharmacokinetic assumptions should be a primary question in establishing clinical effectiveness of antimicrobial drug products.

Other questions arise from these observations.

Does each body site of infection caused by each species of microorganism (or even each strain of microorganism in the event of heterogenous resistance patterns) qualify as a separate "indication" requiring at least two adequate and well-controlled studies? If so, does it become essentially unrealistic to expect truly adequate studies or fully-studied products?

If they are not separate indications, how do we maintain a scientifically sound approach to labeling that furnishes clinicians with valid information yet restrains misleading or disinformative marketing campaigns?

Do the *in vitro* data for certain microorganisms, along with other pharmacokinetic, pharmacodynamic data, and relevant clinical data from comparable body sites provide adequate scientific corroboration of certain clinical data and allow corroboration of effectiveness claims?

What is the value of listing *in vitro* data for microorganism(s) when the microorganism(s) do not cause

infections in the body sites for which the effectiveness of a given antimicrobial drug product has been established?

Does the listing of microorganisms in the *in vitro* **Microbiology** subsection of the labeling furnish the clinician with clinically relevant data, or has it simply become a *de facto* license for the antimicrobial drug product to be promoted by the manufacturer for implied clinical indications that have not been adequately studied?

Does the present Divisional practice of placing asterisks beside certain microorganisms in the **INDICATIONS AND USAGE** section of the product labeling actually satisfy any relevant clinical need, or has this become simply another area for clinically irrelevant "one-ups-man-ship" in the commercial exploitation of Product A *versus* Product B?

These are issues with which the Division of Anti-Infective Drug Products has to contend. "Correct" answers are not easy to formulate. Any policy dealing with these areas must be flexible enough to encompass innovation and medical progress while informing practicing physicians forthrightly and completely. Yet the policy must also be rigid enough to maintain - as level as possible - the regulatory "playing field" on which these products must compete.

Wishing to help clarify for applicants and reviewers the present perspective of the Division of Anti-Infective Drug Products on some of these issues and recognizing that no document can be all inclusive, the following divisional "Points to Consider" are presented.

SPECIFIC POINTS TO CONSIDER:

POINTS REGARDING ANTIMICROBIAL DRUG PRODUCT LABELING:

(I) ISSUES WITH THE DEFINITION OF "INDICATION" AND THE FORMAT FOR THE INDICATIONS and USAGE SECTION OF ANTIMICROBIAL DRUG PRODUCT LABELING:

Background:

21 CFR 201.57(c)(2) states: *All indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in 314.126(b) of this chapter unless the requirement is waived under 201.58 or 314.126(b) of this chapter.*

For the purpose of this paragraph - with respect to antimicrobial drug products -the Division of Anti-Infective Drug Products recognizes the term *"indication"* to mean *"the treatment (and/or prevention) of infection(s) at a specified body site(s) due to a specified, susceptible microorganism(s)"*.

Antimicrobial drug products basically have two potential indications: the treatment or the prophylaxis of infection. At least two statistically adequate and well-controlled clinical trials will be necessary to establish that a given antimicrobial drug product indeed treats or prevents infection. Antimicrobial drug products will not usually be approved for marketing on the basis of only one adequate and well-controlled trial.

Due to diversity in microbiologic, pharmacokinetic, pharmacodynamic, and toxicologic parameters, individual antimicrobial drug products often have varied spectra regarding the types of infections usually amenable to therapy with the compound. Antimicrobial drug products that have been found effective at other body sites of infection and have appropriate antimicrobial activity *in vitro*, nonetheless, at times fail when tested for new uses. Therefore, the **INDICATIONS AND USAGE** section of the product labeling should include only those types of specific infections, including specific pathogens, for which evidence of safety and effectiveness have been established by corroborated data from well-conducted, well-documented, well-controlled trials as outlined subsequently in this document. Two active-comparator, statistically adequate, well-controlled trials for

each specific type of infection may not always be necessary to establish such effectiveness. When an antimicrobial drug product has been subjected to a large, standard clinical development program such as is most common today, it frequently may be possible to extrapolate information from a statistically adequate, well-controlled trial at one body site to corroborate efficacy at another body site under appropriate conditions. However, much depends on the extent of the innovation of the use of the drug product (*i.e.*, a new category of antimicrobial drug product, a new indication for a class of antimicrobial drug products, or a new modality of drug administration may require approaches to establishing effectiveness and safety different from the general suggestion outlined subsequently in this document.)

Suggested Product Labeling (**INDICATIONS AND USAGE** section):

The Division suggests that the **INDICATIONS AND USAGE** section of product labeling for prescription antimicrobial drug products ordinarily read as follows:

Treatment:

(Trade name of compound) is indicated for the treatment of infection as follows:

(Site or name of infection) due to susceptible strains of [name of pathogen(s)].

(List however many infections for which effectiveness and safety are established. The Division suggests using nomenclature specified in section XIII of this document and does not suggest grouping specific infections in body systems, as such an approach has continued to lead to promotional abuses. Ordering of infections in this list should be either alphabetically or by importance of product use in the community.)

Prevention/prophylaxis:

(Trade name of compound) is indicated for the prevention of infection in the following situations:

(List situations - medical and/or surgical for which effectiveness and safety are established.)

(See **DOSAGE AND ADMINISTRATION** section.)
(See **Pediatric Use** and/or **Geriatric Use** subsections.) - as applicable.

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

Effect on Promotional Activities:

It is the position of the Division of Anti-Infective Drug Products that any attempt by an applicant to promote (either directly or by misleading or disinformative promotional practices) an antimicrobial drug product for specific infections other than those listed in the **INDICATIONS AND USAGE** section of the product labeling would not be in compliance with Section 502 of the FD&C Act and implementing regulations. Further, any advertisement or promotional labeling for products will be considered false and misleading under the Act if it does not include the entire **INDICATIONS AND USAGE** section of the labeling when referring to the infections for which these products are approved. The **"NOTES"** and other added statements in the **INDICATIONS AND USAGE** section are considered integral parts of the approved indication and should not be deleted or edited. In advertising or promotional labeling, the **"NOTES"** and other added statements should not be spatially separated from the

wording in the initial part of the **INDICATIONS AND USAGE** section so as to minimize their impact. Such information should be presented in advertising or promotional pieces in at least the same print size and with at least the same impact as any other information from this section of the labeling. The Division of Anti-Infective Drug Products will work closely with the Division of Drug Marketing, Advertising, and Communications to enhance enforcement of this position.

(II) ISSUES WITH RESTRICTED/UNRESTRICTED LABELING:

The minimal scientific information for individual infections discussed subsequently in this document should usually be adequate to support an *"unrestricted"* listing in the **INDICATIONS AND USAGE** section of the final product labeling. Some situations, however, warrant a *"restricted"* label (*e.g.*, a product possesses a significantly improved safety profile or offers some significant advantage to the patient of physician but does not meet the statistical or clinical equivalence requirements for an unrestricted listing), a "restricted" listing should be placed in the **INDICATIONS AND USAGE** section of the product label. Such restriction(s) (*e.g.*, limitations to the treatment of only certain levels of severity of infections, specifications of comparative cure/eradication rates, recommendations that a product not be first line therapy for a given infection, restrictions to treating certain subclasses of pathogens, etc.) should be prominently placed in the label, usually in the form of a **"NOTE"** placed in the **INDICATIONS AND USAGE** section. As discussed previously in Section I, the Division of Anti-Infective Drug Products will work closely with the Division of Drug Marketing, Advertising, and Communications to assure that the spirit of the label and the strength of the submitted scientific data are accurately portrayed in any promotional efforts of a sponsor regarding such "restricted" labeling.

(III) ISSUES WITH THE USE OF ASTERISKS IN THE INDICATIONS and USAGE SECTION OF THE PRODUCT LABELING AND THE LISTING OF MICROORGANISMS IN THE IN VITRO Microbiology SUBSECTION OF THE CLINICAL PHARMACOLOGY SECTION OF THE PRODUCT LABELING:

Background:

Asterisks should no longer be placed by the names of microorganisms in the **INDICATIONS AND USAGE** section of the product labeling as a means of designating those microorganisms studied in between 5 and 10 total patients. Rather, generally, only those microorganisms considered to be an etiologic agent (pathogen) in at least 10% of the evaluable cases of the specific infection successfully treated with the investigative agent should be included in the **INDICATIONS AND USAGE** section of the product labeling. The "at least 10%" here - and throughout this document - should be understood to mean "at least 10% of the evaluable cases meeting both clinical and microbiological evaluability criteria or 10 total cases (as just defined), whichever is higher." Even though a given pathogen may represent "at least 10%" of the evaluable cases successfully treated, the eradication rate of the pathogen should be clinically acceptable in order for that pathogen to be included in this section of the labeling.

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

Suggested Product Labeling (**Microbiology** subsection):

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

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

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

Microorganisms should be listed alphabetically in the following four categories: aerobic gram-positive microorganisms, aerobic gram-negative microorganisms, anaerobic microorganisms, and "other" microorganisms.

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

> The following *in vitro* data are available, **but their clinical significance is unknown.** " (bolded and underlined)
>
> (Generic name of drug) exhibits *in vitro* minimal inhibitory concentrations (MIC's) of (clinically relevant "susceptible" breakpoint) or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of (generic name of drug) in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

To be included in this "*in vitro* only" list (#2), the more easily obtained and tested microorganisms should have a minimum of at least 100 isolates of each individual microorganism (genera and species)

tested. When feasible, it is expected that testing should be by both the diffusion and dilution techniques. It is suggested that the great majority (>75%) of these isolates should be from geographically representative, recent, typical clinical isolates obtained from patients (but not necessarily the specific patients in the NDA clinical trials) throughout the United States. More than one laboratory, using standardized *in vitro* susceptibility methods, should be used in this testing process, and the mean MIC_{90} for the 100+ isolates should be equal to or less than the final clinical "susceptible" breakpoint for the investigational drug.

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

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

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

N.B.: Microorganism susceptibility patterns can differ significantly in various parts of the world. In situations where an applicant chooses to submit microbiologic data derived from sources outside the United States, it is the responsibility of the applicant to demonstrate that the data are microbiologically relevant to the treatment of patients in the United States.

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

(4) The *Susceptibility Tests* subsection should ordinarily be written as follows for each antimicrobial drug product:

Diffusion techniques:

Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure that has been recommended for use with disks to test the susceptibility of microorganisms to [generic name of drug] uses the [x]-μg [generic name of drug in the disk] disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for [generic name of drug].

Reports from the laboratory providing results of the standard single-disk susceptibility test with a [x]-μg [generic name of drug in the disk] disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
a	Susceptible (S)
b	Intermediate(I)
c	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood. A report of "Intermediate"

indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and that other therapy should be selected.

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See **CLINICAL PHARMACOLOGY** section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

Standardized susceptibility test procedures require the use of laboratory control microorganisms. The [x]-μg [generic name of drug in the disk] disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
(complete chart, as appropriate, including ATCC strain numbers)	

Dilution techniques:

Quantitative methods that are used to determine minimum inhibitory concentrations provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure

uses a standardized dilution method[2,4] (broth, agar, or microdilution) or equivalent with [generic name of drug] powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (μg/mL)	Interpretation
d	Susceptible (S)
e	Intermediate (I)
f	Resistant (R)

Interpretation should be as stated above for results using diffusion techniques.

As with standard diffusion techniques, dilution methods require the use of laboratory control microorganisms. Standard [generic name of drug] powder should provide the following MIC values:

Microorganism	MIC (μg/mL)
(complete chart as appropriate including ATCC strain numbers)"	

Anaerobic techniques:

For anaerobic bacteria, the susceptibility to [generic name of drug] can be determined by the reference agar dilution method[3,4] or by alternate standardized test methods."

As with other susceptibility techniques, the use of laboratory control microorganisms is required. Standard [generic name of drug] powder should provide the following MIC values:

Microorganism	MIC (μg/mL)

(complete chart as appropriate including ATCC strain numbers)"

The following references should be added in the **REFERENCES** section of the labeling:

1. National Committee for Clinical Laboratory Standards, Performance Standard for Antimicrobial Disk Susceptibility Tests - Fourth Edition. Approved Standard NCCLS Document M2-A4, Vol. X, No. X NCCLS, Villanova, PA, April, YEAR.

2. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Second Edition. Approved Standard NCCLS Document M7-A4, Vol. X, No. X NCCLS, Villanova, PA, April, YEAR.

3. National Committee for Clinical Laboratory Standards, Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria - Second Edition. Tentative Standard NCCLS Document M11-T2, NCCLS, Villanova, PA, YEAR.

4. National Committee for Clinical Laboratory Standards. Performance standard for antimicrobial susceptibility testing; Third Information Supplement, NCCLS Document M100-S3 (ISBN 1-56238-136-9). NCCLS, Villanova, PA, YEAR.

(These references should be updated with subsequent NCCLS updating of its documents or updating of other recognized references.)

N.B. NCCLS methodology is but one testing methodology. Applicants maintain the ability of submitting for consideration any scientifically validated *in vitro* testing methodology they believe appropriate for their antimicrobial drug product.

Effect on Promotional Activities:

The Division of Anti-Infective Drug Products will work closely with the Division of Drug Marketing, Advertising, and Communications to eliminate any advertising or other promotional efforts that imply greater effectiveness of one compound *versus* other compound(s) based solely on *in vitro* microbiologic data. *In vitro* data provide information, in some circumstances, to compare the *in vitro* antimicrobial activity of two compounds but do not provide information to compare or imply potential clinical effectiveness of various compounds. This is especially true when the *in vitro* data are presented out of context with the known human pharmacokinetic properties of the antimicrobial drug product and out of context with the drug product's clinical experience. Balanced promotional activities with clear delineation between *in vitro* activity and clinical effectiveness should be the standard. Promotional materials dedicated only to *in vitro* data, without equivalent, balanced reference to data on human pharmacokinetic properties of and clinical effectiveness of a given antimicrobial drug product, would be deemed by the FDA, under most circumstances, to be misleading.

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

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

(b) Comparisons between or among products of MIC or "percent susceptible" figures selectively taken from various published or unpublished sources that are presented in such a format as to imply fairly balanced and scientifically rigorous data when, in fact, the data presented are biased through the selection process in favor of the applicant's product in that they eliminate results unfavorable to the applicant's product.

(c) Comparisons of results between or among antimicrobial drug products from various *in vitro* studies of unestablished clinical relevance (*e.g.*, inoculum effect, post-antibiotic effect, time/kill kinetics, serum/tissue kill ratios, mechanisms of action, resistance mechanisms, etc.) that imply superiority, either directly or indirectly, because of the presence or absence of the particular characteristic or which are presented in a format that implies fair balance and scientific rigor when, in fact, the data are selective and biased in favor of the applicant's product.

These *in vitro* microbiology data should be made available in the final product labeling for use by individual physicians in comparing *in vitro* antimicrobial activity of antimicrobial compounds. When taken together with published information on *in vitro* antimicrobial activity and human drug pharmacokinetics, these data may be useful in managing individual patients, nonetheless, they should not be intended to be implicit effectiveness claims for the antimicrobial drug product. Clearly they should not be data upon which supposedly clinically relevant, comparative promotional statements are based.

POINTS REGARDING CLINICAL TRIAL DESIGN/CONDUCT:

(IV) ISSUES REGARDING ADEQUACY OF TRIALS:

The number of evaluable patients and the numbers and designs of trials required to establish the effectiveness and safety of an antimicrobial drug product are determined by many factors.

For example:

the incidence of the infection,

the realistic number of patients available for investigative study in a reasonable time frame,

the knowledge of the natural history of the infection,

the knowledge of available cure rates of other compounds and the state of medical practice at the time,

the knowledge of pharmacokinetic, pharmacodynamic, and microbiologic properties of the compound with respect to certain infections and certain microorganisms,

the knowledge of the general effectiveness and toxicity of the chemical class to which the antimicrobial drug product belongs,

and the knowledge of the clinical activity of the antimicrobial drug product in treating similar infections in other pathophysiologically related body sites.

It must be remembered that the establishment of effectiveness is only part of the burden of proof borne by the sponsor of an antimicrobial drug product marketing application. An acceptable risk-to-benefit profile must also be established. In establishing a comprehensive risk-to-benefit profile for most antimicrobial drug products, the studies of effectiveness in certain infections usually lend themselves to accrual of larger numbers of patients upon which to determine the overall safety profile of the antimicrobial drug product under conditions of use. The Division of Anti-infective Drug Products has attempted to incorporate this element of clinical trial reality into the basis of certain suggestions in this document.

For purposes of this document, "statistically-adequate" usually means a trial with enough numbers of evaluable patients in each arm of a study to establish equivalence or superiority of the test agent to an approved comparator agent or, in special circumstances, an approved effectiveness standard.

The sliding scale method for determination of delta previously included in this document is no longer in use. Further general information on specifying delta can be found in the 1998 Draft Guidance on Developing Antimicrobial Drugs - General Considerations for Clinical Trials (Section XX.A.6) as well as in the 2000 ICH E10 document (section 1.5.1.1 entitled "Historical Evidence of Sensitivity to Drug Effects and Choosing the Noninferiority Margin").

Detailed guidance about delta specification is currently under development. Sponsors are strongly encouraged to specify a delta in their protocols and provide a rationale for that choice. Consultation with the Review Division is recommended.

(V) ISSUES WITH OPEN TRIAL DESIGNS:

Because of concerns of selection bias by the investigator in the open trial designs (*i.e.*, the investigator or assessor is unblinded at time of assessments or before analysis of final data) discussed subsequently in this document, a patient registration log should be maintained by each investigator or site (as appropriate). All patients with the disease under investigation presenting to the investigator (or co-investigators, as appropriate) should be entered by initial in this registration log. The log should also document briefly the reason(s) for not enrolling a given patient in the trial. Registration log books should be submitted as part of any NDA wishing to use such trial results as critical effectiveness data. Generally, any appearance that patients were being pre-selected for one arm of the study with "lesser" degrees of disease than patients selected for the other arm of the study or any other appearance of bias introduction could invalidate the study unless adequate explanation was provided. Likewise, any appearance that patients were being pre-selected for "lesser" degrees of disease generally in both arms of the trial could result in restrictive labeling in the **INDICATIONS AND USAGE** section of the product labeling unless adequate explanation was provided.

(VI) ISSUES WITH MULTICENTER TRIAL DESIGNS:

Multicenter trials are often required to garner requisite clinical data in a more expeditious manner. Likewise, well-performed multicenter trials can provide a corroborative undergirding of data by demonstrating similar outcomes from different investigators in different geographic and clinical settings. Data from many multicenter trials previously submitted to the Division have raised concerns because, more often than not, outcomes reported from centers with large numbers of enrolled patients differed substantially from centers with small numbers of enrolled patients. Treatment by center (or by investigator) analyses raised questions about data reproducibility and data consistency across and within centers. While the Division is interested in receiving data from different, appropriate clinical treatment environments (large institutions, small institutions, primary care environments, tertiary care environments, group practices, solo practices, etc.), individual study integrity should not be sacrificed to a large scale, "shot-gun" approach to patient enrollment for the sake of speed alone.

The Division is not presently setting a minimum number of evaluable patients per study arm that should be enrolled to consider a site or study valid. However, critical multicenter trials should be evaluated closely and critically to establish that the data are not compromised by treatment by center (or by investigator) interactions. For certain infections (*e.g.*, uncomplicated UTI, pharyngitis, uncomplicated SST, GC) where large per center enrollment could be expected, a minimum of 10 evaluable patients per arm should be a goal for investigators participating in multicenter trials.

(VII) ISSUES WITH CHOICE OF COMPARATOR AGENTS:

In active controlled trials, an applicant can routinely choose any comparator that is approved in the United States for the treatment of that infection. If an applicant chooses to use a comparator agent or dosing regimen (in a trial designed to demonstrate equivalence of the two treatment arms) that is not yet approved in the United States, it is the responsibility of the applicant to submit in the NDA the data substantiating the comparator agent or regimen as safe and effective therapy so that the new product can be approved based on its equivalence to the selected comparator arm. Applicants should be aware of the regulatory implications of such an approval relative to the equivalence it publically establishes.

Applicants should be aware that the so-called "bio-creep" phenomenon is always of concern to the Agency. This phenomenon is the selection of successively less effective comparator agents, which individually fit a statistical confidence interval relative to the product to which it was compared. This process, over time, may result in the presumed "equivalence" of statistically and clinically inequivalent products. Also, the recognized effectiveness of certain products changes with time due to alterations in resistance patterns and development of new knowledge. Constraints imposed by FDA staffing, regulatory requirements, and product manufacturers often hinder the rapid re-labeling of approved products. In order to prevent the occurrence of "bio-creep" and the selection of "approved", yet inappropriate, comparator agents - especially when the selected comparator agent was itself approved on the basis of equivalence in active-controlled trials - we advise applicants to discuss comparator agents with the Division, if they have any doubts, prior to the initiation of their clinical development program. Products establishing equivalence to less effective products should have such information readily available to physicians in the product label. Promotion of the such products should also include balanced information regarding the data upon which the product was approved for marketing.

(VIII) ISSUES WITH CERTAIN ELEMENTS OF TRIAL CONDUCT:

Trials designed to provide critical data for an NDA should preferably be randomized, blinded, well-controlled trials. Standard principles of clinical trial design and conduct previously discussed by the Agency should generally be followed. Certain exceptions to this general approach are discussed subsequently in this document for specific infections.

(A) In trials designed to have clinically evaluable only or clinically only and clinically and microbiologically evaluable patients, all randomized patients should be encouraged to complete the trial. In these trials, patients should not be discontinued from the drug simply because they do not have a pathogen isolated at baseline OR simply because the pathogen is resistant to either product. If the patient needs to be discontinued because of failure to progress clinically, then the patient should be discontinued, evaluated as a drug failure, and started off study on appropriate therapy. This approach should facilitate appropriate intent-to-treat and modified intent-to-treat analyses.

(B) In trials where technology limitations or patient acceptability preclude double blinding of treatment, all efforts should be made to maintain blinding of the outcome assessor so as to prevent bias introduction as much as possible.

(C) Unless specified otherwise under each specific infection, multicenter trials to produce critical data for an NDA, should be conducted by a minimum of three investigators located in different geographic areas. No individual study site should be allowed to enroll greater than 40% of the total patients enrolled for a specific multicenter trial. As mentioned earlier in this document, concerns about potential bias created by treatment by center (or by investigator) interaction should be evaluated and adequately addressed.

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

(E) For those infections for which a suggested trial design does not rely on isolation of a pathogen, the presence of any microorganism playing a major etiologic role should not be an entry exclusion criterion for the trial.

(F) Except for the most unusual circumstances (usually involving an outside safety committee), interim analysis of a critical clinical trial should not be performed. If such is performed, standard statistical penalties should be applied to subsequent statistical analysis of the data. Likewise, interim reports should not be submitted to NDA's with the intent of enhancing the study analysis at a later date in the review process with subsequent data.

(G) Of paramount importance to valid analysis of a trial's data is the necessity to delineate <u>clearly</u> and <u>prospectively</u> the primary effectiveness parameter(s) and the evaluability criteria that

should be employed. These prospective criteria should be followed in post-study analysis unless there are special circumstances dictating deviation. Such circumstances should be scientifically defensible and clearly explained in the NDA. Drug development programs for antimicrobial drug products should not be exercises in post-hoc study resuscitations in an attempt to salvage poorly designed, poorly performed, or poorly monitored studies.

(IX) ISSUES WITH FOREIGN DATA:

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

It is the intent of the Division to accept, as critical data for marketing authorization, clinical trials, including multicenter trials, wherever they are conducted, if they characterize drug activity and safety for the U.S. population in a clinically relevant and statistically valid manner.

Applicants should be cognizant of special concerns about the relevance of some foreign infectious disease data to the American population because of known differences in microorganism susceptibility patterns in various parts of the world and known differences in pathogenic etiologies for various infections in various parts of the world. Should an applicant choose to submit foreign clinical or *in vitro* data, critical for the approval of a New Drug Application, it is the responsibility of the applicant to demonstrate that these critical data are clinically and microbiologically relevant to the United States population for which marketing approval is sought. The Division of Anti-Infective Drug Products will not simply assume such relevance. Well in advance of reaching a corporate decision that a foreign study will be critical data for the U.S. NDA, applicants are encouraged strongly to discuss with the Division how the applicant can meet its responsibility to establish the relevance of the critical foreign data to the U.S. population in a specific situation.

Likewise, applicants should be aware of the regulatory requirement for the availability of source documentation for FDA inspection should the necessity for such arise. This requirement is applicable to both domestic and foreign data submitted in the NDA. The Division is aware that this

requirement has been problematic in some situations in the past. With the more widespread acceptance of standard "Good Clinical Practices", hopefully this issue will be less and less problematic for applicants.

(X) ISSUE WITH PEDIATRIC CLAIMS:

Because infectious diseases are frequent diseases in the pediatric population, the Division is committed to providing in drug product labeling scientific data regarding appropriate use of antimicrobial drug products in children. In doing so, however, children cannot be viewed by applicants or by Division reviewers simply as "little adults". Many elements of childhood infectious diseases differentiate them from their adult counterparts, and these factors must be considered to assure that the use of an antimicrobial drug product in a specific pediatric infection will be safe and effective. These factors include, for example: (1) the special growth and development characteristics of children; (2) the special drug absorption, distribution, and elimination characteristics of children at different ages, including immaturity of detoxification and elimination mechanisms and immaturity of drug distribution impediments such as the blood-brain barrier; (3) the special diseases that are inherently pediatric by virtue of the nature of the disease or by virtue of the unique susceptibility of children to the disease; and (4) the special microbiology of certain infectious diseases, *vis-a-vis* adults, when children at different ages experience the "same" disease as adults.

It is neither the intention of the Division nor is it good public health policy for a drug to have to re-establish its effectiveness in children (assuming it has adequately established its effectiveness in adults), if the disease pathophysiology and microbiology are the same in children and adults. In these situations, establishing the correct dosage of the medication in the specific pediatric population under consideration should be undertaken in order to correlate it with the established dose requisite for effectiveness in adults. Likewise in this situation, any specific pediatric safety concerns should be adequately addressed.

However, it is neither the intention of the Division nor is it good public policy to treat children as second-class citizens not worthy of the same scientific rigor required of adult clinical trials when pediatric clinical trials are undertaken to establish efficacy and safety in disease entities different in physiology or microbiology from adult disease entities. In

these situations, the same scientific standards as for adults, where possible, should apply to clinical trials to establish effectiveness and safety of a drug product in pediatric populations.

The **INDICATIONS AND USAGE** and the **DOSAGE AND ADMINISTRATION** sections and the **Pediatric Usage** subsection of the final product labeling should be used to detail data from trials as outlined in the three preceding paragraphs. They should not be used to promote or afford credibility to anecdotal or uncorroborated "data".

(XI) ISSUES ABOUT ADEQUATE SAFETY DATA BASES:

The development of an antimicrobial drug product for the treatment of several infections should usually constitute an acceptable clinical safety base, unless there are unusual safety concerns for a specific product. However, at a minimum, Center standards for minimal clinical safety bases should usually be submitted. Thus, if an applicant chooses to develop a drug product for the treatment of only one or two infections, the applicant is strongly encouraged to discuss with the Division the adequacy of the clinical safety base the proposed studies should provide.

(XII) ISSUES ABOUT PHARMACOKINETIC/-DYNAMIC DATA:

In many of the suggestions regarding specific infections that follow in Section XIII, reference is made to adequate microbiologic data and specific human pharmacokinetic/-dynamic data supportive of clinical effectiveness in the disease entity that is suggested. Such studies would include, but not be limited to, tissue distribution studies that demonstrate that, at the dosing regimen requested in NDA, the investigative agent diffuses into the infected body site in quantities adequate to achieve and maintain concentrations equal to or above the expected MIC_{90}'s of the claimed pathogens for an adequate time period. Such a suggestion should not imply that the Division believes the adequacy of all such testing methodology has been verified for all infected sites or that the relevance of all such data to clinical effectiveness has been established. Rather these are simply suggested data to help support the data derived from the adequate and well-controlled clinical trials to which the antimicrobial drug product has been subjected.

(XIII) ISSUES ABOUT SPECIFIC INFECTIONS:

PREFACE:

The following 24 "infections" constitute the routine infections many applicants desire to have listed in the **INDICATIONS AND USAGE** section of product labeling for antimicrobial drug products. The guidance regarding the depth of scientific data suggested for approval of an antimicrobial drug product in the treatment of these specific infections is not intended to handle many of the intricacies of specific clinical trial designs or many of the intricacies of special product development. **Any scientifically valid trial design will be considered by the Division.** Clearly special circumstances (*e.g.*, special developmental strategies and emergence of new diseases) should result in modifications and additions to these 25 specific categories with time.

An applicant may choose to develop its antimicrobial drug product for any or all of these infections or for other special infections, as desired. This document is not intended to restrict development, but rather facilitate it. The Agency is willing to discuss development plans (trial designs, planned indications, special indications, methods of analysis, effectiveness/safety/evaluability criteria) with applicants prior to and during the drug development process.

The suggestions that follow are based upon the assumption that an applicant will choose to develop a product for at least a minimum of two infections. Should an applicant choose to develop a product for <u>just one infection</u>, two adequate and well-controlled trials of the use of the drug in treating that one infection in different geographic areas should ordinarily be performed, despite the subsequent individual infection suggestions in this document. Likewise, applications for treatment of infections with dosing regimen durations less than generally approved for that infection should ordinarily contain two statistically adequate and well-controlled trials, despite the subsequent individual infection suggestions in this document.

SPECIFIC INFECTIONS: (Please see Section VIII for some study conduct issues related to these trials, especially regarding numbers of sites and percentages of patients from a given site.)

(1) *Uncomplicated urinary tract infections (cystitis):*

(Scenario One)

One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product is suggested. In a study of this infection, an evaluable patient should be both clinically and microbiologically evaluable. Although, generally, the primary effectiveness parameter in this study should be microbiologic outcome at 5 to 9 days after the cessation of therapy, the study should establish the general correlation between clinical cure and bacterial eradication in these patients. Pathogens listed in the **INDICATIONS AND USAGE** section of the product labeling for this infection should be as per Section III of this document.

(Scenario Two)

If the dosage and duration of therapy are the same for complicated urinary tract infections and effectiveness in complicated urinary tract infections is established as below for similar microorganisms, only one statistically-adequate and well-controlled trial, performed at at least two different centers with no more than 55% of the evaluable patients from any one center, should be sufficient to establish effectiveness in uncomplicated urinary tract infections. Any pathogen listed in the complicated infection label should be incorporated into the label for the uncomplicated infection claim, if the pathogen is generally accepted to be associated with uncomplicated urinary tract disease. This suggestion is not intended to suggest that similar dosing regimens for uncomplicated and complicated urinary tract infections should be studied. Applicants should determine the most effective and least toxic dose for each indication.

(Both scenarios)

Adequate microbiologic data and specific human pharmacokinetic/-dynamic data supportive of clinical effectiveness in uncomplicated urinary tract infections should also be submitted. Such studies should include, but not be limited to, tissue distribution studies that demonstrate that, at the dosing regimen requested in the NDA, the investigative agent diffuses into urine in quantities adequate to achieve and maintain urine levels equal to or above the expected MIC_{90}'s of the claimed pathogens for an acceptable period of time.

If an applicant chooses to perform more than one adequate and well-controlled trial in this specific infection, specific pharmacokinetic and pharmacodynamic data relative to this indication should not ordinarily be necessary, though clearly it is of interest.

(2) *Complicated urinary tract infections and pyelonephritis::*

One statistically adequate and well-controlled trial establishing equivalence or superiority to an approved agent and one open trial that establishes statistical equivalence to the success rate of the approved agent in the first complicated UTI trial or to an effectiveness rate agreed upon with the Division are suggested.

For the second trial, the applicant should demonstrate that the patient demographics, the disease severity, the exclusion/inclusion criteria, the evaluability criteria, and the primary effectiveness parameters were not substantively different from those in the adequate and well-controlled first trial. The second trial should be performed by different investigator(s) than those involved in the first trial and the site(s) should represent geographically different area(s).

For studies of this infection, an evaluable patient should be both clinically and microbiologically evaluable. Although the primary effectiveness parameter in these studies should be microbiologic

outcome, the study should establish the general correlation between clinical cure and bacterial eradication in these patients. Pathogens listed in the **INDICATIONS AND USAGE** section of the product labeling should be as per Section III of this document.

The Division recognizes that pyelonephritis can be either an uncomplicated or complicated clinical disease. The Division suggests that it be studied with complicated urinary tract infections as dosing regimens for pyelonephritis and complicated urinary tract infections are routinely similar. If there is not a sufficient number of patients with pyelonephritis successfully treated with the investigative agent (minimum: 30 patients/arm/study), the listing should not include pyelonephritis.

(3) *Uncomplicated Skin and Superficial Skin Structure infections:*

One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product is suggested. It is suggested that the numbers of evaluable patients with simple abscesses, impetiginous lesions, furuncles, and cellulitis should be at least 20% each so that this general claim could be granted. NDA's with critical studies, in which only one or two specific types of uncomplicated skin and skin structure infections were studied, should receive a listing only for those one or two specific types of infection. Protocols used to study an investigative product for treatment of these infections should have very clear inclusion, exclusion, evaluability criteria, and outcome definitions as the primary effectiveness parameter for this infection should be clinical outcome. Nonetheless, at least 50% of the clinically evaluable patients should also be microbiologically evaluable in order that adequate numbers of evaluable cases with specific pathogens are available to assess general effectiveness for specific pathogens.

Please note four caveats:

(1) The simple growth of transient or resident skin flora in a culture should not constitute a microbiologically evaluable patient. Pathogens listed in the **INDICATIONS AND USAGE** section of the product label should be those established in the submitted data that also reflect contemporary beliefs about pathogenicity in these types of skin infections. In addition, the microbiologic culture sample should be obtained in such a manner that biologically meaningful conclusions can be reached based on the data.

(2) The large majority of the microbiologically unevaluable patients in this trial should be patients with diagnoses (such as cellulitis) where low pathogen recovery is the norm. Such cases should be supported as probable bacterial infections by a prospective rigid case definition.

(3) Analysis of treatment outcomes in these infections should be stratified by the presence or absence of therapeutic surgical intervention(s). In certain circumstances where it appears the surgical treatment was required as an adjunct or follow-up therapy due to failure of the investigative agent to successfully treat the uncomplicated skin infection, the patient should be evaluated as a treatment failure.

(4) Analyses of the data should also generally confirm (by means of comparing the direction of the independent 95% confidence intervals testing) the successful outcome rates established for the overall clinically evaluable and for the clinically and microbiologically evaluable subset of patients. Likewise the analyses should establish the correlation between clinical cure and bacterial eradication in the clinically and microbiologically evaluable subset of patients.

Adequate microbiologic data and specific human pharmacokinetic/-dynamic data supportive of clinical effectiveness in this disease entity should be submitted. Such studies would include, but not be limited to, tissue distribution studies that demonstrate that, at the dosing regimen requested in NDA, the investigative agent diffuses into skin and superficial skin structure tissues or other validated surrogate marker in quantities adequate to achieve and maintain skin and superficial skin structure levels equal to or above the expected MIC_{90}'s of the claimed pathogens for an adequate time period.

If an applicant chooses to perform more than one adequate and well-controlled trial in this indication (*e.g.*, to establish a sufficient overall safety data base for the product), specific pharmacokinetic/-dynamic data relative to this indication should not ordinarily be necessary.

(4) *Complicated Skin and Soft Tissue infections:*

One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product or to an approved method of treating these types of infections is suggested. Under this heading should be considered infected ulcers, burns, and major abscesses or other skin structure infections requiring significant surgical intervention along with antimicrobial drug therapy, and infections of the deeper soft tissues. Numbers of patients with each type of these infections should be such that a general claim could be granted. NDA's with critical studies, in which only one or two specific types of these infections were studied, should receive a listing only for those one or two specific types of infection. Protocols used to study an investigative product for treatment of these infections should have very clear inclusion, exclusion, and evaluability criteria and outcome definitions as the primary effectiveness parameter for this infection should be clinical outcome.

Nonetheless, at least 70% of the clinically evaluable patients should also be microbiologically evaluable in order that adequate numbers of evaluable cases with specific pathogens are available to assess general effectiveness for specific pathogens. Analysis of treatment outcomes in these infections should be stratified by the presence or absence of therapeutic surgical intervention(s). In certain circumstances where it appears the surgical treatment was required as an adjunct or follow-up therapy due to failure of the investigative agent to successfully treat the infection, the patient should be evaluated as a treatment failure.

Analyses of the data should also generally confirm (by means of comparing the direction of the independent 95% confidence intervals testing) the successful outcome rates established for the overall clinically evaluable and for the clinically and microbiologically evaluable subset of patients. Likewise the analyses should establish the correlation between clinical cure and bacterial eradication in the clinically and microbiologically evaluable subset of patients.

Pathogens listed in the **INDICATIONS AND USAGE** section of the product labeling should be as per Section III of this document.

Adequate microbiologic data and specific human pharmacokinetic/-dynamic data supportive of clinical effectiveness in this disease entity should be provided. Such studies would include, but not be limited to, tissue distribution studies that demonstrate that, at the dosing regimen requested in the NDA, the investigative agent diffuses into skin and deeper soft tissues or other validated surrogate marker in quantities adequate to achieve and maintain skin and superficial skin structure levels equal to or above the expected MIC_{90}'s of the claimed pathogens for an adequate time period.

If an applicant chooses to perform more than one adequate and well-controlled trial in this indication (*e.g.*, to establish a sufficient overall safety data base for the product), specific pharmacokinetic/-dynamic data relative to this indication should not ordinarily be necessary.

(5) *Community-acquired Pneumonia:*

One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product and one open trial are suggested.

The adequate and well-controlled trial should preferably be performed in the United States for purposes of U.S. product approval. In this trial, the primary effectiveness endpoints should be clinical and radiographic endpoints; however, microbiologic evaluations (culture and gram stain) should also be performed on each patient. Isolation of a pathogen from the baseline sputum culture should not be required for overall evaluability; however, rigid case definitions, including specific entry sputum microscopy and radiographic findings [specific to the type(s) of community acquired pneumonia being studied] should be included in the trial design.

Patients should be analyzed in two separate groups: (1) those who were clinically evaluable (whether or not microbiologically evaluable) and (2) those who were clinically evaluable <u>and</u> microbiologically evaluable. Analyses of the data should also generally confirm (by means of comparing the direction of the independent 95% confidence intervals testing) the successful outcome rates established for the overall clinically evaluable and for the clinically and microbiologically evaluable subset of patients. Likewise the analyses should establish the correlation between clinical cure and bacterial eradication in the clinically and microbiologically evaluable subset of patients.

Also suggested is a second study, which may be an open trial, involving at least 2 investigators in different geographic areas (no one center contributing more than 55% of the evaluable patients) in which 80 evaluable patients are studied. In this trial, the microbiologic etiology of the pneumonia should be confirmed for each patient. For this second trial, the applicant should demonstrate that the patient demographics,

the disease severity, the exclusion/inclusion criteria, the evaluability criteria, and the effectiveness parameters were not substantively different from those in the adequate and well-controlled first trial. The second trial should be performed by different investigator(s) than those involved in the first trial, and the site(s) should represent geographically different area(s). The results of this trial should be consistent with the results obtained in the controlled trial and demonstrate consistency in the action of the drug in treating this infection.

Pathogens listed in the **INDICATIONS AND USAGE** section of the product labeling should be as per Section III of this document.

In situations where atypical microorganisms causing community-acquired pneumonia are evaluated or when different susceptibility patterns are expected for specific microorganisms in different populations, different comparative agents and/or different patient populations may be selected for the two trials that should corroborate one another in the establishment of effectiveness in treating this infection. In these circumstances, it should be appropriate to perform two studies that investigate outcomes in both the clinically evaluable patients and in the clinically and microbiologically (*i.e.*, the pathogen is confirmed by an approved laboratory test methodology) evaluable subset of patients. Analyses of the data should confirm (by means of comparing the direction of the independent 95% confidence interval testing or by appropriate other analysis if the subgroups can be combined from the two separate studies) the successful outcome rates established for the overall clinically evaluable and for the clinically and microbiologically evaluable subset of patients.

(6) *Nosocomial Pneumonia:*

One well-controlled trial that establishes effectiveness equivalent (meets standard 95% confidence interval approach) or generally equivalent (difference in absolute success rates no greater than 5% less effective in clinical parameters) to an approved comparator agent or to a

prospectively agreed upon comparator treatment regimen is suggested. The 5% referred to in the "generally equivalent" comment is not a 95% confidence interval; rather, it is the calculated difference between the absolute successful clinical outcome rates of the evaluable patients in the two arms of this trial. It is suggested that at least 80 patients would be in each treatment arm. In studies of this infection, an evaluable patient should be clinically, radiographically, and microbiologically evaluable. Rigid case definitions, including specific entry sputum microscopy and radiographic findings should be included in the trial design.

Pathogens listed in the **INDICATIONS AND USAGE** section of the product labeling should be as per Section III of this document.

(7) *Acute bacterial exacerbation of chronic bronchitis:*

Two trials are suggested.

One statistically adequate and well-controlled trial establishing equivalence or superiority to an approved product is suggested. In this trial, an evaluable patient should be both clinically and microbiologically (any putative pathogen) evaluable. Analysis of the data should confirm the general correlation between clinical improvement and bacterial eradication (or suppression) in the evaluable patients.

Also suggested is a second study, in which clinical effectiveness should be used as the only primary effectiveness endpoint; however, microbiologic studies should be performed on each patient but pathogen isolation at baseline or susceptibility to either trial drug should not be required for overall evaluability. This trial should preferably be performed in the United States for purposes of U.S. product registration. Patients, in this trial, should be analyzed in two separate groups: (1) those who were clinically evaluable (whether or not microbiologically evaluable) and (2) the subset of patients who were clinically evaluable and

microbiologically evaluable. This trial should employ rigorous entry and evaluability criteria to insure the likelihood of bacteria being responsible for the exacerbation. Analyses of the data should confirm (by means of comparing the direction of the independent 95% confidence interval testing) the successful outcome rates established for the overall clinically evaluable and for the clinically and microbiologically evaluable subset of patients. Likewise, the analyses should establish the general correlation between clinical improvement and bacterial eradication (or suppression) in the clinically and microbiologically evaluable subset of patients.

Only *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* (based on acceptable clinical and microbiologic responses for these three microorganisms in the clinical trials) should presently be listed as pathogens amenable to therapy with the investigative agent in this infection. As evidence accumulates that other microorganisms are pathogenic in this disease, consideration should be given to their addition to the list.

If effectiveness in either of the two pneumonia claims is established by the product at the same dosing regimen (dose and duration) for the three clinically relevant (AECB) microorganisms, only the one "clinically plus microbiologically evaluable" study should be sufficient to establish the effectiveness of the antimicrobial drug product in the treatment of this infection.

(8) *Secondary bacterial infection of acute bronchitis:*

One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product is suggested. In this trial, an evaluable patient should be both clinically and microbiologically evaluable. Analyses of the data should confirm the general correlation between clinical cure and bacterial eradication in the evaluable patients.

Pathogens listed in the **INDICATIONS AND USAGE** section of the product labeling should be as per Section III of this document.

In order to establish, by means of this one trial, effectiveness of the antimicrobial product in treating this infection, the applicant should also have data to support effectiveness in the treatment of "Acute bacterial exacerbations of chronic bronchitis" as outlined previously in this document.

(9) *Acute otitis media:*

Two trials are suggested.

One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product is suggested. In this trial, rigid case definitions should be used with specific subjective and objective diagnostic parameters and effectiveness parameters clearly defined prospectively. This trial should not ordinarily enroll children less than 6 months of age. Baseline tympanocentesis need not be performed in this study; however, tympanocentesis of patients judged to be therapeutic failures is strongly encouraged to document potential specific bacterial pathogens not adequately treated in the trial. This trial should preferably be performed in the United States for purposes of U.S. product approval.

Also suggested would be one open study utilizing tympanocentesis or other validated bacterial etiologic detection methodology at baseline to establish microbiologic etiology. This study should establish acceptable microbial and clinical outcome in at least 25 patients with *H. influenzae*, in at least 25 patients with *S. pneumoniae*, and in at least 15 patients with *M. catarrhalis*. Post-therapy tympanocentesis is strongly encouraged in those patients judged to be therapeutic failures so that bacterial persistence or superinfection could be determined. In this trial, outcomes on all patients enrolled should be reported, not just those patients with the bacterial pathogens mentioned previously in this paragraph.

It would be expected that this trial would be performed by at least two investigators in geographically diverse regions. As etiologic patterns change, the requisite microorganisms listed would also change.

Pathogens listed in the final product label should be those of the three listed above that had acceptable eradication rates. If a product failed to have acceptable clinical and microbiologic effectiveness against all three microorganisms, the product should be listed only for those microorganism(s) that it eradicated. It should also receive a "restricted" listing as "not a product for first line therapy". This restriction should be based on the empiric nature of the treatment of this disease at the present time, and the need for true first-line therapies to be efficacious against all of the presently common bacterial pathogens associated with this infection. To receive an unrestricted label in this infection, the investigative product should be compared to a product with an unrestricted label in the "clinical only trial" outlined previously in this section.

(10) *Acute sinusitis:*

Two studies are suggested.

One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product is suggested. In this trial, rigorous case definitions with specific clinical and either radiographic or ultrasonic entry criteria and endpoints as the primary effectiveness parameters should be used. Sinus aspiration need not be performed in this study, although aspiration of patients judged to be therapeutic failures should be strongly encouraged to document any bacterial pathogen(s) not adequately treated in the trial. This trial should preferably be performed in the United States for purposes of U.S. product approval.

Also suggested would be one open study utilizing sinus aspiration. This trial should establish successful microbial, clinical, and radiographic or ultrasonic outcome in at least 100 patients. This study should establish acceptable microbial and clinical outcome in at least 25 patients with *H. influenzae*, in at least 25 patients with *S. pneumoniae*, and in at least 15 patients with *M. catarrhalis*. Post-therapy sinus aspiration is strongly encouraged in those patients judged to be therapeutic failures so that bacterial persistence or superinfection could be determined. In this trial, outcomes on all patients enrolled should be reported, not just those patients with the bacterial pathogens mentioned previously in this paragraph. This trial should be performed by at least two investigators in geographically diverse regions, and no one center should contribute more than 55% of the evaluable patients.

Pathogens listed in the **INDICATIONS AND USAGE** section of the product labeling should be as per Section III of this document. If a product failed to eradicate the major bacterial pathogens associated with this infection, the product should also receive a "restricted" listing as "not a product for first line therapy". This restriction should be based on the empiric nature of the treatment of this disease at the present time and the need for true first-line therapies to be efficacious against the major bacterial pathogens associated with this infection.

(11) *Streptococcal pharyngitis:*

One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product is suggested. Despite statistical equivalence to an approved product, any product with an absolute eradication rate at follow-up of <85% should not ordinarily be approved as a first line therapy for this infection. Although the primary effectiveness parameter in this study should be microbiologic eradication, the study should establish the general correlation between clinical cure and bacterial eradication in these patients.

In studies of this infection, an evaluable patient should be clinically and microbiologically evaluable.

Adequate microbiologic data and specific human pharmacokinetic/-dynamic data supportive of clinical effectiveness in this disease entity should also be submitted. Such studies should include, but not be limited to, tissue distribution studies that demonstrate the investigative agent diffuses into tonsillar tissues in quantities adequate to achieve and maintain tonsillar tissue concentrations equal to or above the expected MIC_{90}'s of the claimed pathogen for an adequate period of time.

If an applicant chooses to perform more than one adequate and well-controlled trial in this indication (*e.g.*, to establish a sufficient overall safety data base for the product), specific pharmacokinetic/-dynamic data relative to this indication should not ordinarily be necessary.

(12) *Bacterial meningitis:*

In pediatrics, one statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product is suggested. Follow-up to determine neurologic sequelae following treatment is suggested to determine final therapeutic effectiveness of a drug product.

In adult meningitis, one open trial that establishes equivalence to a previously agreed upon mandatory microbiologic eradication rate and clinical cure rate is suggested. The minimally acceptable cure rate should be determined by the particular disease (patient age and microorganisms being studied). Follow-up to determine neurologic sequelae following treatment is also suggested to determine final therapeutic effectiveness of a drug product.

In both pediatric and adult meningitis, adequate microbiologic data and specific human pharmacokinetic/-dynamic data supportive of

clinical effectiveness in this disease entity should be submitted. Such studies should include, but not be limited to, tissue distribution studies that demonstrate the investigative agent diffuses into cerebrospinal fluid in quantities adequate to achieve and maintain cerebrospinal fluid levels of antimicrobial compound equal to or above the expected MIC_{90}'s of the claimed pathogens for an adequate time period.

Pathogens listed in the **INDICATIONS AND USAGE** section of the product labeling should be as per Section III of this document.

(13) *Uncomplicated gonococcal urethritis/cervicitis:*

Effectiveness against this disease entity should be established in both men and women. Effectiveness could be established by two open trials - one trial for each gender (or one trial enrolling adequate numbers of both men and women).

One trial should involve at least 100 men, and one trial should involve at least 100 women.

Bacterial eradication rate should be the primary effectiveness endpoint, and at least 95% bacterial eradication should be expected in both trials (or for both genders if one trial is performed) in order to support the claim for this infection. Initial resistance of a given isolate to the investigative agent should <u>not</u> ordinarily make that patient non-evaluable. Patients could be stratified by presence or absence of resistance to the pathogen and then analyzed. Such an approach may result in a restricted indication, depending on the data outcome.

When beta-lactamase production is not a factor (*i.e.*, in non-beta-lactam antimicrobial drug products), evaluation of infections caused by beta-lactamase-producing microorganisms should not be needed. If beta-lactamase production is a factor, greater than 95% bacterial eradication should be demonstrated in a subset analysis of at least 40 patients (at least 20 men and 20 women) from these two trials in order to support specific wording in

the **INDICATIONS AND USAGE** section that states the product is indicated in the treatment of uncomplicated gonococcal urethritis/cervicitis due to beta-lactamase-positive and beta-lactamase-negative strains of *N. gonorrhoeae*. Without such data, the labeling should be restricted to beta-lactamase-negative *N. gonorrhoeae*, and the labeling should also have a "not first line therapy" restriction depending on the level of beta-lactamase-positive *N. gonorrhoeae* in the country at the time of approval of the final product labeling.

Once effectiveness in uncomplicated gonococcal urethritis/cervicitis has been established, effectiveness in gonococcal pharyngitis or proctitis may be established by scanning data bases from the critical studies and from similar uncomplicated gonococcal urethritis/cervicitis studies recognized by the Division as adequate studies. All patients with gonococcal pharyngitis or proctitis should be pooled, and <u>all</u> patients with these diagnoses should be included in the analyzed data. A minimum of 20 patients each of each gender for each additional body site (*i.e.*, rectum, pharynx) where at least 90% bacterial eradication is demonstrated should be sufficient to establish effectiveness in these additional infections. Applicants should be encouraged to study these additional body sites in both men and women; however, individual gender-specific labeling claims could be approved by the Division if the above criteria are met.

(14) *Non-gonococcal urethritis/cervicitis:*

Applicants are strongly encouraged to study effectiveness of their antimicrobial drug product in treating this infection in <u>both</u> men and women; however the listing for this infection may be supported independently for either men or women. One statistically adequate and well-controlled multicenter trial in men establishing equivalence or superiority to an approved product is suggested to support the claim in men. One statistically adequate and well-controlled multicenter trial in women establishing equivalence or superiority to an approved product is suggested to support the claim in women.

For this infection, an evaluable patient should be both clinically and microbiologically evaluable. Pathogens listed in the **INDICATIONS AND USAGE** section of the product labeling should presently be limited to specific *Chlamydia* species, specific *Ureaplasma* species, and specific *Mycoplasma* species based on acceptable clinical and microbiologic responses for species of these three genera in the clinical trials. As evidence accumulates that other microorganisms are pathogenic in this infection, the Division would consider including them on the list.

Adequate microbiologic data and specific human pharmacokinetic/-dynamic data supportive of clinical effectiveness in this disease entity are also suggested. Such studies should include, but not be limited to, tissue distribution studies that demonstrate the investigative agent diffuses into urethral and cervical exudates in quantities adequate to achieve and maintain urethral and cervical exudate levels of antimicrobial compound equal to or above the expected MIC_{90}'s of the claimed pathogens for an adequate time period.

(15) *Acute prostatitis:*

One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product is suggested. In this infection, an evaluable patient should be both clinically and microbiologically evaluable. Pathogens listed in the **INDICATIONS AND USAGE** section of the product labeling should be those as per Section III of this document.

It is assumed that the compound would have also established effectiveness in complicated urinary tract infections and that the majority of pathogen are similar. Clearly some potential pathogens, such as species of *Chlamydia*, should be evaluated on their responses in this study and in investigations of treatment of other infectious sites involving *Chlamydia*.

Adequate microbiologic data and specific human pharmacokinetic/-dynamic data supportive of clinical effectiveness in this disease entity are also suggested. Such studies would include, but

not be limited to, tissue distribution studies that demonstrate that the investigative agent diffuses into prostatic secretions and tissues in quantities adequate to achieve and maintain prostatic secretions and tissue levels of antimicrobial compound equal to or above the expected MIC_{90}'s of the claimed pathogens for án adequate time period.

(16) *Endocarditis:*

One open trial of at least 50 patients that establishes a predetermined overall clinical and microbiologic success rates is suggested. For this infection, an evaluable patient should be both clinically and microbiologically evaluable. If there is not a reasonable mix of artificial and native valve, right and left sided disease, and acute *versus* subacute clinical presentations, such should be noted in the approved labeling by restricting the labeling in the **INDICATIONS AND USAGE** section of the product labeling to just those types of infection and populations actually studied. This trial should involve at least two investigators in different geographic areas. Pathogens listed would be determined on a case-by-case basis, taking into account various expected success rates for the treatment of specific pathogens.

Adequate microbiologic data and specific human or animal pharmacokinetic/-dynamic data supportive of clinical effectiveness in this disease entity are also suggested. Such studies would include, but not be limited to, tissue distribution studies that demonstrate the investigative agent diffuses into appropriate tissues in quantities adequate to achieve and maintain levels of antimicrobial compound equal to or above the expected MIC_{90}'s of the claimed pathogens for an adequate time period.

(17) *Uncomplicated intra-abdominal infections:*

This entity should encompass intra-abdominal infections that do not require surgical intervention (*e.g.*, mild diverticulitis) and should not include gynecologic infections and pelvic inflammatory disease.

Two statistically adequate and well-controlled multicenter trials establishing equivalence or superiority to an approved product or to a prospectively agreed to therapeutic regimen are suggested. In these infections, an evaluable patient should be clinically evaluable only. As there would be no microbiology in these studies, the actual study results citing types of infections studied and actual effectiveness outcomes should be included as part of the **INDICATIONS AND USAGE** section of the labeling.

If effectiveness in complicated Intra-abdominal infections is established at the same dosing regimen and duration, only one adequate and well-controlled trial in this infection is suggested.

(18) *Complicated intra-abdominal infections:*

This entity should encompass intra-abdominal infections that require surgical intervention, including penetrating and blunt trauma.

One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product or to a prospectively agreed to therapeutic regimen is suggested. At least 80% of the patients should be microbiologically, as well as clinically, evaluable. Pathogens listed in the **INDICATIONS AND USAGE** section of the product labeling should be as per Section III of this document. Analysis of the data should generally confirm (by means of comparing the direction of the independent 95% confidence intervals testing) the successful outcome rates established for the overall clinically evaluable and for the clinically and microbiologically evaluable subset of patients. Likewise the analysis should establish the correlation between clinical cure and (presumed) bacterial eradication in the clinically and microbiologically evaluable subset of patients. To establish effectiveness in treating anaerobic microorganisms in this infection, the investigative agent should also establish effectiveness against anaerobes in either at least one other infection with significant anaerobic etiologies or should

establish an acceptable *in vitro* susceptibility and animal data effectiveness profile in anaerobic infections.

If there was not a reasonable mix of various intra-abdominal infections, such should be noted in the approved labeling by restricting the wording of the **INDICATIONS AND USAGE** section to just those types actually studied.

It should be assumed that an applicant successfully establishing effectiveness of an antimicrobial drug product for treatment of this infection should also establish effectiveness of the product (usually at the same dosing regimen and duration) in the treatment of gynecologic infections in order to support this one complicated intra-abdominal infections trial.

Adequate microbiologic data and specific human pharmacokinetic/-dynamic data supportive of clinical effectiveness in this disease entity are also required. Such studies would include, but not be limited to, tissue distribution studies that demonstrate the investigative agent diffuses into various intra-abdominal tissues or fluids in quantities adequate to achieve and maintain intra-abdominal tissue or fluid levels of antimicrobial compound equal to or above the expected MIC_{90}'s of the claimed pathogens for an adequate time period.

(19) *Gynecologic infections:*

[N.B.: This listing does not include sexually transmitted diseases or acute pelvic inflammatory disease.]

One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product is suggested. At least 50% of the clinically evaluable patients should also be microbiologically evaluable. Pathogens listed in the **INDICATIONS AND USAGE** section of the product labeling should be as per Section III of this document. Analysis of the data should also generally confirm (by means of comparing the direction of the independent 95% confidence intervals testing) the successful outcome rates established for the overall

clinically evaluable and for the clinically and microbiologically evaluable subset of patients. Likewise the analysis should establish the correlation between clinical cure and bacterial eradication in the clinically and microbiologically evaluable subset of patients.

If there was not a reasonable mix of various gynecologic infections, such should be noted in the approved labeling by restricting the wording of the **INDICATIONS AND USAGE** section to just those types of infections actually studied.

It should be assumed that an applicant successfully establishing effectiveness of an antimicrobial drug product for treatment of this infection should also establish effectiveness of the product (usually at the same dosing regimen and duration) in the treatment of complicated intra-abdominal infections in order to support this one gynecologic infections trial.

Adequate microbiologic data and specific human pharmacokinetic/-dynamic data supportive of putative effectiveness in this disease entity are also suggested. Such studies would include, but not be limited to, tissue distribution studies that demonstrate the investigative agent diffuses into appropriate tissues or fluids in quantities adequate to achieve and maintain tissue or fluid levels of antimicrobial compound equal to or above the expected MIC_{90}'s of the claimed pathogens for an adequate period of time.

(20) *Pelvic inflammatory disease:*

One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product is suggested. At least 50% of the clinically evaluable patients would also be microbiologically evaluable. Pathogens listed in the **INDICATIONS AND USAGE** section of the product labeling should be as per Section III of this document. Analyses of the data should also generally confirm (by means of comparing the direction of the independent 95% confidence intervals testing) the successful outcome rates established for the overall

clinically evaluable and for the clinically and microbiologically evaluable subset of patients. Likewise the analyses should establish the correlation between clinical cure and (presumed) bacterial eradication in the clinically and microbiologically evaluable subset of patients.

Adequate microbiologic data and specific human pharmacokinetic/-dynamic data supportive of putative effectiveness in this disease entity are suggested. Such studies would include, but not be limited to, tissue distribution studies that demonstrate the investigative agent diffuses into appropriate tissues or fluids in quantities adequate to achieve and maintain appropriate tissue or fluid levels of antimicrobial compound equal to or above the expected MIC_{90}'s of the claimed pathogens for an adequate time period.

(21) *Bacterial vaginosis:*

Two statistically adequate and well-controlled multicenter trials establishing equivalence or superiority to an approved product is suggested. In this infection, an evaluable patient should be expected to be clinically evaluable only. Rigorous entry criteria, including the presence of a homogeneous vaginal discharge that (a) has a pH greater than 4.5, (b) emits a "fishy" amine odor when mixed with a 10% KOH solution, and (c) contains clue cells on microscopic examination, should be employed in clinical trials. Gram's stain of vaginal discharge should be performed and results should be consistent with a diagnosis of bacterial vaginosis, including (a) markedly reduced or absent *Lactobacillus* morphology, (b) predominance of *Gardnerella* morphotype, and (c) absent or few white blood cells. Other pathogens commonly associated with vulvovaginitis, *e.g.*, *Trichomonas vaginalis*, *Chlamydia trachomatis*, *N. gonorrhoeae*, *Candida albicans*, and *Herpes simplex* virus, should be ruled out. It should also be expected that the antimicrobial drug product exhibits acceptable *in vitro* activity against the major pathogens associated with this clinical entity.

(22) *Osteomyelitis (acute and chronic):*

One open trial involving at least 50 evaluable patients using rigorous prospective clinical, radiographic, and microbiologic entry criteria and evaluability criteria (including at least a one year follow-up period) which demonstrates a successful outcome in at least 90% of the acute patients and 70% in the chronic patients is suggested. At least 40 patients should be acute and 30 chronic if the sponsor wishes to receive labeling in the **INDICATIONS AND USAGE** section of the final product labeling for both types of osteomyelitis. Without the acute/chronic mix, at least 50 patients should be evaluable, and the wording in the **INDICATIONS AND USAGE** section of the product labeling should be restricted to only that type of infection actually studied.

Pathogens listed in the **INDICATIONS AND USAGE** section of the product labeling would be determined on a case-by-case basis.

Adequate microbiologic data and specific human pharmacokinetic/-dynamic data supportive of putative effectiveness in this disease entity are also suggested. Such studies should include, but not be limited to, tissue distribution studies that demonstrate the investigative agent diffuses into bone tissues in quantities adequate to achieve and maintain bone tissue levels of antimicrobial compound equal to or above the expected MIC_{90}'s of the claimed or prevalent pathogens for an adequate time period.

(23) *Acute bacterial arthritis:*

One open trial of at least 50 evaluable patients using rigorous prospective clinical, radiographic, and microbiologic entry criteria and evaluability criteria that demonstrates a successful outcome in at least 90% of the patients is suggested.

Pathogens listed in the **INDICATIONS AND USAGE** section of the product labeling should be determined on a case-by-case basis. Gonococcal arthritis should not be an appropriate entity to study for this specific listing. Also, if

prosthetic joints are involved, the study should include at least 25 evaluable patients with artificial joints and 25 evaluable patients without artificial joints to support a specific listing for both entities. Otherwise, the listing should be restricted to either artificial or natural joints.

Adequate microbiologic data and specific human pharmacokinetic/-dynamic data supportive of putative effectiveness in this disease entity are required. Such studies would include, but not be limited to, intra-articular tissue distribution studies that demonstrate the investigative agent diffuses into intra-articular tissue in quantities adequate to achieve and maintain tissue levels equal to or above the expected MIC_{90}'s of the claimed and prevalent pathogens for an adequate time period.

(24) *Empiric therapy in febrile neutropenic patients:*

One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product or to a prospectively agreed upon therapeutic regimen is suggested. This trial should use rigorous prospective clinical, radiographic (as appropriate), and microbiologic entry criteria and evaluability criteria.

Prior to approval for this entity, the compound should also have established effectiveness in at least three of the following infections: nosocomial pneumonia, complicated intra-abdominal infections, complicated urinary tract infections, complicated skin and skin structure and soft tissue infections, acute osteomyelitis, or acute bacterial arthritis.

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1992 ADDENDUM

DOSE-RESPONSE TESTING

One of the primary goals of drug development is to develop data that permit physicians to select the appropriate starting dose of the drug and subsequently to adjust dosage to the needs of a particular patient or group of patients. Ideally such knowledge should allow the physician to increase the likelihood of achieving the intended therapeutic effect while reducing the risk of causing adverse events. One clinical development approach utilized with other drug classes to achieve this goal has been prospective, randomized, multi-dose-level clinical parallel dose-response testing. However, it has been the experience of the Division that few applicants have approached the clinical development of antimicrobial drug products from this particular perspective.

The Division would be particularly keen on exploring with applicants the feasibility of such an approach with antimicrobial drug products. We are aware such a development approach requires a minimum of three, and, ideally, more dosing regimens to begin to characterize the shape and location of the dose response curve from which clinical dosing recommendations can be deduced. Likewise we are cognizant of the fact that, for this approach to work, some group or groups in this randomized trial scheme would most likely receive an inherently sub-therapeutic dosing regimen or a regimen on which most of the individuals would likely be therapeutic failures. The ethical problems presented in such a trial design involving individuals with infections that could otherwise be treated effectively do not go unnoticed. Likewise the ethical problems of such a trial design involving children are apparent.

Nonetheless, the Division would like to explore with applicants mechanisms for addressing such concerns and the possibility of studying infections such as uncomplicated urinary tract infections, uncomplicated skin and skin structure infections, uncomplicated abdominal infections, acute bacterial exacerbations of chronic bronchitis, acute or chronic sinusitis, and, perhaps, gonorrhea (although the public health implications of failed therapy here would need special attention). Perhaps these infections would be amenable to this approach, as therapeutic failure does not necessarily means acute life- or tissue-threatening consequences for the patient. Such trials would need to be conducted under tight clinical observation so that any therapeutic failure could be quickly noted and the patient begun on appropriate alternative therapy. Outside safety monitoring committees could perhaps also be utilized to assure that a study demonstrating a significant difference between treatment arms was stopped as soon as such was known without compromising the integrity of the trial. Depending

on the number of arms selected and the therapeutic differences inherent in the different dosing regimens, the numbers of patients required in each arm could be considerably less that those required for routine active controlled trials. In any event, arguably, the data generated by such a trial could prove much more useful from a clinical and regulatory perspective than the data generated by a standard active-controlled trial trying to establish "equivalence". Economically, money spent by an applicant on each patient, would be spent garnering information on the applicants product, not re-establishing the effectiveness of a marketed competitive product.

The Division believes an applicant could use *in vitro* microbiologic susceptibility data and human pharmacokinetic/-dynamic data to select the initial dosing regimen believed to be the "optimal" dose. Dosing regimens above and several regimens below that "optimal" dose could be selected to try to demonstrate the shape of the dose-response curve. For some infections, the applicant may discover that, because of the self-limited nature of the infection, all doses are on the upper plateau of the dose-response curve. Though not as "clean" as a significant dose-response curve, such could still lead to rational choices about dosing based on the toxicity profile and therapeutic/toxic index of the product under study. In these situations, time to resolution of symptoms and eradication of bacterial infection, as appropriate, may offer an approach to product a "cleaner" dose-response curve. Either way, the Division believes such an approach should fulfill regulatory and scientific requirements for adequate and well-controlled clinical trial design.

Specifics of trial design, including masking, prospective clinical and microbiologic entry criteria, evaluability criteria, stopping criteria, and statistical analysis, should be developed prospectively in concert between the applicant and the Division. Input on trial design, execution, and analysis from outside experts, including our Advisory Committee, would be most welcome.

Once an appropriate dosing regimen is selected based on this approach, a confirmatory clinical-use trial of that dosage regimen could be conducted, as necessary. Dose-response data, from which relationships to both effectiveness and safety can be derived, along with confirmatory clinical use and safety trial data as required, could provide the requisite information for approval of a range of doses for the treatment of a specific infection that encompass an appropriate benefit-to-risk ratio. If discussion at the Advisory Committee undergirds this approach, applicants are strongly encouraged to consider this alternative approach to antimicrobial drug development.