AMERICAN COLLEGE OF NEUROPHARMACOLOGY

Proposal to the Food and Drug Administration

For the development of detailed guidelines for the evaluation of antianxiety and antidepressant agents.

Contract Administration

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Program Administration

Same as Contract Administration

ACNP Task Force

PROPOSAL

In the February 1972 meeting of the FDA Neuropharmacology Advisory Committee agreement was reached that more detailed guidelines are needed for the evaluation of new antianxiety and antidepressant agents. This consensus stemmed from attempts by the committee to review new or supplemental drug applications for these agents and the realization by committee members that the ambiguity within the academic community in this field has created considerable confusion in the pharmaceutical industry and the FDA. Without increased consensus among the clinical pharmacologists on the evaluation of antianxiety/antidepressant agents and without more precise guidelines the pharmaceutical companies have been confused in designing proper studies and in presenting their data. The 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 has major import.

The ACNP proposes to establish a Task Force which will subdivide into two teams during part of this project to develop detailed guidelines for the evaluation of antidepressant and antianxiety agents. These

guidelines are viewed as an extension of the guidelines recently developed for the FDA, which were based in large part on the principles elaborated in the book, "Principles and Problems in Establishing the Efficacy of Psychotropic Agents." Several of the proposed Task Force members participated in the preparation of the book and in the development of the FDA guidelines.

The ACNP proposes to complete the first draft of these guidelines by December 1972 and to submit this draft to the membership of the organization for their approval at the annual meeting on December 14. After revisions a final draft will be submitted to the Neuropharmacology Advisory Committee (NP Committee) in March 1973 for final approval and recommendation to the FDA.

Following the NP Committee Meeting in February 1972, an initial task force was established to develop this proposal. At a meeting in March 1972, Dr. Richard Wittenborn, president-elect of the ACNP was selected as Chairman of the proposed Task Force. The charge to the two teams was elaborated at this meeting and a subsequent meeting at the time of the American Psychiatric Association annual meeting on May 15, 1972.

It was agreed that the expanded guidelines for clinical evaluation of antidepressant and antianxiety agents would be comparable to a generic protocol with an explication of specific portions of the current guidelines. These expanded guidelines would give specific attention to the

following four areas:

1. Minimal standards for defining a suitable and appropriate patient population for a clinical trial and instruments which would be useful for sample selection.
2. Specific methods and instruments for the assessment of change.
3. Criteria for defining clinically meaningful change as distinct from statistically significant change.
4. The need and methods for training raters to improve reliability.

The Task Force also will give attention to (a) necessary variations due to differing conditions of treatment, (b) methods of handling data and (c) clinical interpretation of data.

It is recognized that these expanded guidelines must be reviewed annually and revised as needed. The Government-Industry Liaison Committee of the ACNP would provide a readily available and appropriate forum for such review.

Consideration must be given to the use of symptomatic volunteers, particularly in the study of antianxiety agents. Guidance is needed regarding the weight to be given this type of study compared to the clinical trial with outpatient samples. This would be important in deciding upon the use of these psychoactive agents in "normal" populations. In the selection of acceptable scales for assessment of change three or four categories will be considered: psychiatric interview for symptoms, self report and mood, social adjustment and nurses or other

professional ratings. It is recognized that scales for both patient selection and assessment of change should have population norms; the Task Force will have to conduct a literature search or consult with others to be certain that all the appropriate instruments have been considered.

If some degree of consensus can be obtained on the criteria for selection of study populations and on the assessment of change (particularly on the criteria for clinical significance), this could also serve as a model and stimulus for other areas of clinical pharmacology to do likewise.

At the May meeting Dr. Gerald Klerman and D. E. H. Uhlenhuth were selected to chair the two subdivisions of the Task Force. Dr. Kleerman's team will include Dr. Jonathan Cole, Dr. Alberto DiMasico, Dr. Douglas McNair, Dr. Martin Katz (NIMH), Dr. Allen Raskin (NIMH) and will focus on the evaluation of antidepressant agents. Dr. Uhlenhuth's team will include Dr. Karl Rickels, Dr. Seymour Fisher, Dr. Burton Goldstein, Dr. Ronald Lipman and will focus on the evaluation of antianxiety agents. Both teams will also consider studies for the drug treatment of anxiety-depression states. Each team will invite representatives from industry and/or from other professional organizations to participate with them at appropriate points in the development of the guidelines.

After each team has developed its own set of guidelines, a series of joint meetings will be held to prepare the one set of guidelines to be presented at the ACNP meeting in December 1972.

These guidelines will provide minimal standards or criteria for the evaluation of antianxiety/antidepressant agents. This should be particularly useful for companies in the design of studies and for FDA staff in their review and judgment of the studies submitted in drug applications.

An estimate of costs for this project is attached.

AMERICAN COLLEGE OF NEUROPHARMACOLOGY

Task Force for development of antianxiety/antidepressant guidelines

1 July 1972 - 31 March 1973

Draft Estimate of Costs

Personal Services	
Consultants	$16,500
Research Assistants (2 - part time)	3,000
Secretarial-Clerical (2 - part time)	3,500
Travel	
(approximately 18 meetings)	18,850
Administrative Costs	
(Telephone, Stationary, Duplicating, computer time)	4,000
Total	45,850