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Dear Dick:

I am writing with regard to the ACNP-FDA Guideline Task Force Report dated October 1, 1973. I have not responded to that mailing earlier because I anticipated a meeting with the group in Palm Springs. As that meeting did not take place, I am taking this opportunity to respond with some comments.

I have read the three major sections carefully and, in view of the Introduction, believe that this document may be used as part of the regulatory actions of the FDA. My comments are based on this eventual use. With this in mind, it seems to me that brevity is a virtue to be highly commended; and negative statements, however well intended, should be carefully expunged.

My principal criticism of the document, therefore, is that Sections 1 and 2, the Introduction and General Principles, are much too lengthy, much too specific, and contain a number of pejorative statements which may reflect the opinions of the writers but should be reviewed carefully. I believe that these sections should be reduced to no more than a few paragraphs of introduction.

I note that many comments are made in the document which ordinarily would carry with them citations. I am struck that this lack of citations leaves the reader with no recourse but to assume that the statements are opinion and not based on experimental fact. Nevertheless, there are many statements which are based on experiments and I believe that citations should be provided.

The Guideline Statements, Section 3, seem well written and quite clear. It is in these sections in particular that citations ought to be requested.

Specific examples upon which these opinions are based follow.

The Introduction (Pp. 3-5) contains such pejorative statements as, "The 'gold rush' into the manufacture...," and "This possibility is already viewed with alarm by some drug houses' research directors...." Page 7, Line 1, contains an error, I believe, that "June, 1950," should be "June, 1970." As an example of the specific nature of the Introduction which is undocumented, is the recommendation that certain rating scales be used, such as the IMPS, BPRS, and WPRS. Nowhere does it state the use to which these scales have already been put, and the reader is left with a catalogue without any clarification. Perhaps citations indicating those kinds of studies in which these scales have been used successfully would be helpful. Indeed, a simple count of the number of studies each of these scales has been used in might be useful information.

Another example is the reference to psychomotor tests (Pp. 21-22), in which it is alleged that a "Neckar Cube drawing or a reversible staircase drawing has been seen to increase in response to effective anti-depressant medication." I do not think that this statement would be substantiated by the reference, for when we tried this test we failed to discriminate imipramine from chlorpromazine. Perhaps someone else was more successful, and the citation should be given.

In Section 3, "Antianxiety Agents," I found a number of gratuitous statements. For example, on Page 9 the paragraphs on indirect verbal measures, indirect clinical measures, physiological measures, and behavioral measures each start with an assertion followed by an opinion. For example, "These measures provide estimates of affective states and other areas of function through content analysis of spoken or written verbal samples from the patient, by carefully trained technicians according to procedures specified in detail," is followed by "Although these procedures are less subject to some of the distortions encountered in direct measures, they are difficult and time consuming," The first sentence is useful; the second an opinion which, if true, should be documented. I believe the first sentence can stand in the record without the second. This is true for the other three paragraphs as well.

I hesitate to suggest an addition, but it seems to me that the section on Phase III studies (Pp. 14-17) might raise the question of the degrees of effectiveness of certain compounds

with continued use, i.e., "tolerance." I think this is an aspect of Phase III studies that is important for the protection of the user.

On Page 12, the "Criteria of drug effect" make no recommendation regarding the statistical problems involved in such an evaluation. It is here, in particular, that the Committee can be very helpful in providing materials to the academic community and the FDA regarding statistical procedures and their pitfalls. Citations would be most helpful, particularly with regard to the problems of small samples, parametric and non-parametric statistics, and multivariate computer analyses. A note as to the meaning of levels of significance may or may not be added.

Some of the comments with regard to the anti-anxiety section are equally applicable for the anti-depressant section, particularly the need for references and guidelines to statistics. In addition, the opinions of the Committee are expressed on Pages 12-14 with admirable restraint--except Items 7 and 8. I hesitate to suggest that EEG measures provide evidence of efficacy and indices of change at least equivalent to verbal sample techniques. Indeed, in the studies which I carried out with Bob Kahn and Joseph Jaffe more than 10 years ago, we found a greater sensitivity to EEG measures than linguistic measures. I have followed Lou Gottschalk's data with interest but do not believe that the distinction implicit in Items 7 and 8 can be substantiated.

On Page 17 in Phase III studies, the Committee recommends a comparison of new anti-depressants with tricyclics, MAO inhibitors, and psychomotor stimulants. It might be useful to suggest that comparison of new treatments should be made with the most effective anti-depressant therapy available, that of repeated induced convulsions (ECT or ICT).

I wish to commend the members of the Committee for a generally excellent set of guidelines.

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry

MF/cis
cc: G. Klerman, M.D.
E. Uhlenhuth, M.D.