Regulatory Requirements for Clinical Evaluation of Antimicrobial Agents

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Evaluation of antimicrobial agents in governed mainly by interaction between the pharmaceutical industry and regulatory authorities. The 1977 FDA guidelines have been setting the standards for more than a decade now. Basic principles of the 1977 guidelines remain valid, however changes in the definition of end-points of response, as measured by both clinical and microbiological criteria, have occurred. The new (draft) FDA guidelines and the 1989 guidelines of the British Society of Antimicrobial Chemotherapy are more consistent with contemporary concepts of treatment. In general, the differences in the requirements are minimal with a few exceptions, namely the requirements concerning blinding and assessment of clinical efficacy by site of infection and by organism in the FDA guidelines.

The objective of all stages of therapeutic drug development is to evaluate the risk/benefit ratio of the new drug and, providing the ratio is considered acceptable, make it available commercially. In most countries a formal regulatory process governs the assessment of therapeutic drugs before they can be marketed. In many countries this extends to the conduct of trials in patients before licensing and monitoring of safety after licensing. Clinicians performing trials in humans must ensure that appropriate regulatory requirements have been fulfilled before undertaking such studies.

Four important collections of guidelines for the clinical evaluation of antibacterial/anti-infective drugs exist:
1. the old FDA guidelines of 1977 (1)
2. the new (draft) FDA guidelines of 1990 (2)
3. the guidelines prepared by the British Society for Antimicrobial Chemotherapy and published in 1989 (3)
4. the guidelines of the WHO Regional Office for Europe of 1987 (4).

The European Economic Community has not yet prepared special guidelines concerning anti-infective drugs. The USA and UK guidelines have been prepared by working groups selected by scientific societies and represent the present standards desired by the respective scientific community for the clinical evaluation of new antibacterial drugs. These standards are principally of global importance because the development of a new antibacterial drug is so expensive that only companies operating multinationaly can afford to perform such studies. This means that the quality of preclinical and clinical studies must meet standard requirements which are accepted by the most important countries with respect to marketing, i.e. the USA, Japan and the European countries.

In general, the differences in the requirements are small with some exceptions; the exceptions concerning requirements on blinding and assessment of clinical efficacy by the site of infection and by the microorganism in the FDA guidelines. In the USA microbiological efficacy is emphasized much more than in Europe. If the European Community becomes stronger in the near future, mutual discussions might lead to preparation of guidelines which are accepted worldwide.

Guidelines for the clinical evaluation of antimicrobial agents form a complex covering in vitro evaluation of antimicrobial activity, studies in animals on toxicity, pharmacokinetics and efficacy, clinical trials in man and evaluation of safety in man.

Studies Required prior to the Conduct of Clinical Trials in Man

Preliminary laboratory and animal studies are required before a new anti-infective drug is administered to humans. These studies should be designed to demonstrate that the new drug has favourable in vitro antimicrobial activity against
microorganisms that produce infection in man, has an acceptable safety profile in animals and is active in experimental infections. The pharmacologic properties of the drug need to be defined in order to anticipate the manner in which it might be administered to man.

The antimicrobial activity of a new anti-infective agent should be determined by a series of standardized in vitro studies. These include determination of the antimicrobial spectrum by measurement of the minimum inhibitory concentration (MIC), and minimum bactericidal concentration (MBC) for appropriate microorganisms. Other pertinent studies might deal with the post-antibiotic effect, emergence of resistance, mechanisms of resistance, or additive, synergistic or antagonistic effects. The activity of metabolites, if present in blood or other body fluids, should be studied by determining the MICs and MBCs. The activity of the new drug should be determined against a wide variety of strains of pathogenic microorganisms, including obligate anaerobes.

Appropriate studies must be performed in animals to assess the toxicity (acute and chronic), pharmacokinetics and general pharmacological behaviour of the drug.

In the case of a new anti-infective agent it is desirable to demonstrate therapeutic efficacy in more than one standardized model of infection against microorganism(s) found to be susceptible in in vitro studies. Efficacy should be shown in more than one animal species. Therapeutic studies in animals are less important in the case of anti-bacterial agents than in the case of antifungal agents, where such studies are essential.

Before an investigational drug can be given to a patient, the sponsor must provide the regulatory authorities with the results of laboratory and animal research. The sponsor must also provide information available on the use of the drug in other countries.

Initial Studies in Man (Phase I Studies)

The primary focus of phase I (clinical pharmacology) studies is safety. Pharmacokinetic and dose-ranging studies as well as preliminary evaluation of efficacy may also be performed.

Phase I studies of anti-infective drugs are usually conducted in normal volunteers. On some occasions, it may be desirable to evaluate patients with specific diseases. Normal volunteers are individuals who are free from abnormalities which might complicate the interpretation of the experiment or increase the risk of the toxic potential of the drug. Individuals with mild but stable chronic diseases may be included in the initial studies of an anti-infective drug.

It is usual to perform such studies in adult males aged 18 to 40 years. In general, women of childbearing potential are excluded from early phase I studies. This raises the question as to whether male volunteers are representative of the population later to be treated with the drug.

The number of subjects required is not usually stated in guidelines. The number tested for each regimen will vary according to the parameters used and the differences, if any, that require detection (variation coefficient). Usually between six and 25 volunteers will suffice.

Single dose pharmacokinetic studies should cover the full dose range intended for clinical administration to detect dose-dependent pharmacokinetics. Pharmacokinetic studies may require standardization of diet (for oral administration) and activity (for intramuscular administration), as these can affect bioavailability and the rate of absorption from the gut and muscle.

In new drug applications (with full clinical documentation) data on human pharmacokinetics and metabolism form an essential part of the registration data, with few exceptions. Whenever possible, the absolute bioavailability of all new drug products should be studied in man. Problems of bioavailability most commonly arise with products administered by the oral route (e.g., poor absorption). Fixed combinations containing at least one new chemical entity are treated as a new drug product.

In the case of suppositories and drug formulations applied topically or intravaginally, the percentage of an administered dose entering the systemic circulation should be determined for toxicological reasons. Usually the determination of the drug excreted with the urine as a measure for the amount of the drug systemically present is performed.

It is recommended that an investigator with experience in pharmacokinetics give advise on study design, sample collection, assay technique and analysis of the data. The parameters normally measured are as follows: area under the concentration-time curve, plasma/serum half-life (including dominant and terminal half-life), recovery of active drug and metabolites in urine, different clearance parameters (plasma, renal, extra-renal, total body clearance), apparent volume of distribution, maximum concentration, time to reach the maximum concentration, lag-time, and various kinetic constants used to evaluate data according to the compartment model.