CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

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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.

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