Chapter I

Introduction

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Guideline statements for the clinical investigation of new psychotropic compounds are required by many of the persons who must plan, conduct, interpret, or evaluate these investigations. Most of the investigators in clinical psychopharmacology are new to the field and find themselves in the process of combining new skills and understandings with their pre-existing training in order to meet the challenge of their emerging perception of the subtleties, potentialities, and limitations of clinical investigation in this area. The development of clinical psychopharmacology has generated clinician investigators who draw upon areas of knowledge which are not brought together under any one university curriculum and which do not accrue from experience in any one of the traditional clinical or research settings.

In addition to a first hand acquaintance with psychopathology, the clinical psychopharmacologist must have a working knowledge of the various settings in which psychopathological disorders are treated. He must also have a working knowledge of psychometric conventions and of the assumptions underlying the development of the most pertinent assessment devices. Because of both the complex, multi-faceted nature of behavior disorders and the diversity of settings in which they are treated, the clinical psychopharmacologist must also recognize the multivariate nature of the phenomena which he examines and be willing to incorporate the principles of modern research design in the planning of his investigation and, when indicated, to use multivariate approaches to the analysis of his data.

When modern psychotropic substances made their appearance almost twenty years ago, the efficacy of the new pharmacotherapies was readily identified, and elaborate controls and formal procedures were unnecessary. In contrast, current evaluation of psychotropic substances is conducted in a greatly different context. The public is much more acceptant of behavior disorders than it was 20 years ago, psychotherapeutic services are available from many potential sources, and psychotropics are accepted and used in the various medical specialties. Thus, the new drug today must be established as efficacious in a society which is almost blasé about mental disorders and in the presence of many different confounding, if not obscuring, therapeutic influences and services.

The FDA has become aware of an increasing difficulty of establishing unambiguous evidence of efficacy and has published a set of regulatory statements. The most relevant statements are found in subchapter C, Drugs, Part 130 New Drugs, Subpart A, Procedural and Interpretative Regulations. Of this section, paragraph 130.12 Refusal to Approve the Application (for marketing of a new drug) contains the regulatory statements which establish the need and scope for guidelines to aid those who are interested in formulating or evaluating claims for the large scale therapeutic efficacy of psychotropic compounds.

"130.12 Refusal to approve the application.

(a) If the Commissioner determines upon the basis of the application, or upon the basis of other information before him with respect to the new drug, that:

(5) (i) Evaluated on the basis of information submitted as part of the application and any other information before the Food and Drug Administration with respect to such drug, there is lack

of substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

(ii) The following principles have been developed over a period of years and are recognized by the scientific community as the essentials of adequate and well-controlled clinical investigations. They provide the basis for the determination whether there is "substantial evidence" to support the claims of effectiveness for "new drugs" and antibiotic drugs.

(a) The plan or protocol for the study and the report of the results of the effectiveness study must include the following:

(1) A clear statement of the objectives of the study.

(2) A method of selection of the subjects that---

(i) Provides adequate assurance that they are suitable for the purposes of the study, diagnostic criteria of the condition to be treated or diagnosed, confirmatory laboratory tests where appropriate, and, in the case of prophylactic agents, evidence of susceptibility and exposure to the condition against which prophylaxis is desired.

(ii) Assigns the subjects to test groups in such a way as to minimize bias.

(iii) Assures comparability in test and control groups of pertinent variables, such as age, sex, severity, or duration of disease, and use of drugs other than the test drug.

(3) Explains the methods of observation and recording of results, including the variables measured, quantitation, assessment of any subjective response, and steps taken to minimize bias on the part of the subject and observer.

(4) Provides a comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be stated and an explanation given of the methods used to minimize bias on the part of the observers and the analysts of the data. Level and methods of "blinding," if used, are to be documented. Generally, four types of comparison are recognized:

(i) No treatment: Where objective measurements of effectiveness are available and placebo effect is negligible, comparison of the objective results in comparable groups of treated and untreated patients.

(ii) Placebo control: Comparison of the results of use of the new drug entity with an inactive preparation designed to resemble the test drug as far as possible.

(iii) Active treatment control: An effective regimen of therapy may be used for comparison, e.g., where the condition treated is such that no treatment or administration of a placebo would be contrary to the interest of the patient.

(iv) Historical control: In certain circumstances such as those involving diseases with high and predictable mortality (acute leukemia of childhood), with signs and symptoms of predictable duration or severity (fever in certain infections), or, in case of prophylaxis, where morbidity is predictable, the results of use of a new drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations with no treatment or with a regimen (therapeutic, diagnostic, prophylactic) the effectiveness of which is established.

(5) A summary of the methods of analysis and an evaluation of data derived from the study, including any appropriate statistical methods."

The foregoing reasons for refusing to approve an application clearly indicate the desiderata of evidence of clinical efficacy. They obviously do not set forth the method by which these goals may be met or illuminate the concepts which must give wisdom and pertinence to the efforts of the investigators as they apply available methods to the pursuit of these goals.

Clinical psychopharmacology is in a process of rapid metamorphosis, and the emerging standards for appropriate clinical research and concepts which rationalize them reflect the experience of the participants in the field. Guideline statements also are in process of metamorphosis, and as

long as progress in the field continues guideline statements which represent a frontier today may have become obsolete in a few years. This possibility is already viewed with alarm by some drug house research directors who fear that a characteristically long-term research program required to establish clinical efficacy and based on a currently acceptable plan may not meet future requirements which will have evolved in the few short years before the anticipated application for a new drug can be submitted to the FDA for approval.

It is important, therefore, that the guidelines offered emphasize considerations which are pertinent to most investigations and which offer the greatest promise of continuing pertinence through the nest few years.

In some instances the awareness of needed refinements and stipulations in guidelines accrues from the limitations in the research that some pharmaceutical houses have conducted in support of a new drug application. In other instances the need for modification in guidelines expresses an interest in and an awareness of a clinically significant population which was relatively unnoticed in the past, either because of a lack of a pertinent treatment or because limitations in traditional diagnostic nomenclature had allowed the population to go improperly defined, undefined, or unnoticed.

Some of the recent efforts of the FDA to generate guidelines adapted to current problems were reported in the April, 1972 issue of the Psychopharmacology Bulletin:

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"In June 1950, the Food and Drug Administration (FDA) announced that it would formulate guidelines for the clinical investigation of 29 classes of therapeutic agents. Three of these classes were antipsychotic, antidepressant, and antianxiety agents. Originally, FDA staff and representatives of the drug industry, acting through the Pharmaceutical Manufacturing Association, were to draft the guidelines. However, because of strong concerns of the scientific community expressed through the Government-Industry Liaison Committee of the American College of Neuropsychopharmacology (ACNP), the FDA sought consultation from other scientists also. Relying heavily on many of the same individuals who prepared the recent publication, "Principles and Problems in Establishing the Efficacy of Psychotropic Agents" (see Psychopharmacology Bulletin, Vol. 7, No. 3, July 1971), the FDA recently completed the guidelines.

1.21 Phase I, human pharmacology, follows completion of appropriate pharmacological and toxicological studies in lower animals. . . . . Phase I studies should provide evidence as to the safety, pharmacological effects, and dose-related side effects in normal volunteers and/or psychiatric patients based on both single dose and time-limited multiple dose studies. Evidence as to drug absorption, distribution, excretion, and metabolism is also desirable but is often technically impossible to obtain.

1.22 PhaseII studies are designed to provide reasonable evidence of clinical efficacy and usually proceed from carefully conducted open or single-blind studies in appropriate patient groups toward controlled studies designed to clearly establish efficacy in well-defined patient populations.

1.23 Phase III more extensive controlled studies are conducted to confirm and extend the findings in Phase II, aiming at more extensive evidence of efficacy under a wider range of patient groups and settings as well as more specific information about symptoms or patient types in which the drug is especially effective. Larger samples of patients are usually involved in the total work of this phase so as to obtain more information about the incidence of both common and rarer adverse effects.

[illegible].3 General Methodology: . . . Both anxiety and depression are [illegible]ve symptoms occurring in association with a variety of other [illegible] of psychopathology and both symptoms often occur in the same [illegible] in varying proportions. . . . This makes it impossible to [illegible]ear, universally applicable diagnostic criteria for use in [illegible] of the three classes of drugs for which guidelines have been [illegible]ed. Thus, it is even more necessary that individual study [illegible]ocols describe explicitly their operational criteria for selection [illegible]ion) of patients and that each patient be characterized

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to the presence and intensity of various aspects of psychopathology only observed in anxious, depressed, or schizophrenic patients. Otherwise, the results of several studies cannot be compared or pooled.

1.4 Monitoring: . . . Only good communication between investigator, sponsor, monitor, and FDA will enable the monitoring of an investigational drug through its several phases to be sensible, reasonably efficient, and conducive of the data necessary to competently evaluate both the drug's efficacy and its safety. There must be sufficient allowance for flexible exploratory studies to insure that a compound which might be effective in condition A is not restrictively consigned to evaluation only in condition B where it is ineffective.

1.6 Data Collection and Recording: Definitive, accurate, and appropriate documentation of clinical trials is an absolute necessity if valid conclusions regarding safety and efficacy are to be made by investigators, the industry, and the FDA. A perfectly designed and executed clinical trial without adequate documentation is a wasted effort. . . . In general, it is necessary to document 1) the samples studied and the nature of the population or populations to which the results of clinical trials may be generalized, 2) the procedures followed during the trial, 3) the criterion measures (for psychopathology, laboratory and physical examinations, and side effects), and 4) other variables which may have an influence on the results of the trial. To the extent that previously standardized and validated forms and measures are available and appropriate to assess the populations and drugs being evaluated, these are preferred since results are then more easily interpreted. The emphasis or extent of documentation for measures of safety versus efficacy or degree of specificity regarding efficacy will obviously and appropriately vary from Phase I to Phase II to Phase III. These will be in keeping with the objectives of the phases and the hypotheses of the individual studies.

1.7 Data Presentation: Once the individual appropriate items of information have been accurately collected during the clinical trial (documentation), it then becomes necessary to organize and present the data in a form which allows results to be viewed and conclusions to be reached. For a single clinical trial or study this is done by: 1) summarizing on an individual case record for each patient, 2) summarizing data according to the treatment groups (or other meaningful groupings) in tabular and graphic form (essentially showing frequencies), and 3) performing appropriate statistical inference tests which indicate how the observed results are (un)likely to have occurred by chance. The way in which the data may be presented cannot be detailed here but must be appropriate to the measures employed and the design employed. The use of well validated and documented statistical procedures enhances the interpretation of results, but novel (well documented) approaches which enhance the understanding of the results

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of a trial are encouraged. It should be possible in a well documented and well presented study to trace an individual patient's raw data through to its contribution in arriving at a probability statement."

The specific origins of the present statement of guidelines is best indicated by paraphrasing a proposal which was submitted to the FDA by the ACNP after a series of preliminary conferences.

"At the February 1972 meeting the FDA Neuropharmacology Advisory Committee agreed that more detailed guidelines are needed for the evaluation of new antianxiety and antidepressant agents. This agreement was a consequence of attempts by the committee to review new and supplemental drug applications for these agents. The committee members came to realize that uncertainties and inconsistencies within the academic community concerning this area of interest created confusion in both the pharmaceutical industry and the FDA. Without consensus among the clinical pharmacologists concerning the evaluation of antianxiety/antidepressant agents and without precise guidelines for the conduct and evaluation of the required clinical investigations, the pharmaceutical companies have been needlessly confused and inept in designing proper studies and in presenting their data. In addition, FDA review officers have been hampered in their evaluation of the studies submitted and have been inconsistent in their judgments. Given the number of antianxiety/antidepressant agents already marketed, the increasing utilization of these drugs, the number of new agents in various stages of development, and the growing efforts to utilize low doses of phenothiazine or phenothiazine-like agents for these indications, the proper design, conduct, and evaluation of clinical drug trials in this area assumes a major significance.

"The ACNP proposes to establish a Task Force which will develop detailed guidelines for the evaluation of antidepressant and antianxiety agents. These proposed guidelines are viewed as an extension of guidelines recently developed for the FDA, and were based in part on the principles elaborated in Principles and Problems Underlying the Efficacy of Psychotropic Agents developed under the auspices of American College of Neuropsychopharmacology and U. S. Department of Health, Education, and Welfare and published in 1971 by the U. S. Government Printing Office. Several persons who participated in the preparation of the book and in the development of the guidelines are recommended for inclusion in the proposed Task Force."

Section V of the guideline material comprises the various essays and discussions prepared by the members of the Task Force during the development of the guideline statements comprising Section III and Section IV.

Section VI will be prepared by Dr. Scoville of the FDA and will comment on the work of the present Task Force and the function of the materials presented in the foregoing sections.