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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

GUIDELINE FOR THE FORMAT AND CONTENT OF THE MICROBIOLOGY SECTION OF AN APPLICATION

(DOCKET NO. 85D-0245)

U.S DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
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INTRODUCTION

Antimicrobial drugs differ from other classes of drugs in that they are intended to affect microbial, rather than patient, physiology. For this reason, the technical reports of in vivo and in vitro effects on microorganisms are critical for establishing effectiveness.

Microorganisms vary widely in susceptibility to antimicrobials, and effectiveness must be demonstrated against each indicated organism by means of standardized susceptibility tests. Accurate identification of the species of microorganisms by means of microbiological and biochemical tests is a requirement.

Development of resistance in the microorganism is the greatest obstacle to the use of antimicrobials. A previously effective antimicrobial drug may become useless when resistance to the new drug develops. Studies of the mechanism of resistance and its epidemiology are critical.

Antimicrobial drugs are intended for use against infections in a variety of anatomic sites. These may constitute distinct pharmacokinetic compartments, each with different levels of the antimicrobial agent. A drug may be particularly suitable or unsuitable for use in infections at a particular site. Absorption, distribution, metabolism, and excretion

studies are important. Antimicrobial drugs are often metabolized into other compounds with altered or no antimicrobial activity. They may be inactivated by binding to serum proteins. One objective is to establish a relationship between levels of antimicrobial agents in vitro needed to inhibit growth of microorganisms and levels of active agents that can be obtained at the site of infection. The bioavailability assay system must be a "performance test," which measures the microbiologically active form by either microbiological assays or highly specific chemical or physical tests which have been shown to correlate with microbiological assays.

The bioavailability and in vitro microbiological studies, taken together, provide critical information regarding dosage, routes of administration, and effectiveness.

It may be necessary to compare the drug that is the subject of the application with closely related antimicrobials whose performance is known. Results of the new drug's microbiological studies should be consistent with prior in vitro and human therapeutic information for related compounds, and any significant differences should be documented.

Testing bacteria for their susceptibility to antimicrobial drugs requires carefully prescribed procedures which provide reproducible results. More important than the variability of results obtained with imprecise methods is the bias that can be introduced by minor changes in the in vitro

conditions of the test. For instance, minor change in medium composition, or changes in inocula of the organism being tested can result in an inaccurate indication of susceptibility.

Microbiological studies of an antimicrobial drug typically are performed in the following sequence: (1) determination of the drug's in vitro antimicrobial spectrum; (2) study of its mechanism of action; (3) study of its pharmacokinetics in order to establish serum levels attained after various doses and to choose an appropriate route of administration; (4) development of clinical laboratory susceptibility test methods and materials; (5) clinical trials with microbiological studies of actual clinical isolates; and (6) the epidemiology of resistance to the drugs.

The regulations in 21 CFR Part 314 establish general requirements for the data needed to obtain marketing approval of a new drug or antibiotic for human use. If the drug is an anti-infective agent, § 314.50(d)(4) requires that each application include a technical section on microbiology data describing: (1) the biochemical basis of the drug's action on microbial physiology; (2) the antimicrobial spectrum of the drug, including results of in vitro preclinical studies demonstrating concentrations of the drug required for effective use; (3) any known mechanisms of resistance to the drug including results of any known epidemiologic studies demonstrating prevalence of resistance factors; and (4) clinical microbiology laboratory methods needed to evaluate effective use of the drug.

Data submitted for each section specified in the guideline should be complete. Full reports of the studies, summary tables, and a summary narrative should be included for each section.

This guideline is issued under 21 CFR 10.90. An applicant may, but is not required to, rely upon the guideline in preparing the microbiology section of an application. When a different approach is chosen, the applicant is encouraged to discuss the matter in advance with FDA to prevent the expenditure of money and effort on preparing a submission that may later be determined to be unacceptable.

GUIDELINES FOR APPLICATIONS

A. Mechanism of Action

Describe the mode of action of the drug. Include the chemical structure of the drug and describe any structural or other similarities to known antimicrobial drugs.

B. Pharmacokinetics

In quantitative terms, briefly describe the pharmacokinetics for systemic dosage forms including: absorption, routes of excretion, degree of serum binding, metabolic changes to compounds of lesser or greater activity, and distribution into various pharmacokinetic compartments.

Reference the volumes and pages in the application where the full pharmacokinetic studies are filed.

C. Antimicrobial Activity

Describe the antimicrobial spectrum of the drug and provide a summary table of the major in vitro susceptibility studies, including for each study: the name and geographic locations of each investigator; the quantitative susceptibility test results for each species, preferably obtained by diffusion testing methods; the results of control organism tests; the minimal inhibitory concentration (MIC) values when available.

If the results in each clinical investigator's laboratory have not been confirmed, cultures should be exchanged with an established reference laboratory for confirmation.

Include full reports of each study with the summary.

D. Enzyme Hydrolysis Rates

When applicable, describe the stability of the drug in the presence of enzymes produced by microorganisms. Summarize each study and tabulate the results.

Include full reports of such studies.

E. Miscellaneous Studies

When applicable, summarize any miscellaneous studies such as those showing bactericidal effects, activity of major metabolites, or relationships to other known drugs.

Include full reports of such products.

F. Assessment of Resistance

Some organisms (e.g., certain fungi) are either uniformly resistant or susceptible and are not tested routinely in clinical laboratories. For all other organisms, provide a brief summary of resistance to the drug. Include a detailed discussion of the studies of resistant microorganisms and include a description of any resistance known to occur among normally susceptible species of microorganisms. A table should be included indicating: each species or type of microorganism tested; antimicrobial drugs to which each microorganism is resistant; number of microorganisms tested; and percentage of microorganisms susceptible to the drug at each level of resistance (in terms of minimal inhibitory drug concentration or zone diameters).

G. Clinical Laboratory Susceptibility Test Methods

Provide a detailed discussion of the development of a clinical laboratory susceptibility test method. Summarize each step in development of the method. Include peer laboratory studies using

the method, control organism studies, and the criteria for interpretation. Except for the interpretative criteria, the studies should be completed prior to phase III studies.

H. In Vivo Animal Protection Studies

Briefly summarize the results of any efficacy studies in experimentally infected animals.

I. In Vitro Studies Conducted During the Clinical Trials

Briefly summarize the susceptibility testing of clinical isolates obtained in the clinical investigations. Detailed culture and susceptibility test results should be included in each case report filed elsewhere in the application.

J. Conclusions

Provide a brief narrative summary of the overall results of and conclusions about the drug.

K. Published Literature

Include a bibliography and copies of all published reports of studies used by the applicant in support of the data and information contained in the microbiology section.

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