CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18467/S13

ADMINISTRATIVE DOCUMENTS

MEMORANDUM

CENTER FOR DRUG EVALUATION AND RESEARCH

Date: August 16, 1992

From: Wiley A. Chambers, M.D.
Acting Director, HFD-160

To: E. H. Chacalos, M.D.
Medical Officer, HFD-160

Subject: Review of NDA 18-467 Hepatolite

The Medical Officer's Review dated July 9, 1992 for supplement 14 of NDA 18-467 identifies a number of conclusions which are listed below:

"1. Submission and the 87 reprints or references are inadequate to support the 3-4 new indications. Applicant has done no adequate and well-controlled studies at all."

Comments: *The regulations do not require a sponsor to perform their own studies.*

"2. Publications from the open literature as sole support for new indications are unacceptable for the following reasons:

2a. There is a strong tendency for only positive studies to get published whilst negative studies seem rarely to get published if at all and are often times not ever submitted to journals."

Comments: *A tendency for positive studies in the literature is not a sufficient reason to reject all studies.*

"2b. It is difficult if not impossible to clearly establish that a published study is adequate and well-controlled as required by law since often much pertinent information is left out."

Comments: *The characteristics of an adequate and well-controlled trial are identified in §314.126(b)(1-7). They include:*

1. *A clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results.*

2. *The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect.*

3. *The method of selection of subjects provides adequate assurance that they have the disease or condition being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis is directed.*

4. *The method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables such as age, sex, severity of disease, duration of disease, and use of drugs or therapy other than the test drug.*

5. *Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data.*

6. *The methods of assessment of subjects' response are well-defined and reliable. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response.*

7. *There is an analysis of the results of the study adequate to assess the effects of drug.*

These criteria are frequently identified in published reports.

"2c. It is impossible to determine whether there was a preselection of favorable data and an exclusion of much unfavorable data, or if mentioned at all whether the reasons for exclusion were flimsy and invalid. In brief the authenticity of statements cannot be checked and validated."

Comments: *This statement is true of all studies regardless of how they are conducted. It is not a reason to invalidate all studies.*

"2d. There is no way we could get a hold of all the individual patient report forms or the raw data. Would the investigator and his studies be available for an FDA inspection?"

Comments: *This is not a requirement of an adequate and well-controlled study.*

"2e. We would not be able to validate the studies with an FDA inspection or substantiate that protocols were actually followed and adequate safeguards imposed which rule out biases on unwarranted exclusions of data."

Comments: *This is not a requirement of an adequate and well-controlled study.*

"3. If the clinical diagnoses of acute cholecystitis is confirmed by the scan or largely based on the scan and used as the controls then the accuracies of the scan would ultimately amount to comparing scan findings with themselves and almost perfect results would be achieved which indeed has been the case in the past."

Comments: *If the method of establishing the diagnosis is biased then please provide an alternative which would not be biased.*

"4. The selections of patients for surgical intervention and therefore confirmations by surgical pathology are themselves biased in the direction of few false positives and no false negatives. (see above)"

Comments: *As listed above, if the method of establishing the diagnosis is biased then please provide an alternative which would not be biased. Any proposed new methods must be consistent with ethical medical practice.*

"5. Applicant has not identified and analyzed two adequate and well-controlled studies amongst the many publications for each of the 3-4 indications."

Comments: *The sponsor is not required to identify two studies. Any study which meets the definition of "adequate and well controlled" would be considered adequate. In addition, the sponsor is required to provide all published studies which pertain to the safety or efficacy of the product.*

The proposed recommendations included:

"1. Reject in toto this submission clearly stating that these reprints alone suffice not to support the 3-4 indications."

Comments: *The review does not support this recommendation.*

"2. Give submission to medical officer who originally approved the acute cholecystitis indication for a second opinion (Dr. Zolman)."

Comments: *It is always appropriate for the reviewing medical officer to solicit additional opinions from other reviewers within the agency. This should have been requested while the review was in progress. In addition, the proposed additional indications recommend the use of additional drug products. Consultations should be sent to the divisions which review morphine sulfate and cholecystokinin.*

"3. If the firm wishes to pursue these indications they should be asked to do their own prospective adequate and well controlled studies and with their product. ..."

Comments: *Sponsor's are not required to conduct additional studies if sufficient information is already available.*

"Moreover they should be asked to identify which studies in the publications they deem as pivotal and adequate and well controlled for each of the four indications. ..."

Reviewer's Comments: *All relevant studies should be reviewed, it is not appropriate for the sponsor to just identify two.*

Summary:

1. It is not possible to determine from the Medical Officer's Review whether the information in the application is sufficient to support or reject the supplemental application.

2. All studies should be reviewed to determine whether they are sufficient to support the proposed supplemental application.

3. The review should specifically identify the reason any study is rejected from consideration.

4. Consultation requests should be sent to the ODE Divisions with primary responsibility for the review of morphine sulfate and cholecystokinin.

/S/

Wiley A. Chambers, M.D.

cc: HFD-160/Jones
HFD-160/Lange
HFD-160/Chambers