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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.

For establishing equivalence, one method suggested by the Division is a "two-tailed 95% confidence interval around the difference in outcomes" data analysis approach. For primary clinical or microbiologic effectiveness endpoints with values greater than 90% for the better of the two agents, a confidence interval that crosses zero and remains within a lower bound delta of - 0.10 or less will usually be required to establish equivalence. For primary clinical or microbiologic effectiveness endpoints with values of 80% to 89% for the better of the two agents, a confidence interval that crosses zero and remains within a lower bound delta of -

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0.15 or less will usually be required to establish equivalence. For primary clinical or microbiologic effectiveness endpoints with values of 70% to 79% for the better of the two agents, a confidence interval that crosses zero and remains within a lower bound delta of - 0.20 or less will usually be required to establish equivalence.

Obviously, there are situations where the morbidity or mortality of the illness under evaluation will dictate that an absolute difference in success rates, which may fit the statistical definition of equivalence, will, nonetheless, be clinically unacceptable. In these situations, the clinical unacceptability would mean that effectiveness had not been established. In other special situations, modifications of these suggestions may need to be made on a case-by-case basis. However, these situations should be the "exception" rather than the "rule". It is highly encouraged that special circumstances be discussed by the applicant with the Division during the early clinical development phases of such products, and clear agreement be reached at that time regarding specific requirements or alternate statistical approaches that may be appropriate in special circumstances.

(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.