supplement to the fourth edition. Comments received too late for consideration for the first supplement will be considered for later supplements.)

ADDRESSES: Submit written comments and supporting data and documentation to the NAS/IOM Committee on Food Chemicals Codex, National Academy of Sciences, 2101 Constitution Ave. NW., Washington, DC 20418. Copies of the new monographs and proposed revisions to current monographs may be obtained upon written request from NAS (address above) or from the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Requests for copies should specify the monographs desired by name. New and revised monographs may also be obtained through the Internet at http://www2.nas.edu/codex.

FOR FURTHER INFORMATION CONTACT:

Fatima N. Johnson, Committee on Food Chemicals Codex, Food and Nutrition Board, National Academy of Sciences, 2101 Constitution Ave. NW., Washington, DC 20418, 202–334–2580; or

Paul M. Kuznesof, Center for Food Safety and Applied Nutrition (HFS–247), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3009.

SUPPLEMENTARY INFORMATION: By contract with NAS/IOM, FDA supports the preparation of the Food Chemicals Codex, a compendium of specification monographs for substances used as food ingredients. Before any specifications are included in a Food Chemicals Codex publication, public announcement is made in the Federal Register. All interested parties are invited to comment and to make suggestions for consideration. Suggestions should be accompanied by supporting data or other documentation to facilitate and expedite review by the committee.

In the Federal Register of May 31, 1995 (60 FR 28413) , FDA last announced that the committee was considering an additional monograph and a number of monograph revisions for inclusion in the fourth edition of the Food Chemicals Codex. The fourth edition of the Food Chemicals Codex was released by the National Academy Press (NAP) in March 1996. It is now available for sale from NAP (1–800–624–6242; 202–334–3313; FAX 202–334–2451; Internet http://www.nap.edu) 2101 Constitution Ave. NW., Lockbox 285, Washington, DC 20055.

FDA now gives notice that the committee is soliciting comments and information on additional proposed new monographs and proposed changes to certain current monographs. These new monographs and changes will be published in the first supplement to the fourth edition of the Food Chemicals Codex, which is scheduled for publication in late summer, 1997. Copies of the proposed new monographs and revisions to current monographs may be obtained upon written request from NAS at the address listed above or through the internet at http://www2.nas.edu/codex.

FDA emphasizes, however, that it will not consider adopting and incorporating any of the committee's new monographs or monograph revisions into FDA regulations without ample opportunity for public comment. If FDA decides to propose the adoption of new monographs and changes that have received final approval of the committee, it will announce its intention and provide an opportunity for public comment in the Federal Register.

The committee invites comments and suggestions by all interested parties on specifications to be included in the proposed new monographs (12) and revisions of current monographs (22) that follow:

I. Proposed New Monographs

Beta-Cyclodextrin
Calcium Lignosulfonate
Dimethyl Dicarbonate
Glyceryl Palmitostearate
4-Hexylresorcinol
Sodium Lignosulfonate
Sucrose Fatty Acid Esters
Sugar Beet Fiber
Reduced Lactose Whey
Reduced Minerals Whey
Whey Protein Concentrate
Autolyzed Yeast

II. Current Monographs to Which the Committee Proposes to Make Revisions

Aspartame (delete transmittance test)
Calcium Phosphate, Dibasic (decrease lead limit)
Calcium Phosphate, Monobasic (decrease lead limit)
Calcium Phosphate, Tribasic (decrease lead limit)
Calcium Silicate (revise fluoride test)
Carbon Dioxide (combine nitric oxide and nitrogen dioxide limits, and revise test)
Dextrin (add sulfur dioxide test)
Dioctyl Sodium Sulfosuccinate (revise identification test)
Enzyme-Modified Fats (modify enzyme-modified milkfat monograph)
L-Glutamic Acid (revise identification test B)
Konjac Flour (revise identification test B)
Magnesium Phosphate, Dibasic (decrease loss on ignition limits)
Niacin (revise identification tests)
Niacinamide (revise identification tests, assay)
Pectins (revise identification tests)
Potassium Phosphate, Dibasic (decrease lead limit)
Potassium Phosphate, Monobasic (decrease lead limit)
Sodium Acid Pyrophosphate (revise assay limit)
Sodium Carboxymethylcellulose (change primary name to *Cellulose Gel*)
Sodium Tripolyphosphate (reduce lead limit)
Spice Oleoresins (add oleoresin rosemary)
Whey

Interested persons may, on or before February 18, 1997, submit to NAS written comments regarding the monographs listed in this notice. Timely submission will ensure that comments are considered for the first supplement to the Fourth Edition of the Food Chemicals Codex. Comments received after this date may not be considered for the first supplement, but will be considered for subsequent supplements. Those wishing to make comments are encouraged to submit supporting data and documentation with their comments. Two copies of any comments regarding the monographs listed in this notice are to be submitted to NAS (address above). Comments and supporting data or documentation are to be identified with the docket number found in brackets in the heading of this document and each submission should include the statement that it is in response to this Federal Register notice. NAS will forward a copy of each comment to the Dockets Management Branch (address above). Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: November 14, 1996.

Fred R. Shank,

Director, Center for Food Safety and Applied Nutrition.

[FR Doc. 96–30727 Filed 12–2–96; 8:45 am]

BILLING CODE 4160–01–F

[Docket No. 84N–0168]

Cyclospasmol®; Final Decision on Proposed Withdrawal of Approval of New Drug Application

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that the Commissioner of Food and Drugs (the Commissioner) is issuing his Final Decision on the proposal to withdraw approval of the new drug application (NDA) for the human drug product Cyclospasmol® (cyclandelate) (NDA 11–544). This drug is labeled for use in two indications: specifically, as a treatment for intermittent claudication caused by arteriosclerosis obliterans and as a treatment for cognitive dysfunction in patients suffering from senile dementia of the multiinfarct or Alzheimer's type. The Commissioner has determined that Cyclospasmol® has not been shown to be effective for such uses, and the Commissioner hereby withdraws approval for this drug. The Commissioner's Decision sustains the Initial Decision of the Administrative Law Judge (ALJ), who found that Cyclospasmol® had not been shown by sufficient evidence of adequate and well-controlled studies to be effective for its intended uses.

EFFECTIVE DATE: January 2, 1997.

ADDRESSES: The transcript of the hearing, evidence submitted, and all other documents cited in this decision may be seen in the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Drive, rm. 1–23, Rockville, MD 20857, from 9 a.m. to 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Nancy E. Pirt, Office of Health Affairs (HFY–1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–1382.

SUPPLEMENTARY INFORMATION: The purpose of this proceeding has been to determine whether FDA should withdraw approval of the NDA for the human drug product Cyclospasmol® (cyclandelate). This drug is being offered for use in two indications, specifically: (1) As a treatment for intermittent claudication caused by arteriosclerosis obliterans (AHP Exceptions at 14; AHP Post-Hearing Brief at (1), and (2) as a treatment for cognitive dysfunction in patients suffering from senile dementia of the multiinfarct or Alzheimer's type. (AHP Exceptions at 111; AHP Post-Hearing Brief at 1.)

Under § 12.130 (21 CFR 12.130), the Commissioner makes the following decision adjudicating the significant issues raised by the parties following the administrative hearing. The effect of this decision is that this drug may no longer be marketed in the United States.

Because the Commissioner's discussion of the issues is necessarily detailed, an outline of this discussion is being given for the reader's convenience:

I. The Commissioner's Final Decision

A. Background

Cyclospasmol® is a drug consisting of 200 milligrams (mg) of cyclandelate. (G–33.2 at 7.)[1] The NDA for Cyclospasmol® (NDA 11–544) was approved at a time when the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 *et. seq.*) (the act) required only proof of safety. In 1962, the act was amended by the Drug Amendments Act of 1962 (Pub. L. 87–781) to provide that drugs could no longer be approved unless both safety and efficacy had been proved.

The act, as amended, also required FDA to evaluate drugs approved before 1962 to determine whether such drugs were effective and to withdraw approval for any NDA where ''substantial evidence'' of the drug's effectiveness was lacking. (Section 505(e)(3) of the act (21 U.S.C. 355(e)(3)).) FDA's review of these pre-1962 drugs for effectiveness is known as the Drug Efficacy Study Implementation (DESI) program. The act placed the burden of coming forward with evidence of effectiveness on the manufacturer of the drug. (*Weinberger* v. *Hynson, Westcott and Dunning,* 412 U.S. 609, 617 (1973), citing 21 U.S.C. 355(e)(3).)

The Commissioner announced in a notice published in the Federal Register of July 20, 1971 (36 FR 13347), that he had evaluated a report received from the National Academy of Sciences/National Research Council (NAS/NRC) Drug Efficacy Study Group pertaining to certain peripheral vasodilators for oral use, including Cyclospasmol® Capsules and Tablets. Under the NAS/NRC report, the Commissioner classified Cyclospasmol® as possibly effective for its labeled indications, except for those claims specifically found in the notice to lack substantial evidence of effectiveness.

In a notice published in the Federal Register of December 14, 1972 (37 FR 26623), the FDA announced that it would permit Cyclospasmol® capsules and tablets, as well as other peripheral vasodilators, to remain on the market beyond the time limits prescribed for implementation of the DESI program. In a subsequent notice published in the Federal Register of July 11, 1973 (38 FR 18477), FDA required that by September 10, 1973, persons interested in conducting clinical studies to determine the effectiveness of peripheral vasodilators to submit protocols and provide the agency with notice of the date when such studies were expected to begin.

On June 20, 1978, the manufacturer of Cyclospasmol®, Ives Laboratories, a wholly owned subsidiary of American Home Products (hereinafter referred to as ''AHP''), submitted to FDA's Bureau of Drugs (currently the Center for Drug Evaluation and Research (hereinafter referred to as ''the Center''), a status report of five completed studies for peripheral vascular disease and five completed studies for cerebral vascular disease studies. These studies were reviewed by the Center and found not to provide substantial evidence of adequate and well-controlled studies indicating the effectiveness of Cyclospasmol® for its labeled indications. In two subsequent notices published in the Federal Register of May 25, 1979 (44 FR 30436; 44 FR 30443), FDA proposed to withdraw approval for Cyclospasmol®'s NDA and offered an opportunity for a hearing on the proposed withdrawal. Ives Laboratories (hereinafter referred to as ''AHP'') was also given until May 26, 1980, to complete any studies which were still in progress.

On June 25, 1979, AHP filed a request for a hearing, and this request was granted by the Commissioner on October 18, 1984 (49 FR 40972). Under

[1] The Dockets Management Branch used the letter ''G'' to refer to the Government exhibits by the participants.

21 CFR 12.45, both the Center and AHP filed notices of participation. A prehearing conference was held on January 15, 1985. Following the submission of written testimony and documentary evidence, a hearing was held before ALJ Daniel J. Davidson beginning on June 18, 1985, and ending on June 27, 1985.

Subsequently, on September 25, 1986, Judge Davidson issued his decision, in which he found that the efficacy of Cyclospasmol® had not been proved by substantial evidence of adequate and well-controlled clinical trials, and concluded that the approval of NDA 11–544 should be withdrawn. Both AHP and the Center filed exceptions to various points in Judge Davidson's decision and appealed to the Commissioner, under 21 CFR 12.125.

B. The Legal Standard

I am issuing this Final Decision under § 12.130. In taking this action, I have all the powers I would have had in making the Initial Decision. (§ 12.130(a); see also Commissioner's Decision on Polychlorinated Biphenyls (49 FR 21514 at 21519, May 22, 1984).) Further, under § 5.10 (21 CFR 5.10(a)(1)), I have been delegated the authority by the Secretary of the Department of Health and Human Services ''to determine, after giving full consideration to all of the evidence that has been submitted, including expert opinions, if the (evidence) meet(s) the regulatory criteria and show(s) effectiveness.'' (*Warner-Lambert Co.* v. *Heckler*, 787 F.2d 147, 154 (3d Cir. 1986).)

In the present case, I have fully reviewed the complete administrative record, including: (1) The transcript of the hearing that was held before the ALJ from June 18, to June 27, 1985; (2) the written testimony and documentary evidence submitted by AHP and the Center before, during, and after the Hearing; (3) the exceptions which AHP and the Center filed to the ALJ's Decision; and (4) all briefs filed by AHP and the Center pursuant to this matter. My Decision is based upon a full review of the facts and arguments that appear in the record, and my independent conclusions are based upon that review.

AHP first argues that the ALJ's decision did not meet the minimum standard required by the Administrative Procedure Act and by FDA regulations pertaining to initial decisions following formal adjudicatory proceedings. (AHP Exceptions at 3, citing 5 U.S.C. 557(c) and 21 CFR 12.120(b).) In support of its argument, AHP cites the Administrative Procedure Act for the requirement that all initial decisions shall include a statement of ''findings and conclusions, and the reasons or basis therefor, on all the material issues of fact, law, or discretion presented on the record * * *.'' (AHP Exceptions at 3, quoting 5 U.S.C. 557(c).) AHP also cites FDA regulations requiring that initial decisions contain findings of fact based upon relevant, material and reliable evidence in the record and also contain ''(a) discussion of the reasons for the findings and conclusions, including a discussion of the significant contentions made by any participant'' with ''(c)itations to the record supporting the findings and conclusions * * *.'' (AHP Exceptions at 3, quoting 21 CFR 12.120(b).)

AHP argues that the ALJ did not state how he arrived at his findings of fact. (AHP Exceptions at 8.) Ignoring the bulk of the ALJ's decision, AHP refers to the concluding section of the ALJ's decision, which is appropriately entitled ''Conclusions,'' to argue that the ALJ simply announced his findings in one sentence decrees. (AHP Exceptions at 9, citing the ALJ's Initial Decision (I.D.) at 23.)

An identical issue was addressed in the Commissioner's Decision on Lutrexin, wherein the Commissioner stated:

> (The manufacturer) implies that the findings and order are deficient because the numbered findings of fact at the end of the narrative do not contain the evidentiary details that (the manufacturer) feels would justify the judge's ruling. Those details, however, are fully set out in the judge's narrative explanation. Stating, discussing, and resolving factual issues in narrative form rather than in numbered paragraphs is a commonly used format that has been specifically recognized as fulfilling the Administrative Procedure Act requirement of a ''statement of * * * findings and conclusions * * * on all the material issues of fact, law, or discretion. 5 U.S.C. 557(c). *Gilbertville Trucking Co.* v. *United States*, 196 F. Supp. 351 (D. Mass. 1961); *State Corporation Comm.* v. *United States*, 184 F. Supp. 691 (D. Kan. 1959). ''An agency which issues opinions in narrative and expository form may continue to do so without making separate findings of fact and conclusions of law.'' Attorney General's Memorandum on the Administrative Procedure Act 86 (1947). So too may an Administrative Law Judge.

(Commissioner's Decision on Lutrexin, 41 FR 14406 at 14410, April 5, 1976.)

I have reviewed the ALJ's decision in the present matter, and I find that it comports with the previously cited requirements of the Administrative Procedure Act and FDA regulations. As in the Commissioner's decision regarding Lutrexin, I find that the ALJ fully set out the reasons for his decision in the narrative explanation section of the Initial Decision. Therefore, I find no merit in AHP's argument.

AHP further argues that the ALJ erred in concluding that at least two adequate and well-controlled studies are necessary to establish efficacy. (AHP Exceptions at 2 n.1; I.D. at 8.) As with AHP's previous objection, this issue, too, has been settled in previous Commissioner's decisions. In the Commissioner's Decision on Oral Proteolytic Enzymes (OPE), it was held that, except in certain limited cases, a minimum of two adequate and well-controlled studies are required. (Commissioner's Decision on OPE, slip op. at 23, FDA Docket No. 75N–0139 (FDA May 30, 1985), aff'd sub nom. on other grounds *Warner-Lambert Co.* v. *Heckler*, 787 F.2d 147 (3d Cir. 1986).) This requirement arises from the statutory language of the act at 21 U.S.C. 355(d), which mandates the submission of a plural number of adequate and well-controlled investigations. (Commissioner's Decision on OPE, slip op. at 23; Commissioner's Decision on Deprol (58 FR 50929 at 50936, September 29, 1993).)

FDA has permitted exceptions to the requirement for at least two adequate and well-controlled studies in limited circumstances, including: (1) When the disease is very rare and it is extremely difficult to obtain enough subjects for two studies, (2) when the disease process is expensive to study experimentally, (3) when the study conducted is very large and multicentered, and (4) when the disease is rapidly fatal and there is no alternative therapy. (Commissioner's Decision on OPE, slip op. at 24; Commissioner's Decision on Deprol, 58 FR 50929 at 50936.) AHP does not argue that any of these exceptions apply to the present case, nor do I find these exceptions to be applicable. Therefore, I find no merit in AHP's objections to the ALJ's ruling that at least two adequate and well-controlled studies are necessary to demonstrate the efficacy of Cyclospasmol®.

Finally, AHP argues that many sections of the ALJ's Decision paraphrase, or contain recitations of, portions of the post-hearing briefs filed by the Center and AHP. AHP states that, as a result, ''(t)he substantive statements made by the ALJ raise questions as to the ALJ's understanding of the issues.'' (AHP Exceptions at 12.) AHP has not cited, however, any authority which indicates that it is impermissible for an ALJ to paraphrase or recite in his decision statements from the post-hearing briefs. After reviewing the ALJ's Decision, I find that the ALJ fully set out the reasons for the conclusions he reached. Additionally, I find that AHP's claim that ''(t)he ALJ's Decision fails to

meet the requirements of the APA or of FDA's regulations'' (id.) because the ALJ paraphrased or reproduced language which was submitted in the post-hearing briefs is without merit.

Moreover, I have fully reviewed the administrative record, and, as discussed above, have reached independent conclusions from the evidence presented to the agency and to the ALJ. For the following reasons, I find that there is a lack of substantial evidence that Cyclospasmol will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling, and I therefore affirm the Initial Decision of the ALJ.

C. *The Intermittent Claudication Indication*

The labeling for Cyclospasmol previously described its first indication as being for an ''adjunctive therapy in intermittent claudication; arteriosclerosis obliterans; thrombophlebitis (to control associated vasospasm and muscular ischemia); nocturnal leg cramps; (and) Raynaud's phenomenon.'' (G–33.2 at 7; see also A–89 at 2–4; G–57 at 2–4.) However, AHP has modified this proposed indication to limit it to treatment of intermittent claudication caused by arteriosclerosis obliterans. (See AHP Post-Hearing Brief at 1; AHP Exceptions at 14.)

Peripheral vascular disease is a generic name given to diseases that affect the arteries, veins, and lymphatics in the arms and legs. (Coffman, G–58 at 1; Vyden, G–59 at 3.) The most common peripheral vascular disease is arteriosclerosis obliterans, in which a buildup of cholesterol and fatty acids accumulates in the lining of the arteries of the legs. This condition results in a narrowing of the lumens of these vessels, with consequent decreased blood flow to the muscles. (Coffman, G–58 at 2; Vyden, G–59 at 3.)

The first indication for which Cyclospasmol is labeled is as a treatment for intermittent claudication caused by arteriosclerosis obliterans. (AHP Exceptions at 14; AHP Post-Hearing Brief at 1.) Arteriosclerosis obliterans can cause intermittent claudication, which is pain, cramps, fatigue, or weakness in the legs during exercise. (Coffman, G–58 at 1–2.) A patient with intermittent claudication experiences exercise-induced pain in the calf or thigh muscles caused by a lack of oxygen in the blood being supplied to the leg muscles after walking a certain distance. (Reich, Tr. Vol. V at 17; Vyden, G–59 at 3.) Typically, pain is relieved within 1 to 3 minutes after resting. (Reich, Tr. Vol. V at 17; see also Coffman, G–58 at 2 (Dr. Coffman testified that relief should come within 5 to 10 minutes).) If relief takes longer to come, then the problem is not likely to be intermittent claudication. (Reich, Tr. Vol. V at 17.)

AHP submitted two studies—the MDS–96 (Reich) study and the five-center study—in support of the indication for intermittent claudication. Each of these studies will be discussed in turn.

1. The MDS–96 (Reich) Study

The MDS–96 study, also referred to as the Reich study, was conducted by Dr. Theobald Reich as a 12-week, crossover study of 39 patients with arterial insufficiency. The stated purpose of the study was ''(t)o determine the effect of cyclandelate (Cyclospasmol®), in comparison with a placebo, on the clinical course and certain vasomotor reflexes in patients with peripheral vascular disease.'' (G–25.2 at 163.) Each patient was in the study for 12 weeks, assigned to either 6 weeks on the test drug followed by 6 weeks on the placebo, or vice versa. (G–9.1 at 2.) Patients included in the study were to have a diagnosis of peripheral vascular disease, including one or more of the following symptoms: Intermittent claudication, rest pain, cold extremities, or peripheral cyanosis. (G–25.2 at 163.)

The evaluation of the subjects included skin temperature, skin color, pulse, distance walked prior to claudication, and severity of pain at rest. (G–25.2 at 164.) Additionally, skin temperature of the toes and foot, reactive hyperemia time, blanching time on elevation, and rubor time on dependence was also to be measured. (G–25.2 at 164.) The protocol further stated that vasomotor reflexes of the leg and calf blood flow were to be measured at the beginning of the study and at 2-week intervals during the study by means of venous occlusion plethysmography with a mercury-in-rubber strain gauge. (G–25.2 at 164.) Blood flow was to be measured at rest in the recumbent position, and after exercise on a foot pedal ergometer. (G–25.2 at 164.)

Exercise on a foot pedal ergometer was performed by a patient in a supine position, with the patient using his or her foot to repeatedly raise a weight attached to the foot ergometer pedal. (Reich, A–112 at 29; Denton, A–121 at 3–4.) Exercise on the foot pedal ergometer was to be continued until claudication or, if pain did not appear, was to be discontinued after 500 plantar flexions of the foot. (G–25.2 at 164.)

Thirty-nine patients were entered into the study. (Reich, A–112 at 13.) While all 39 patients completed the study, only 32 were found to be suitable for inclusion in the statistical analysis. (G–9.1 at 252.) Seven patients were excluded from analysis for failure to take the required dose during a 2-week interval. (G–9.1 at 252.) The results of the analysis reported a statistically significant difference in favor of Cyclospasmol® on the mean number of foot pounds of work that could be performed on the foot pedal ergometer. (Reich, A–110 at 10.)

The ALJ concluded that the Reich study was not an adequate and well-controlled investigation because: (1) The protocol failed to clearly identify the condition to be studied, (2) patient selection was marred by the lack of an objective test to determine the presence of the disease, and (3) reliance on the foot pedal ergometer to measure patient improvement in walking ability was not shown to be proper. (I.D. at 23.)

a. *Objective of the study*. The ''objective'' section of the Reich study protocol read in its entirety, ''To determine the effect of cyclandelate, in comparison with a placebo, on the clinical course and certain vasomotor reflexes by objective measurement in patients with peripheral vascular disease.'' (G–25.2 at 163.) The ALJ, after reviewing the arguments by both AHP and the Center (see I.D. at 12), ruled, ''Because the objective of the Reich study was to determine the effect of the drug on certain vasomotor reflexes, it failed to clearly identify and isolate the condition to be studied.'' (I.D. at 55.) AHP raises several issues regarding this ruling.

First, AHP argues that the ALJ erred in restricting himself to a reading of the section of the protocol entitled ''Objective'' when the ALJ determined the study's objective. (AHP Exceptions at 25.) AHP argues that under FDA regulations, AHP was not required to have a separate section in its protocol for the objective, and that it was acceptable if the objective of a study could be ascertained from a reading of the complete study protocol. (AHP Exceptions at 26.) AHP also questions what the ALJ meant by finding that the Reich protocol ''failed to clearly identify the condition to be studied.'' (AHP Exceptions at 28, quoting I.D. at 23.) AHP further asks how the ALJ concluded that the sole objective of the Reich study was to determine the effect of the drug on ''certain vasomotor reflexes.'' (AHP Exceptions at 28, quoting I.D. at 55.)

The Center counters by arguing that the vagueness of the objective for the Reich study lies in the absence of a clear statement in the protocol identifying

intermittent claudication as the focus of the study. (Center Response to AHP Exceptions at 7–11.) The Center points to the fact that intermittent claudication was only one of a number of symptoms in the patient selection criteria, and that patients were not required to have intermittent claudication in order to enter the study. (Center Response to AHP Exceptions at 8.) In sum, the Center is arguing that although AHP is now submitting the Reich study as proof of Cyclospasmol®'s efficacy in treating intermittent claudication, the Reich study's protocol was vague in identifying this as the objective of the study. I find the Center's arguments to have merit.

For a study to be considered adequate and well-controlled, FDA regulations require the study to contain ''a clear statement of the objectives of the investigation.'' (§ 314.126(b)(1) (21 CFR 314.126(b)(1)); see also Commissioner's Decision on Cothyrobal (42 FR 28602 at 28613, June 3, 1977).) The reason for requiring a clear statement of objective was aptly summarized by Dr. Marvin Schneiderman, a statistician and one of the witnesses for the Center, who testified, ''Having a vague objective means that you have a free hand to examine any kind of data and decide after the fact what data are important to report in relation to this kind of objective.'' (Schneiderman, G–65 at 5.)

Turning first to that section of the protocol entitled ''Objective,'' I note that the Reich study set out its focus in general terms as being on ''the clinical course and certain vasomotor reflexes * * * in patients with peripheral vascular disease.'' (G–25.2 at 163.) In another section of the protocol, entitled ''Number and Kind of Subjects,'' the protocol stated that it was anticipated that the underlying diagnosis for the patients would be ''atherosclerosis of the arterial vessels of the extremities.'' (G–25.2 at 163.) As described in this section, patients admitted to the study were required to have ''one or more of the following symptoms: intermittent claudication, rest pain, cold extremities, or peripheral cyanosis.'' (G–25.2 at 163.)

While AHP is correct in stating that FDA regulations do not require a section entitled ''objective'' in the protocol, nevertheless, I am not persuaded by AHP's argument because I find the objective of the Reich study to be vague even after having read the entire protocol. As is evident from reading the entire protocol, intermittent claudication was not a necessary requirement for inclusion in the study. I find that the protocol does not clearly identify intermittent claudication as the intended object of the study. A clear statement of objectives is required by the regulations. (§ 314.126(b)(1).) Not finding the objective to be clear in the protocol, I therefore find no error in the ALJ's decision on this point.

Next, AHP argues that the ALJ failed to read the ''Objective'' section of the protocol correctly. (AHP Exceptions at 27.) AHP argues that in the ALJ's opinion, the ALJ incorrectly quoted from the ''Objective'' section of the MDS–96 protocol.

As previously discussed, the ALJ wrote in his opinion that he had found that the objective of the Reich study was ''to determine the effect of cyclandelate on certain vasom(otor) reflexes in patients with peripheral vascular disease as compared to those patients on placebo.'' (I.D. at 12–13.) The verbatim statement of objective in the protocol read, ''To determine the effect of cyclandelate, in comparison with a placebo, on the clinical course and certain vasomotor reflexes by objective measurement in patients with peripheral vascular disease.'' (G–25.2 at 163.) In the ALJ's ruling, the ALJ left out the phrases ''on the clinical course'' and ''by objective measurement,'' which AHP argues contributed to the ALJ's assertedly erroneous conclusion regarding the objective. I find AHP's argument to be without merit. With or without the phrases in question, the identification of the study's objective fails because the purpose of the study is not clear from a reading of the protocol.

AHP also takes exception to the ALJ's decision on the grounds that the ALJ did not expressly state how much weight he gave to the testimony of AHP's witnesses who testified in support of the objective contained in AHP's protocol. (AHP Exceptions at 28.) AHP offers no legal authority as a basis for asserting that the ALJ must expressly assign a weight to the testimony of witnesses, and I find this argument to be without merit. The ALJ is not required to make findings on all the evidence when the findings he has made support his decision. (See *Immigration and Naturalization Serv.* v. *Bagamasbad*, 429 U.S. 24, 25 (1976); *Deep South Broadcasting Co.* v. *FCC*, 278 F.2d 264, 266 (D.C. Cir. 1960); *Community & Johnson Corp.* v. *United States*, 156 F. Supp. 440, 443 (D.N.J. 1957).) If the ALJ identified at least one conclusive deficiency in each of the studies proffered, the ALJ's decision must be upheld. (*American Cyanamid Co.* v. *FDA*, 606 F.2d 1307, 1314 & n.53 (D.C. Cir. 1979); *SmithKline Corp.* v. *FDA*, 587 F.2d 1107, 1120–21 (D.C. Cir. 1978); *Masti-Kure Products, Inc.* v. *Califano*, 587 F.2d 1099, 1104 (D.C. Cir. 1978); *Cooper Laboratories, Inc.* v. *FDA*, 501 F.2d 772, 779–81 (D.C. Cir. 1974).) Also, the ALJ is not required to accept the opinion of expert witnesses, as such testimony is only as strong as the studies on which it is based. (*Warner-Lambert Co.* v. *Heckler*, 787 F.2d 147, 154 (3d Cir. 1986); Commissioner's Decision on OPE, slip op. at 22, citing *Upjohn Co.* v. *Finch*, 422 F.2d 944 (6th Cir. 1970); Commissioner's Decision on Deprol, 58 FR 50929 at 50930.) For these reasons, I find no error in the ALJ's decision on this matter.

AHP also argues that the objective of the MDS–96 protocol is indistinguishable from another protocol which AHP identifies as an ''FDA/Industry protocol.'' (AHP Exceptions at 32–33.) AHP, citing exhibit G–6, argues that document is a protocol drafted by the pharmaceutical industry in conjunction with FDA, and that the protocol used in the MDS–96 study is comparable. (AHP Exceptions at 32–33.) The Center argues that AHP is incorrectly characterizing this document as an ''FDA/Industry protocol,'' and the Center further argues that the document is actually a protocol from another study, the MDS–176 study, performed by Dr. Reich as part of the multicenter Five-center study, the second study submitted by AHP in support of the intermittent claudication indication for Cyclospasmol®. (Center Response to AHP Exceptions at 15.) I find that the Center is correct in its argument.

I therefore conclude that the ALJ was correct in finding that the MDS–96 study did not clearly state its objectives.

b. *Test for presence of the disease.* The ALJ ruled that patient selection in the MDS–96 study was marred because the study lacked an objective test to determine the presence of intermittent claudication. (I.D. at 23, 55.) AHP argues that the ALJ did not express his views as to what he concluded were the shortcomings of evaluating patients for intermittent claudication on the basis of a personal history and a physical examination, the latter which included the palpation of pulses. (AHP Exceptions at 38.) In a related argument, AHP charges that the ALJ did not give his rationale for concluding that some type of objective instrumentation should have been used to make the diagnosis of intermittent claudication. (AHP Exceptions at 40.) I disagree with AHP's characterization of the ALJ's opinion.

It must be noted that the Reich study's protocol did not require the patients to have intermittent claudication as a condition of entering the study. Rather, under the protocol, patients included in the Reich study were to have a diagnosis of peripheral vascular disease, with one or more of the following symptoms:

Intermittent claudication, rest pain, cold extremities, or peripheral cyanosis. (G–25.2 at 163.) Intermittent claudication was mentioned only as one symptom among a number of symptoms of peripheral vascular disease which patients entering the study could have.

I further note that while ''claudication'' was marked on most patient forms as a symptom reported by the patient, intermittent claudication was not listed in the physician's diagnosis for most patients. In fact, only one patient had intermittent claudication marked as a diagnosis. (G–29.1 at 16.) Most other patients had a diagnosis of arteriosclerosis obliterans.

However, even assuming for the moment that intermittent claudication was the physician's diagnosis, my review of the patients' forms nevertheless reveals a number of instances where it is not at all clear that the patient in fact had intermittent claudication. For example, rest pain is an indication that the patient has a condition other than intermittent claudication. (See Reich, Tr. Vol. V at 17, 58 (speaking generally about intermittent claudication).) Dr. Scheiner, an AHP witness, testified that patients with rest pain were excluded from the study (Scheiner, Tr. Vol. V at 14), but this does not appear to be the case. A review of the records reveals that at least four patients had ''rest pain'' checked as a symptom on their case records (G–29.1 at 21, 34, 46, 82), and a fifth patient had a question mark entered into the box for rest pain on the case record. (G–29.1 at 65.) A sixth patient had night cramps in calves listed as a symptom (G–29.1 at 5), which is also distinct from intermittent claudication.

Additionally, another patient was diagnosed as having Raynaud's syndrome, and not intermittent claudication. (G–29.1 at 21.) Also, two patients accepted into the study, Patient Nos. 39 and 62, had ulceration marked as a symptom (G–29.1 at 42; G–29.1 at 75), which in itself can be a cause of pain and which was a basis for exclusion under the protocol. (G–25.2 at 163.) While one of these two patients with ulcerations, Patient No. 39, was excluded at the completion of the study for failure to follow the medication regimen, I note that the existence of this patient's leg ulcerations was not discussed. (G–29.1 at 4.) The other patient with reported leg ulcerations, Patient No. 62, remained in the study.

The problem with the patient histories for the Reich study is that these histories are not well documented. The patient histories do not provide sufficient information to support the diagnosis of intermittent claudication. For example, as previously discussed, although several patients complained of rest pain, these patients were included. Dr. Reich testified that these patients ''may have pains at night, and this is certainly rest pain of sorts but it is not ischemic neuritic rest pain.'' (Reich, Tr. Vol. V at 58.) However, there is nothing in the patient records which reveals how this diagnosis was made. The patient records do not elaborate on the type of rest pain which the patients experienced, and so this aspect of the study cannot be reviewed.

Regarding the necessity in a clinical study for documentation supporting a diagnosis, Dr. Lipicky, a witness for the Center, testified:

> The protocol did not specify the diagnostic aspects of the disease. Ordinarily, if one is doing a specific hypothesis testing protocol, the diagnostic criteria would be explicitly laid out. * * * * Such specificity was lacking from the protocol under question. From an overall point of view, *the inclusion of patients was entirely dependent upon the clinical judgment and the clinical opinion of the investigator. No documentation of the validity of that opinion was made available.* This is not acceptable.

(Lipicky, G–61 at 6 (emphasis added).)

I find that the reliability of the diagnosis of intermittent claudication for the patients in the Reich study was properly called into question, and that the ALJ was correct when he ruled that ''(t)he method of patient selection failed to limit entry into the study to patients with intermittent claudication. This could easily have been rectified with the use of an objective test to determine the presence of the condition under review.'' (I.D. at 55.)

Additionally, further tests were needed to confirm the diagnosis of intermittent claudication because there are other conditions which may present as intermittent claudication arising from arteriosclerosis obliterans, but in actuality be another disease or condition. Regarding this point, Dr. John Vyden, a witness for the Center, testified:

> Over half of the patients that I have seen in my professional career, which amounts to thousands of patients sent to me for investigation of intermittent claudication, do not in fact have intermittent claudication. *The commonest cause of full leg pain is, in fact, degenerative joint disease of the (lumbar) spine and sciatic nerve radiation.*

(Vyden, G–59 at 7 (emphasis added).)

Specifically with regard to the Reich study, Dr. Vyden testified:

> A major problem with this study is that there is no evidence that these people really suffered from intermittent claudication. By this I mean that they should have been tested by the technique named oscillometry to insure that, in fact, they did have narrowing of the arteries in the legs. The feeling of pulses is not an adequate substitute because it is misleading. One must actually examine by oscillometry the status of the arteries in the thighs and legs to see whether in fact there is arterial disease in the person or not.

(Vyden, G–59 at 6–7.)

AHP argues that Dr. Vyden's testimony should not be credited because oscillometry, the type of instrument which was identified by Dr. Vyden as an objective measure of intermittent claudication, is an outmoded technique. AHP's arguments do not change my ruling.

Firstly, AHP's argument fails to address the main point of Dr. Vyden's testimony, i.e., that a common cause of full leg pain is degenerative joint disease of the lumbar spine and sciatic nerve radiation. This is a possible confounding factor to the Reich study.

Secondly, Dr. Reichle, a witness for AHP who criticized oscillometry as outmoded, conceded that he, too, had used oscillometry as recently as 1 year before the Reich study was conducted. (Tr. Vol. II at 14.) While oscillometry may have been eclipsed by newer technology, such as the Doppler, I note that this does not diminish Dr. Vyden's main point, i.e., that an objective test was needed to confirm a suspected diagnosis of intermittent claudication.

FDA regulations require adequate assurance that patients have the disease or condition being studied. (§ 314.126(b)(3).) As was ruled in the Commissioner's Decision regarding the drug Cothyrobal, ''Clearly, a study * * * must be conducted in patients who have one of the labeled indications if that study is to be used a proof of effectiveness for those indications.'' (Commissioner's Decision on Cothyrobal, 42 FR 28602 at 28610.) Therefore, I find no error in the ALJ's ruling on this basis.

AHP next argues that the ALJ did not consider Dr. Reich's testimony in which he stated that he had tested the MDS–96 study patients with a Doppler instrument even though that was not required by the protocol. (AHP Exceptions at 39–40; Reich, Tr. Vol. V at 61–62.) On this point, Dr. Reich testified:

> Every patient had a Doppler study in the MDS- 96 study, every single one of them. * * * As a matter of fact, you know, in the '70s when this was being done, in the early '70s, the Doppler was just being introduced for this sort of a measurement. I was using the Doppler for at least ten years earlier than that. In the '70s they were coming out with commercial instruments. Now, blood pressure—you know, measuring ankle blood

pressure was just being introduced in clinical medicine and, as I say, the cheap Doppler instruments—the low cost Doppler instruments were being made available and I was doing this just out of curiosity to see how my numbers would stack up with other people's. You know, there was no big clinical mass of data to evaluate the significance of it but I have Doppler measurements on all of my patients, probably going back about 16—

(Question from the Center's Attorney): Did you report the Doppler measurements?

(Answer from Dr. Reich): *No, the protocol didn't call for it—not the protocol but the report sheet didn't have a thing but I have it in my own records.*

(Reich, Tr. Vol. V at 61–62 (emphasis added).)

As is clear from Dr. Reich's testimony, no written reports were submitted to the Center to show what values were obtained with the Doppler and what criteria were used to determine whether the patients had intermittent claudication. FDA regulations require that the report of a study ''provide sufficient details of study design, conduct, and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present.'' (§ 314.126(a).) I find that the mere fact that Dr. Reich obtained some Doppler measurements for patients in the study to be of no moment if those measurements were never recorded in the study results, nor submitted to the Center for review, nor were in evidence before the ALJ for his consideration. For this reason, I find no error in the ALJ's decision on this matter.

AHP further argues that the ALJ erred when he considered Dr. Travis V. Winsor's testimony regarding a previous, similar study that Dr. Winsor conducted in 1972. (AHP Exceptions at 41–43.) Specifically, Dr. Winsor testified that in 1972 he conducted a study which required, in addition to the clinical estimation of the patient's condition at baseline, an objective evaluation of the pulse volume by segmental plethysmogram obtained at one wrist and both ankles. (Winsor, Tr. Vol. III at 105.) A segmental plethysmogram was not performed in the MDS–96 study. The ALJ found that the implication was that the MDS–96 study protocol was deficient in not requiring some form of objective evaluation. (I.D. at 15.) AHP challenges this conclusion.

I find no error in the ALJ's reliance on this evidence as one of the factors in his decision. Dr. Winsor's testimony regarding this matter was in evidence (Winsor, Tr. Vol. III at 105), as was a copy of the protocol for that study. (G–25.2 at 176–180.) This evidence was available for the ALJ's review, and I find that his use of it was proper.

Based on my review of the evidence, I find that the ALJ's conclusion is supported by the evidence. The ALJ's conclusion that the MDS–96 study should have included an objective test for the presence of intermittent claudication was correct. Therefore, I find no error in the ALJ's ruling.

c. *Foot pedal ergometer as an evaluative measure.* The ALJ determined that the evidence was insufficient to show that the foot pedal ergometer was a useful measure of Cyclospasmol®'s efficacy in treating intermittent claudication. (I.D. at 18–21, 56.) AHP takes several exceptions to the ALJ's ruling on this matter. (AHP Exceptions at 48–53.) (AHP also disputes the ALJ's findings with regard to the Winsor study, which was a study submitted by AHP to show the correlation between the foot pedal ergometer measurements and treadmill measurements. I will discuss the Winsor study separately in section I.C.1.d. of this document.)

First, to reiterate the specifications of the Reich protocol regarding the foot pedal ergometer, the protocol provided that blood flow was to be measured both with the patient at rest in a recumbent position, and after the patient exercised on a foot pedal ergometer. (G–25.2 at 164.) Exercise on a foot pedal ergometer was performed by the patient in a supine position, with the patient using his or her foot to repeatedly raise a weight attached to a foot pedal. (Reich, A–112 at 29; see also Denton, A–121 at 3–4.) Exercise on the foot pedal ergometer was to be continued until claudication or, if pain did not appear, was to be discontinued after 500 plantar flexions of the foot. (G–25.2 at 164.) The protocol further stated that vasomotor reflexes of the leg and calf blood flow were to be measured at the beginning of the study and at 2-week intervals during the study by means of venous occlusion plethysmography with a mercury-in-rubber strain gauge. (G–25.2 at 164.)

In AHP's first objection on this point, AHP questions ''what the ALJ's basis'' was for ruling that the foot pedal ergometer used in the Reich study was not an accurate predictor of walking ability. (AHP Exceptions at 48.) The basis for the ALJ's decision is set forth in the Initial Decision. More important, however, is the question of whether the evidence was sufficient to support AHP's claim that the foot pedal ergometer was an accurate predictor of walking ability, and it appears that this is the issue which AHP is arguing and which I will address.

In considering this issue, I have reviewed the ALJ's decision, and I find that the ALJ adequately summarized the evidence on both sides of the issue before making his ruling. (I.D. at 18–20.) This evidence included the testimony of Drs. Vyden and Lipicky, witnesses for the Center, who both testified that the foot pedal ergometer was not shown to be an accurate predictor of walking distance. (Vyden, G–59 at 9; Lipicky, Tr. Vol. IV at 60–66.) Specifically, Dr. Vyden testified:

> A foot ergometer, in my judgment, is not a satisfactory testing device (as compared to a treadmill) on whether a drug is effective in treating intermittent claudication. Now the reason for this is that, let us say we have a patient who is 150 pounds. That patient has to walk and support 150 pounds of weight when walking. It is a total bodily exercise. Now, when they are using the ergometer they are, in fact, not measuring the leg muscle when it is supporting the entire body weight. Therefore, the amount of work being done on the ergometer does not reflect whether a patient can walk further since most of their body is not being used in this exercise.

(Vyden, G–59 at 9.)

Similarly, when Dr. Lipicky was asked to comment on the use of the foot pedal ergometer as a measure of efficacy, he testified that while the foot pedal ergometer was a measure of the ability of the muscles to perform certain work, the foot pedal ergometer measurement was different from walking in that the patient using the foot pedal ergometer was not required to support the body's weight while exercising. (Lipicky, G–61 at 9.)

Witnesses for AHP expressed the view that the foot pedal ergometer was a valid indication of efficacy for Cyclospasmol ®. (Reichle, A–110 at 4–5;[2] Winsor, A–111 at 5; Reich, A–112 at 30- 31; Porter, A–109 at 7–8; Scheiner, A–122 at 2–3; Denton, A–121 at 3–4.) However, I note that none of the AHP witnesses can be said to have refuted the basic point of the testimony of the Center's witnesses, that being that work on a foot pedal ergometer is different from walking because walking entails more of the cardiovascular system, in addition to the joints and skeletal system, and requires a person to carry the weight of his or her body while exercising. I note that the testimony given by AHP's witnesses is consistent with the testimony of the Center's witnesses on this point. For example, Dr. Winsor, an AHP witness, testified as follows:

> Ergometry and treadmill testing are different in some respects. Exercising on a

[2] The Dockets Management Branch used the letter ''A'' to refer to the exhibits of Ives Laboratories, a wholly owned subsidiary of American Home Products.

treadmill increases the cardiac output and this increased cardiac output helps the circulation of blood in the leg. Exercising on an ergometer, however, does not have a significant cardiac aspect to it. The ergometer measures the ability of a set of muscles to perform work with a near constant cardiac participation, but exercising on a treadmill involves both cardiac and peripheral circulation.

(Winsor, A–111 at 5.)

Similar testimony was given by Dr. Porter, another AHP witness, who expanded on the differences between the foot pedal ergometer and the treadmill as follows:

The correlation (between the ergometer and the treadmill) will not be one-to-one for two reasons. First, the patient's ability to perform work on a treadmill will vary somewhat from day to day depending on a variety of physical and emotional factors, such as whether the patient got a good night's sleep and whether he is angry or depressed. Second, the ergometer focuses on the capacity of two muscles, the gastrocnemius and the soleus muscles, to perform work. While the treadmill involves principally the use of the gastrocnemius and soleus muscles, it also involves the use of other muscles in the body and of the patient's cardiovascular system. These other muscles and the cardiovascular system may affect a patient's conclusion as to when he feels forced to stop walking on a treadmill.

(Porter, A–110 at 8.)

I find that the difference between the testimony of the Center's witnesses and of AHP's witnesses lies in their disparate views as to whether the limits of the focus of the foot pedal ergometer was a positive factor because it isolated the work of certain muscles, or whether the foot pedal ergometer exercise was so dissimilar from the actual outcome of interest, i.e, walking ability, that the foot pedal ergometer could not be said to be a useful measure of a patient's walking ability.

The ALJ, after reviewing the evidence presented by both parties, ruled:

(T)he suitability of the ergometer as a measurement of walking ability is called into question since a treadmill is more commonly used in studies where the relevant function to be tested is walking. Thus if the ergometer is to be used as a measurement of walking ability, some basis is needed to correlate these factors.

(I.D. at 20.)

I find the ALJ's ruling to be sound. As stated previously in this section, the evidence indicates that exercise on a foot pedal ergometer is different in many respects from walking. Therefore, I find that the evidence offered by AHP, in which witnesses described their personal experiences with ergometers and expressed their own estimations that a foot pedal ergometer was an accurate measure of walking ability, was insufficient to show that the foot pedal ergometer was a useful measure of Cyclospasmol®'s efficacy in treating intermittent claudication, absent other sufficient evidence demonstrating such a correlation. (Again I note that the Winsor study, which was offered by AHP for the purposes of correlating the foot pedal ergometer with walking on a treadmill, will be discussed in a subsequent section of this decision. (See section I.C.1.d. of this document.))

AHP further argues that the ALJ did not consider the views of three AHP witnesses who testified regarding the foot pedal ergometer, Drs. Reichle, Scheiner, and Denton, and that the ALJ mischaracterized the views of three other AHP witnesses, Drs. Porter, Winsor, and Reich. (AHP Exceptions at 49.)

Regarding the testimony of Drs. Reichle, Scheiner, and Denton, I note that the ALJ is not required to make findings on all the evidence when the findings which the ALJ has made support the ALJ's decision. (See *Immigration and Naturalization Serv.* v. *Bagamasbad,* 429 U.S. at 25; *Deep South Broadcasting Co.* v. *FCC,* 278 F.2d at 266; *Community & Johnson Corp.* v. *United States,* 156 F. Supp. at 443.) Also, as has been established in prior cases, the ALJ is not required to accept the opinion of expert witnesses. (*Warner-Lambert Co.* v. *Heckler,* 787 F.2d at 154; Commissioner's Decision on OPE, slip op. at 22; Commissioner's Decision on Deprol, 58 FR 50929 at 50930.) Such testimony is only as strong as the studies upon which it is based. (Commissioner's Decision on OPE, slip op. at 22, citing *Upjohn Co.* v. *Finch,* 422 F.2d 944 (6th Cir. 1970).)

Regarding the testimony of Drs. Porter, Winsor, and Reich, AHP argues that the ALJ mischaracterized their testimony by failing to make it clear that these witnesses testified that they had used ergometry extensively and had testified without qualification that they believed the foot pedal ergometer was a reliable predicator of walking ability. (AHP Exceptions at 50.) I have reviewed the testimony of these witnesses, and I do not find that their testimony changes my ruling regarding the foot pedal ergometer used in the Reich study. As I stated previously, the testimony of AHP's witnesses is consistent with the testimony of the Center's witnesses, in which the latter testified that the foot pedal ergometer exercise was different in several key respects from the exercise of walking. Therefore, I find that the ALJ was correct in ruling that the suitability of the foot pedal ergometer as a measurement of walking ability was not established, and that a correlation between the foot pedal ergometer and walking ability needed to be demonstrated.

AHP also takes exception to the ALJ's decision on the grounds that the ALJ did not expressly state how much weight he gave to the testimony of the Center's witnesses who testified against the foot pedal ergometer as an evaluative measure. (AHP Exceptions at 51.) AHP offers no legal authority as a basis for asserting that the ALJ must expressly assign a weight to the testimony of witnesses, and I find this argument to be without merit. As I stated in a previous paragraph, the ALJ is not required to make findings on all the evidence when the findings which have been made support the decision. (See *Immigration and Naturalization Serv.* v. *Bagamasbad,* 429 U.S. at 25; *Deep South Broadcasting Co.* v. *FCC,* 278 F.2d at 266; *Community & Johnson Corp.* v. *United States,* 156 F. Supp. at 443.)

AHP further avers that the ALJ mischaracterized the Center's position on the use of the foot pedal ergometer when the ALJ wrote, ''However, the Center believes that the ergometer measurement is not an accurate predictor of walking distance since walking is a 'total bodily exercise.' '' (I.D. at 18–19, citation omitted.) I find this objection to be without merit, since the ALJ correctly quoted the testimony of Dr. Vyden, the Center's witness. (Vyden, G–59 at 9.)

For the above reasons, I conclude that the ALJ did not err in his consideration of the testimony of AHP's experts regarding the foot pedal ergometer.

d. *The Winsor study.* The Winsor study was an additional study performed by AHP for the purpose of correlating measurements taken on a foot pedal ergometer with measurements taken on a treadmill. (Winsor, A–111 at 4–6; A–124 at 31–44.) The Winsor study did not have a written protocol. The subsequent report on the study indicated that 13 patients were tested on both a foot pedal ergometer and on a treadmill. (A–124 at 31; AHP Post-Hearing Brief at 21.) It was reported that the two tests were carried out 30 minutes apart. The report stated that patients were randomized with respect to the order of the two tests. (Winsor, A–111 at 7; A–124 at 31.)

Of the 13 patients in the Winsor study, 4 patients were brought back for a second day of tests. One patient, Patient No. 2, was reported to have had the concomitant condition of arthritis in the knee, and it was further reported that at the patient's first test, arthritis affected this patient's performance. For this reason, Dr. Winsor decided that

Patient No. 2's first test results would not be used in the statistical analysis. (A–124 at 31.) Instead, this patient's second day test results on both the ergometer and the treadmill were used in the statistical analysis. (A–124 at 31.)

The other three patients who were tested twice—Patient Nos. 8, 9, and 12—were reported to have had peripheral vascular disease in both legs. For this reason, Dr. Winsor decided to retest these three patients on a second day on both the ergometer and the treadmill, using the other leg on the ergometer. (A–124 at 31.) In the subsequent statistical analysis, results for these three patients were analyzed in three ways. Initially, the first day test results of these patients were used in the analysis. (A–124 at 32.) Next, the results were reanalyzed twice more, once using these patients' lowest reported ergometer test results, and then using these patients' highest reported ergometer test results. (A–124 at 32.) As for the treadmill results, it appears that the treadmill readings taken on the same day as the corresponding ergometer results were used. (A–124 at 32; 36.)

The post-study report stated that there was a ''significant correlation'' between the treadmill distance and ergometer foot-pounds. (A–124 at 32.) The ALJ, describing the Winsor study as hastily organized and conducted, ruled that the study was not adequate to prove that the foot pedal ergometer was a useful measure of the efficacy of Cyclospasmol® for intermittent claudication. (I.D. at 56.) AHP disputes the ALJ's conclusions. (AHP Exceptions at 53–72.)

As one of its objections, AHP asks whether the ALJ gave any weight to the Center's contention that the Winsor study should be disregarded because it was not carried out under a written protocol. (AHP Exceptions at 58–59; see Center Post-Hearing Brief at 28.) While the ALJ did not expressly make a ruling on this point (see I.D. at 19), I find that the fact that the Winsor study lacked a written protocol is a matter properly considered in evaluating and weighing the Winsor study.

The Winsor study was not a study to prove efficacy, and therefore, strictly speaking, was not bound to comply with all of the requirements for an adequate and well-controlled study, such as blinding. In this respect, the Winsor study is comparable to a safety study, which similarly does not necessarily have to satisfy every requirement of an adequate and well-controlled clinical trial. (Commissioner's Decision on Cothyrobal, 42 FR 28602 at 28614; Commissioner's Decision on Deprol, 58 FR 50929 at 50942.) Nonetheless, safety studies and, by the same reasoning, supportive studies such as the Winsor study, must be adequately designed so that scientists can draw reasonable conclusions from them. (Commissioner's Decision on Cothyrobal, 42 FR 28602 at 28614.) For this reason, all of the factors that are relevant to a determination as to whether an efficacy study is adequate and well-controlled are also relevant in determining whether other supportive studies are adequate for their purposes. (Commissioner's Decision on Deprol, 58 FR 50929 at 50942 n.5.)

One of the most basic requirements for a study is a written protocol. The regulations provide that ''the protocol for the study * * * should describe the study design precisely * * *.'' (§ 314.126 (b)(2).) As is noted in the regulations, this characteristic, along with the other characteristics set forth in this section of the regulations, has been developed over a period of years and is recognized by the scientific community as an essential of an adequate and well-controlled clinical trial. (§ 314.126(a).) The written protocol should have included a summary of the proposed or actual methods of analysis and a description of the method of selection of subjects. (§ 314.126 (b)(1) to (b)(7).) The necessity for a written protocol is clear. It is a key factor in preventing bias, whether intentional or unintentional, from influencing a study's outcome. The problems created by the absence of a written protocol can be seen in the Winsor study. For example, Dr. Winsor retested one of the patients after noting an ''abnormality'' in the patient's first test results, an abnormality said to be attributed to the subject's arthritis. Dr. Winsor also tested three patients in a different manner from the rest, by testing each leg separately on the foot pedal ergometer. (I.D. at 19.) These types of variations in testing among patients raise serious questions of bias, and the questions of bias are only exacerbated by the absence of a written protocol describing the testing protocol.

Also, because of the absence of a written protocol, the basis for patient selection was not set forth in advance of the Winsor study. While the post-study report stated that all patients in the Winsor study had intermittent claudication, the report failed to describe the basis for this diagnosis. AHP argues that it was not necessary to have a written protocol describing the selection criteria since Dr. Winsor was familiar with all of the patients' conditions because he had been the patients' doctor for quite some time. (AHP Exceptions at 65.) The regulations state that the method of selecting subjects for a study should provide adequate assurance that the subjects have the disease or condition being studied. (§ 314.126(b)(3).) I do not find the undocumented, prestudy experience of Dr. Winsor with the study patients to be sufficient evidence of the patients' conditions.

AHP next challenges the ALJ's opinion on the grounds that the ALJ did not state what he understood to be Dr. Lipicky's central criticism of the Winsor study. (AHP Exceptions at 66–67.) AHP further questions whether the ALJ understood the Winsor study, the focus of this argument being whether the ALJ should have given any weight to Dr. Lipicky's testimony in which Dr. Lipicky questioned aspects of the Winsor study. (AHP Exceptions at 70–72.)

Dr. Lipicky testified at some length regarding the Winsor study. One of the aspects of Dr. Lipicky's testimony which AHP is challenging is Dr. Lipicky's review of certain graphs drawn by Dr. Wang, an AHP witness, based on the data points from the Winsor study. (AHP Exceptions at 71; AHP Post-Hearing Brief at 22–24.) As part of its post-study report, AHP submitted several graphs plotting the results of the Winsor study. (A–124 at 38–44.) Of particular focus in the present issue are two graphs plotting treadmill feet versus ergometer foot-pounds.[3] (A–124 at 42–43.) These graphs are of interest because the post-study report stated that there was ''significant correlation between treadmill distance and ergometer ft-lb.'' (A–124 at 32.)

As described in the post-study report, ''Regression of the work performed (was) carried out using linear regression with or without forcing through the origin (i.e. assume that if the ergometer work is zero, the treadmill work should also be zero).'' (A–124 at 32.) In other words, a straight-line graph was plotted which most closely fit the data points, and another straight-line graph was plotted forcing the graph through the origin of the graph. Regarding the former of these two graphs, Dr. Lipicky had testified that the graph ''says that when a patient cannot pump an ergometer that patient can walk 200 ft, which clearly is a nonsensical result. It defies common sense that that would be the case.'' (Lipicky, Tr. Vol. IV at 64.) Regarding the graph forced through the origin, Dr. Lipicky testified, ''most of the data points, (especially) the early ones, are well above that line and a couple of

[3] The other graphs plotted ergometer foot-pounds versus treadmill foot-pounds. (A–124 at 38–41.) There was also a scatter diagram plotting treadmill foot-pounds/minute versus ergometer foot-pounds/minute. (A–124 at 14.)

data points later on lie well below that line—to my eye, not a very good fit at all.'' (Lipicky, Tr. Vol. IV at 64.)

Using the same data points, Dr. Lipicky drew and offered several other possible graphs. (G–67 at 2–4.) Dr. Lipicky cited one of his graphs in particular as fitting the data points best of all. In this graph, the line began at slope, the slope then decreased and at one point flattened out for the later data points. (G–67 at 2–3.)

AHP criticizes Dr. Lipicky's testimony on several grounds. First, AHP argues that Dr. Lipicky is essentially testifying that the Winsor study was deficient because it did not yield a mathematical formula that described the relationship between the foot pedal ergometer measure and the treadmill measure. (AHP Post-Hearing Brief at 22.) AHP argues that Dr. Lipicky's testimony on this point is faulty because he did not disclose why such a mathematical formula would be useful. I disagree with AHP's position.

Dr. Lipicky testified that the issue raised by the results of the Winsor study was what is ''the explicit relationship between the two variables. Given a specific ergometer value, whatever its units, what can one predict would be the walking distance on (the) treadmill in the absence of having measured it?'' (Lipicky, Tr. Vol. IV at 124.) In considering this evidence, it must be kept in mind that the Winsor study was undertaken to supplement the MDS–96 study, since the results of the MDS–96 study were expressed in terms of foot pedal ergometer units, despite the fact that other evidence indicated that the treadmill is more commonly used. For this reason, I find that Dr. Lipicky was correct in noting that it was necessary for the Winsor study to demonstrate the value of the foot pedal ergometer to predict walking distance on a treadmill.

AHP further argues that Dr. Lipicky's testimony should not be credited because the graphs which he submitted, in particular the graph described in the above discussion as flattening-out, reflects only Dr. Lipicky's hypothesis. (AHP Post-Hearing Brief at 22–23.) AHP argues that Dr. Lipicky's testimony fails because Dr. Lipicky offered no physiological or other explanation to explain why his graph of the data points shows that a person might be able to increase his or her performance on the foot pedal ergometer without correspondingly increasing his or her performance on the treadmill. (AHP Post-Hearing Brief at 22–24.)

I find that Dr. Lipicky's testimony indicates that the data may be interpreted in more than one way. Indeed, Dr. Lipicky stated in his testimony that his graphs represented ''an alternate way of looking at the same data and that there's no way from that data to choose between those two interpretations.'' (Lipicky, Tr. Vol. IV at 65; see I.D. at 20.) As Dr. Lipicky noted, while there may be some relationship between the foot pedal ergometer and the treadmill, the crux of the matter at issue lies in defining the relationship between the two. (Lipicky, Tr. Vol. IV at 65, 124.)

Dr. Lipicky offered testimony indicating that the graphs submitted by AHP either did not fit the data results or suggested a result that did not make sense. The graphs submitted by Dr. Lipicky reflected a better fit with the data. Why the Winsor study's data came out as they did was not an issue which Dr. Lipicky was required to explain. While Dr. Lipicky, as a witness for the Center, suggested several possible other graphs, the Center does not have the burden of proof. AHP has the burden of proving the nature of the relationship, if any, between the results on the treadmill and the results on the foot pedal ergometer. The correlation between the two measures needed to be defined, and the burden of proof lay with AHP as proponent for approval of the efficacy of Cyclospasmol®. (*Weinberger* v. *Hynson, Westcott & Dunning*, 412 U.S. 609, 617 (1973), citing 21 U.S.C. 355(e)(3).) Therefore, I find no merit in AHP's argument.

AHP also contends that the ALJ devoted only two sentences of his opinion to the Winsor study. (AHP Exceptions at 71.) As I previously discussed, the ALJ gave adequate reasons why he did not credit the Winsor study. Also, the ALJ devoted several pages of his opinion to a review of the Winsor study. (I.D. at 19–21, 23, 56.) I find that the evidence supports a finding that the ALJ did understand the Winsor study, and I affirm his decision with respect to it.

AHP further argues that the ALJ did not indicate how much weight he gave to the following arguments of the Center: (1) That the Winsor study should be disregarded because it was not carried out pursuant to a written protocol, (2) that the Winsor study should be disregarded because Dr. Winsor undertook the study after he had agreed to be a witness for AHP, (3) that Dr. Winsor retested 4 of the patients, and (4) that although it was reported that the patients in the study had intermittent claudication, there was no objective evidence that the 13 patients in the Winsor study had intermittent claudication. (AHP Exceptions at 58–66; see Center Post-Hearing Brief at 27–30.) There is no rule in law or regulations which requires the ALJ to explicitly assign a weight to the evidence which the ALJ considers. As I previously stated, the ALJ is not required to make findings on all the evidence when the findings which have been made by the ALJ support the decision. (See *Immigration and Naturalization Serv.* v. *Bagamasbad*, 429 U.S. at 25; *Deep South Broadcasting Co.* v. *FCC*, 278 F.2d at 266; *Community & Johnson Corp.* v. *United States*, 156 F. Supp. at 443.)

AHP further questions the ALJ's conclusions that the suitability of the foot pedal ergometer as a measure of walking ability was called into question because the treadmill is more commonly used, and that if the foot pedal ergometer was to be used, some basis was needed to correlate these two measures. (AHP Exceptions at 68–69.) I addressed this issue in section I.C.1.c. of this document, wherein I ruled that it was necessary to correlate the measures taken on the treadmill with measures taken on the foot pedal ergometer because the evidence indicated that the foot pedal ergometer exercise was different in several key respects from the exercise of walking on a treadmill.

In my judgment, the ALJ was correct in concluding that AHP did not prove that the foot pedal ergometer was useful in demonstrating Cyclospasmol's® efficacy in treating intermittent claudication. I find sufficient justification to support the ALJ's rejection of the Winsor study.

e. *Adequacy of the MDS–96 (Reich) study*. In sum, I find that the Reich study was not adequate and well-controlled. In making this determination, I have considered the aggregate effect of the protocol violations. As I previously discussed: (1) The objective of the study was vague and the protocol was not clear in identifying intermittent claudication as the focus; (2) the reliability of the diagnosis of intermittent claudication was properly called into question and an objective test for intermittent claudication should have been included in the study; and (3) the evidence did not establish that the foot pedal ergometer was a suitable measure of walking ability.

Regarding the Winsor study, I find that the ALJ properly concluded that AHP did not prove that the foot pedal ergometer was useful in demonstrating Cyclospasmol's® efficacy in treating intermittent claudication. As detailed above: (1) The Winsor study did not have a written protocol; (2) not all patients in the study were tested in the same manner; (3) the basis for patient selection was not set forth in advance of the study; and (4) the study did not

demonstrate the value of the foot pedal ergometer in predicting walking distance on the treadmill.

2. The Five-Center Study

The five-center study was, as its name indicates, a multicenter study conducted at five sites. The study's stated objective was to ''evaluate the efficacy of Cyclospasmol® versus placebo, as an adjunct to generally accepted therapy, for the amelioration of symptoms (including intermittent claudication) in the lower extremities of patients with chronic occlusive arterial disease (atherosclerosis) who have no manifestations of severe (advanced) disease * * *.'' (G–6 at 3.) Severe disease was defined in the protocol as:

> severe (advanced) chronic occlusive arterial disease as manifested by major trophic changes (e.g., atrophic shiny skin, major nail changes and/or muscle atrophy), ischemic rest pain, ulceration and/or gangrene, marked pallor or rubor with the extremity in the horizontal position. Also those in whom prior arteriography has demonstrated combined aortoiliac and femoropopliteal disease; or popliteal disease involving the trifurcation; or distal arterial (tibial) disease or arteriolar disease such as may be associated with diabetes mellitus.

(G–6 at 5–6.)

The five-center study employed a crossover design. (G–9.1 at 85.) Initially, a 6 to 8 week, single-blinded placebo washout period was used. (G–9.1 at 85.) Patients were then randomly assigned to one of two groups in a double-blinded manner. Group I received a placebo for 12 weeks and then Cyclospasmol® for 12 weeks, with no intervening washout period. Group II underwent the reverse sequence, also with no intervening washout period. (G–9.1 at 85.) One hundred and sixteen patients were enrolled in the study, with 91 completing it. (G–9.1 at 85.) Of those who completed the study, 65 patients were adjudged to be ''acceptable,'' for analysis, i.e., capable of being evaluated. (G–9.1 at 85.)

Statistical analysis of the pooled data from the five centers indicated no statistically significant difference between Cyclospasmol® and placebo. (G–9.1 at 86, 93, 142–46; AHP Exceptions at 80.) The pooled data were then reanalyzed using only the first half of the study (the initial 12 weeks) and the inclusion/exclusion decisions for each patient were reconsidered. (A–108 at 1–11.) Using one-tailed tests of significance, the reanalysis indicated a statistically significant, drug-over-placebo effect. (A–108 at 1–11; AHP Exceptions at 81.)

The ALJ ruled that the five-center study could not be considered adequate and well-controlled, in part because the reanalysis of the initial 12 weeks of the five-center study was performed only after the failure to find a positive drug effect in the initial analysis. (I.D. at 26, 30–31.) AHP has challenged the ALJ's findings on the following matters: (1) The weight to be accorded the reanalysis of data, (2) the inclusion and exclusion of patients, (3) the calculation of treadmill distances, and (4) the inconsistency of results among the five centers in the reanalysis. I address AHP's exceptions below.

a. *Reanalysis of the five-center study.* AHP takes exception to the ALJ's conclusion that no weight should be given to the reanalysis of the data from the five-center study. (AHP Exceptions at 78–88, citing I.D. at 30, 56.) As previously discussed, the five-center study was conducted using a crossover design. After statistical analysis of the study failed to demonstrate a statistically significant difference between drug and placebo (I.D. at 26; G–9.1 at 86), the data were reanalyzed as if the study had been conducted with a parallel design. (A–108 at 1–11.) To do this, the data from the second half of the study—the final 12 weeks—were dropped. (Lipicky, Tr. Vol. IV at 68.) Also, the decisions on inclusions and exclusions of all patients were reexamined. (Issues pertaining to the reexamination of exclusions will be discussed in section I.C.2.b. of this document.) AHP's reasons for electing to perform this type of reanalysis were not communicated to the Center, either orally or in writing. (Lipicky, Tr. Vol. IV at 68.) In the reanalysis, a statistically significant improvement was reported in the Cyclospasmol®-treated group over the placebo group. (A–108 at 3.)

In support of its decision to reanalyze the first 12 weeks of the data as a parallel study, AHP cites to the testimony of Dr. Nathan Mantel, a witness for AHP who was critical of crossover protocols in general. (Mantel, A–127 at 10–12.) In relevant part, Dr. Mantel testified:

> When AHP turned to me for advice with respect to the proper analysis of the five-center study, I voiced my own long-standing criticism of use of a crossover design, albeit this is a design greatly emphasized in standard statistical texts. Biological and medical realities just do not correspond to the simple mathematical model underlying use of the crossover. When a patient receives treatment A, followed in due course by treatment B, the final response observed is not a response to treatment B. Rather, it is a response to the sequence of treatments used, including all lapses of time. Another crossover design example, one not even involving any initial values, is where half the patients get treated on the right side with A, on the left side with B, these being switched for the remaining half of patients. A crossover analysis could be invalid if treatment on one side influenced the response on the other side.

(A–127 at 11.)

AHP further cites the testimony of Dr. Lipicky, a witness for the Center, who testified that crossover studies are often analyzed as parallel studies for the first half of the data, and that he himself had probably spoken in favor of such analyses. (AHP Exceptions at 81, citing Lipicky, Tr. Vol. IV at 92.) It is to be noted, however, that Dr. Lipicky clarified his position in this regard by adding that, while such reanalyses are a ''common practice,'' in his opinion it was very often not an appropriate exercise. (Lipicky, Tr. Vol. IV at 94.) On this point, Dr. Lipicky testified:

> Well, I guess if one is talking about appropriateness, I think that reanalyses are not appropriate very often—commonly done but not appropriate very often; sometimes useful if, indeed, there are particular things that one is trying to get to and if there is an analysis that one can think of doing that, indeed, was not thought of ahead of time and where the major intent of the trial is not singularly or singly dependent upon that analysis.

(Lipicky, Tr. Vol. IV at 94.)

Other testimony on this issue was offered by Dr. Schneiderman, a statistician and witness for the Center, who gave the following testimony:

> And, thus, in a cross-over experiment if a phase or a sequence effect can be shown—a carry-over effect—then it would be inappropriate, I think, to continue the analysis as if there were no carry-over effect because that's one of the conditions, essentially, from which you create a cross-over design. *The original analysis of these data did not show such a * * * carry-over effect and, therefore, quite obviously it was appropriate to have designed the experiment as it was designed and to continue to analyze it as the indication had been for the analysis.* I see no justification really for discarding the cross-over design, which people who knew the biology had designed, and, thus, discarding half the data.

(Schneiderman, Tr. Vol. VII at 5–6 (emphasis added).)

In addressing AHP's argument, I first note that it is a requirement of an adequate and well-controlled study that there be an analysis of the results of the study adequate to assess the effects of the drug. (§ 314.126(b)(7).) Additionally, because faulty analysis can introduce bias, adequate measures must be taken to minimize bias on the part of the analysts of the data. (§ 314.126(b)(5).) Also, the study's protocol should describe the study design precisely, including information on the duration of treatment periods, whether

treatments are parallel, sequential, or crossover, and whether the sample size is predetermined or based upon some interim analysis. (§ 314.126(b)(2).) One of the most important reasons for requiring protocol decisions to be made in advance of the clinical investigation is to avoid bias.

As AHP acknowledged in its Post-Hearing Brief, FDA regulations provide that a sponsor may use an analytical method that is not set out in the protocol, but the sponsor should inform FDA as to how it selected that analytical method. (AHP Post-Hearing Brief at 39; § 314.126(b)(1).) AHP did not inform the Center of the reasons for switching from analyzing the entire data as a crossover study to instead analyzing the first half of the study as a parallel study. (Lipicky, Tr. Vol. IV at 68.) The testimony of Dr. Mantel fails as an explanation because Dr. Mantel's reason for objecting to crossover studies—specifically, the failure of patients to return to baseline at the time of crossover (Mantel, A–127 at 10–12)—was not identified as a problem with the five-center study. (See Schneiderman, Tr. Vol. VII at 5–6.) Moreover, AHP's reliance upon Dr. Mantel's broad indictment of all crossover studies is difficult to accept, in view of the fact that the second study submitted by AHP in support of the indication of intermittent claudication for Cyclospasmol®, the MDS–96 study, was a crossover study and was analyzed as such by AHP. (See section I.C.1. of this document.)

The reanalysis of the five-center study was more than a mere mathematical check. It was a reconsideration of the protocol after the clinical trial had been completed. While circumstances can arise that justify analyzing only the first half of a crossover study as a parallel study, such as when a sequence effect occurs, a decision to throw out half of the data cannot be made arbitrarily if a study is to be considered adequate and well-controlled. Where, as in the five-center study, a ''reanalysis'' means that: (1) Initially no statistically significant difference between the drug and the placebo was found, (2) the inclusion and exclusion decisions for each patient were reconsidered, (3) the second half of the crossover trial was dropped, and (4) the first half of the crossover data was reviewed as if the trial had been a parallel trial, then certainly the sponsor should expect that an explanation for these changes would be in order.

AHP further challenges the ALJ's decision on the grounds that the ALJ purportedly took the position that he would not consider a parallel analysis of any study that is designed to gather data on a crossover basis. (AHP Exceptions at 82–83, citing I.D. at 25.) The ALJ did not make such a broad pronouncement. The ALJ rejected AHP's reanalysis because AHP did not provide a ''good reason'' as to why AHP analyzed only the first half of the data collected. (I.D. at 30.)

AHP also argues that the ALJ ignored evidence indicating that the 1985 reanalysis was precisely the type of analysis that the Center itself would have required to establish efficacy. (AHP Exceptions at 84.) By this argument, AHP is apparently referring to the testimony of Dr. Lipicky, a Center witness, who testified that crossover studies are often analyzed as parallel studies, and that he himself had probably spoken in favor of such a procedure. (Lipicky, Tr. Vol. IV at 92.) However, as I noted above, Dr. Lipicky explained his position by adding that while such reanalyses are commonly done in clinical studies, they are very often not appropriate. I find AHP's interpretation of Dr. Lipicky's testimony as a requirement for analysis of all crossover studies as if these were parallel studies to be incorrect. Moreover, I note that another witness for the Center, Dr. Schneiderman, was clearly critical of AHP's reanalysis of this crossover study as a parallel study. (Schneiderman, Tr. Vol. VII at 5–6.) In any event, regardless of any statements by Dr. Lipicky, or any other witnesses for either party, the Commissioner is not required to accept the testimony of expert witnesses but is to make his or her own decision regarding efficacy. (*Warner-Lambert Co.* v. *Heckler,* 787 F.2d at 154; Commissioner's Decision on OPE, slip op. at 22; Commissioner's Decision on Deprol, 58 FR 50929 at 50930.)

AHP additionally argues that the ALJ erred in his understanding of Dr. Schneiderman's testimony. (AHP Exceptions at 84.) AHP alleges that Dr. Schneiderman did not indicate that the parallel analysis was inappropriate, and that the ALJ erred in using Dr. Schneiderman's testimony as part of his rationale for rejecting the reanalysis. I have reviewed Dr. Schneiderman's testimony, and I find that the ALJ was correct in his interpretation. Dr. Schneiderman's testimony could not be more clear on this point, ''I see no justification really for discarding the cross-over design, which people who knew the biology had designed, and, thus, discarding half the data.'' (Schneiderman, Tr. Vol. VII at 5–6.)

AHP further argues that the ALJ should have required the Center to support its criticism of the reanalysis by preparing its own crossover analysis using the values submitted by AHP in its reanalysis. (AHP Exceptions at 86–87.) There is no basis in law for AHP's argument. The burden of proving safety and efficacy lies with the applicant. (*Hynson,* 412 U.S. at 617; 21 U.S.C. 355(e); 21 CFR 12.87(e).) The Center, therefore, was not obligated to perform its own crossover analysis, particularly using the results as they were calculated in the reanalysis in this case.

Notwithstanding my ruling on this issue, I nevertheless note that the Center did perform an analysis using the original crossover data; in this analysis, the Center followed the protocol for the five-center study by using maximum, rather than average, treadmill measurements. (G–71 at 1–4; Lipicky, Tr. Vol. V at 74–79.) However, this exhibit was stricken on motion of AHP. (Tr. Vol. V at 6.) Additionally, I note that, as Dr. Lipicky testified, in order for the Center to perform an independent reanalysis, the Center would have to have access to the raw data, i.e., the case report forms, and these were not submitted to FDA. (Lipicky, G–61 at 19.)

AHP further contends that the ALJ erroneously concluded that AHP had given no reason for submitting a parallel study. (AHP Exceptions at 87.) AHP is misstating the ALJ's decision. The ALJ held that AHP did not provide a *sufficient* reason for its submission of a parallel analysis for a crossover study. (I.D. at 30.) I uphold the ALJ's conclusion.

AHP argues that the ALJ failed to consider the views of AHP's expert witnesses regarding peripheral vascular disease. (AHP Exceptions at 87–88.) AHP avers that its witnesses testified that the reanalysis of the five-center study demonstrated a treatment effect. (AHP Exceptions at 88, citing: Porter, A–109 at 22–25; Reichle, A–110 at 18–20; Winsor at A–111 at 15–16; Reich, A–112 at 49–51.) As is apparent from the ALJ's Initial Decision, the ALJ did consider AHP's evidence, but the ALJ was not persuaded by it.

In any case, as I stated previously (see section I.C.1.c. of this document), the Commissioner is not bound by the conclusions of expert witnesses. (*Warner-Lambert Co.* v. *Heckler,* 787 F.2d at 154; Commissioner's Decision on OPE, slip op. at 22; Commissioner's Decision on Deprol, 58 FR 50929 at 50930.) Expert opinion testimony is only as strong as the studies on which it is based. (Commissioner's Decision on OPE, slip op. at 22, citing *Upjohn* v. *Finch,* 422 F.2d 944, 955 (1970).)

Having reviewed all of the evidence, I am in agreement with the ALJ's conclusion that AHP did not provide a sufficient reason showing that it was proper to analyze only the first 12 weeks

of this 24 week study. In a study such as the five-center study, where major changes to the protocol were made but the decision to make those changes was arrived at only after the data had been analyzed without showing a statistically significant drug effect, it is not possible in the subsequent reanalysis to ''distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.'' (§ 314.126(a)) For the above reasons, I therefore hold that AHP's reanalysis of the five-center study can not be relied upon as substantial evidence of efficacy from an adequate and well-controlled clinical trial.

b. *Inclusion/exclusion decisions.* As part of AHP's reanalysis of the five-center study, Dr. Clarence Denton and Dr. Stuart L. Scheiner reviewed the case reports for all of the 92 patients who completed the first 12 weeks of the five-center study and reconsidered the inclusion/exclusion decisions pertaining to each patient. (AHP Exceptions at 89; A–108 at 2.) In their reanalysis, Drs. Denton and Scheiner were said to have been blinded to such factors as whether a particular patient had been included in the initial analysis, whether a patient had been on drug or placebo, and as to a patient's outcome at the conclusion of the five-center study. (AHP Exceptions at 89; AHP Post-Hearing Brief at 42; Denton, Tr. Vol. VII at 10–11, 47.) However, it is not clear that Drs. Denton and Scheiner were also blinded regarding the center to which a patient had been assigned during the trial.

A total of 23 changes in the selection of patients for analysis were made between the original analysis and the reanalysis. These changes included 11 new inclusions and 11 new exclusions of patients, and one reclassification of a patient who originally had been listed as a placebo patient but upon discovery of a coding error was reclassified as a Cyclospasmol® patient. (I.D. at 27; A–108 at 11.) The ALJ determined that these decisions were made post hoc and ruled that this was another factor for which the reliability of the reanalysis can be called into question. (I.D. at 56.) AHP disputes the ALJ's conclusions. (AHP Exceptions at 88–98.)

The first objection raised by AHP on this point is to ask ''why'' the ALJ questioned the reliability of the 1985 five-center study. (AHP Exceptions at 90–91.) This is a very broad and not well-defined issue, but it appears that its gist is the argument that the ALJ did not adequately explain the basis for his ruling on this issue. (AHP Exceptions at 91.) I do not find this argument to be persuasive. The ALJ devoted several pages of his decision to a discussion of the reanalysis. (See I.D. at 26–31, 56.) In relevant part, the ALJ noted: (1) That the five-center study was originally designed, conducted, and analyzed with a crossover design, (2) that when the original analysis failed to find a statistically significant drug effect, AHP sought to rely upon the results from only one of the five centers, (3) that AHP subsequently chose instead to reanalyze the first 12 weeks of the study as if it had been a parallel study, (4) that in the reanalysis, the inclusion and exclusion decisions for every patient were reconsidered and 23 changes were made in patient selection, and (5) calculation of the treadmill baseline data was not done in strict accordance with the protocol, i.e., average values were used instead of the highest value. (I.D. at 56.) As I ruled at the outset of this Final Decision, I find that the ALJ's Initial Decision comports with the requirements of the Administrative Procedure Act and FDA regulations, and that the ALJ fully set out the reasons for his decision in the narrative explanation section of his decision. (See section I.B. of this document.) Therefore, I find no merit in AHP's argument.

AHP also challenges the ALJ's statement that the reanalysis should be given a ''higher degree of scrutiny'' than the initial analysis. (AHP Exceptions at 92–93.) As the ALJ stated in his opinion, ''(A) higher degree of scrutiny is warranted here not because the reanalysis was termed as such but because the reanalysis was undertaken in response to the initial lack of a statistically significant difference between the drug and placebo.'' (I.D. at 26.) The ALJ's statement was appropriate, and I find no error in it.

AHP further argues that the ALJ misunderstood AHP's response to Dr. Lipicky's ''accusations of manipulation.'' (AHP Exceptions at 93.) The portion of Dr. Lipicky's testimony to which AHP refers reads as follows regarding the reanalysis:

> The first analysis showed that different investigators had different results. If I had to search for a means of turning a negative trial positive, I would retrospectively search for reasons to exclude patients studied by investigators who did not produce results favoring drug over placebo and include patients studied by investigators who did favor drug over placebo. Remarkably, the reanalysis, in addition to restricting attention to only ½ of the entire time of the study, excluded 7 patients from the Batson study, 3 patients from the Raines study (both Batson and Raines having not favored drug over placebo) and included 4 patients from the Reich study (Reich having favored drug over placebo). Yet other inclusions and exclusions resulted in a total of 20 patients (almost 25% of the patients analyzed) to be declared now analyzable whereas previously being declared non-analyzable.

(Lipicky, G–61 at 18.)

AHP argues that Dr. Lipicky's testimony was refuted in AHP's Post-Hearing Brief, wherein AHP had argued that ''(a)n examination of the difference between the initial analysis and the reanalysis show that AHP's inclusion/exclusion decisions in the reanalysis *contradict(ed)* Dr. Lipicky's manipulation theory with respect to *four* of the centers; only the Reich center was consistent with Dr. Lipicky's theory * * *.'' (AHP Post-Hearing Brief at 42 (emphasis in original).) The ALJ's finding regarding this aspect of the reanalysis, with which AHP takes issue, reads as follows:

> In addition, AHP claims the Center's allegation is incorrect with respect to four of the centers since patients were added, not subtracted to the Raines center and excluded from the Batson-Hollier and Abbott centers with no changes to the String center. Only the Reich center showed a positive drug effect and had four patients added to it.

(I.D. at 26–27.)

AHP now argues that in its Post-Hearing Brief, it had refuted Dr. Lipicky's assertions in their entirety, and that the ALJ was in error in finding that AHP had argued that the Center's allegation was incorrect with respect to four of the five centers. (AHP Exceptions at 93.) I find this argument to be clearly without merit. As the previously quoted excerpt from AHP's Post-Hearing Brief plainly shows, AHP did say that it found that Dr. Lipicky's testimony was correct with regard to the Reich center, just as the ALJ had ruled. (AHP Post-Hearing Brief at 42.) I find no indication that the ALJ misunderstood AHP's response to Dr. Lipicky's testimony, and, therefore, I find no merit in AHP's argument.

AHP also argues that the ALJ was in error in stating that the Reich Center was the only one of the five centers to show a ''positive drug effect.'' (AHP Exceptions at 94.) In this statement, the ALJ was referring to the initial analysis of the five-center study, in which only the Reich Center showed a statistically significant drug effect. (See I.D. at 26–27; G–9.1 at 85.) The ALJ also noted that when the reanalysis was performed, four patients were added to the Reich Center. (I.D. at 27.) The ALJ's statements were correct, and I find no error in them.

AHP further challenges the ALJ's decision by asking what the ALJ's rationale was for ruling that two patients who had been included in the initial analysis—Patient Nos. 15 and 16

from the Batson-Hollier center—were improperly excluded from the reanalysis. (AHP Exceptions at 94–98, citing I.D. at 28.) This issue refers to the setting of a baseline treadmill measurement for patients under a section of the protocol that has been termed the ''salvage'' provision. (AHP Exceptions at 95.) (Other issues related to the salvage provision are discussed below in section I.C.2.c. of this document.)

Basically, the salvage provision was a contingency that required a fairly stable treadmill measurement for the baseline for a patient's entry into the study. Each patient entered into the five-center study was enrolled in a 6 to 8 week, pretreatment washout period during which all patients were given a placebo. (G–6 at 9.) A set of two treadmill tests were performed each time a treadmill reading was required by the study. (G–6 at 10.) To establish a patient's baseline value on the treadmill, the maximum value recorded on the last visit of the pretreatment period was to be used as the baseline. (G–6 at 10, 21.) The protocol also provided that if the maximum values recorded on the last two consecutive, pretreatment visits differed from one another by more than 20 percent of the value of the larger of these two readings, then up to two additional sets of treadmill tests at weekly intervals could be made. (G–6 at 10–11.) Only the last two consecutive set of tests would be considered for qualification of the patient into the study. If agreement within 20 percent failed to be found after four visits, the patient was to be dropped from the study. (G–6 at 11.)

In the initial analysis, Patient Nos. 15 and 16 from the Batson-Hollier center were said to have entered the study under the salvage provision, i.e., these patients required additional pretreatment visits and treadmill tests to establish an acceptable baseline. (AHP Exceptions at 95.) While these patients were included in the initial analysis, these patients were excluded from the reanalysis. (AHP Exceptions at 95.) Regarding this change in inclusion/exclusion decisions, the ALJ wrote, ''AHP cannot exclude these patients after the initial analysis failed to demonstrate a positive drug effect. There is no reason why AHP could not have identified this problem area sooner.'' (I.D. at 28.)

I am in agreement with the ALJ's ruling on the exclusion of these two patients. As I said before, inclusion/exclusion decisions made after randomization may affect the initial randomization and assignment of subjects in such a way as to bias the results. (Commissioner's Decision on OPE, slip op. at 238–39; Commissioner's Decision on Deprol, 58 FR 50929 at 50939 and 50940.) In the present case, the issue of bias has been raised all the more strongly because the exclusions also involved a change in the protocol and subsequent reanalysis after the initial analysis failed to find statistical significance. I find AHP's exclusion of these patients effectively to be a change in the entry criteria made after the data were collected, analyzed, and failed to show statistically significant results. The ALJ was right to question it. Therefore, I uphold the ALJ's rejection of the inclusion/exclusion decision regarding these two patients in the reanalysis.

AHP further argues that the ALJ misunderstood AHP's evidence regarding the exclusion of Patient Nos. 15 and 16 from the Batson-Hollier center. (AHP Exceptions at 98.) On this point, AHP takes issue with the following statement by the ALJ: ''This (exclusion of patients who would have qualified for entry in the study by means of the 'salvage provision'), according to AHP, explains why the patient population at the Batson-Hollier Center was different than that of the other centers.'' (I.D. at 28; see AHP Exceptions at 98.) I have reviewed the record, and I find that the ALJ's opinion accurately summarizes the statements made by AHP in its Post-Hearing Brief, particularly this language from that brief: ''The patient population studied at the one center (the Batson center) was, as a consequence (of the salvage provision), different from the patient population studied in the other four centers.'' (AHP Post-Hearing Brief at 52.) Therefore, I find no merit in AHP's argument.

I am in agreement with the ALJ's determination that the inclusion/exclusion decisions called the reliability of the reanalysis into question. An adequate and well-controlled study must ensure that adequate measures are taken to minimize bias on the part of the analysts. (§ 314.126(b)(5)) Exclusion decisions made after randomization may affect the initial randomization and the assignment of subjects in such a way as to bias the results. (Commissioner's Decision on OPE, slip op. at 238–39; Commissioner's Decision on Deprol, 58 FR 50929 at 50939–40.) Under the facts in the present case, it is not possible in the reanalysis to distinguish the effect of a drug from other influences, such as biased observation. (See § 314.126(a).) Therefore, for the reasons previously discussed I reject AHP's exceptions.

c. *Calculation of treadmill distances.* As previously indicated, each patient entered into the five-center study was enrolled in a 6 to 8 week, pretreatment washout period during which all patients were given a placebo. (G–6 at 9.) As provided under the protocol, a set of two treadmill tests were to be performed each time a treadmill reading was required by the study. (G–6 at 10.) To establish the baseline value for a patient on the treadmill, the maximum value recorded on the last visit of the pretreatment period was to be used as the baseline. (G–6 at 10, 21.) The protocol also stipulated that if the maximum values recorded on the last two consecutive pretreatment visits differed from one another by more than 20 percent of the larger of these two values, then, under a section of the protocol referred to as the ''salvage provision'' (AHP Exceptions at 95), up to two additional sets of treadmill tests at weekly intervals could be made. (G–6 at 10–11.) Only the last two consecutive sets of tests would be considered for qualification of the patient into the study. If agreement within 20 percent failed to be found after four visits, the patient was to be dropped from the study. (G–6 at 11.) The protocol contained a comparable requirement for the measurement of treadmill values throughout the study, in that ''*(t)he test resulting in the longer claudication time (was to) be used for calculating the maximum distance walked*.'' (G–6 at 21 (emphasis in original).)

The report of the initial analysis for the five center study stated that ''the baseline measurement used was the maximum of the two values from the last visit'' of the pretreatment period. (G–9.1 at 90.) However, it is not clear that, in fact, the maximum values were used for all five of the centers, for in a separate report on the MDS–176 (Reich) center it was stated that the baseline measurement was ''the *average* of the last two visits of the single blind pre-medication placebo phase'' (G–9.1 at 180 (emphasis added)), rather than the maximum value as provided in the protocol. Moreover, in the reanalysis, AHP calculated the baseline values for each patient by averaging the two treadmill measurements from the pretreatment results rather than by using the maximum value, as per the protocol. (Lipicky, Tr. Vol. IV at 70; see also A–108 at 2–11; AHP Exceptions at 100.)

In his Initial Decision, the ALJ found, ''AHP also did not calculate all the treadmill data in strict accordance with the instruction of the protocol.'' (I.D. at 56.) AHP takes exceptions to the ALJ's findings on this point. (AHP Exceptions at 98.) AHP first avers that no witness

for the Center criticized the 1985 five-center study analysis on the basis of the manner in which the baseline treadmill values for patients were calculated, and that the issue was raised for the first time by the Center in its brief. (AHP Exceptions at 101.) However, my review of the hearing transcript reveals that Dr. Lipicky, a witness for the Center, testified, ''(E)ven though the protocol clearly stated that the analysis was to be based upon the longest walking distance measured at any of the visits, AHP chose to use mean values of the two treadmill walking times that were measured at each visit.'' (Lipicky, Tr. Vol. IV at 70.) The calculation of treadmill values was identified as a protocol violation by the Center at the hearing, and so AHP's assertions to the contrary are simply incorrect.

AHP next argues that the Center, in preparing its own analysis of the data, computed baseline and final treadmill measurement by averaging the measurements from the study. (AHP Exceptions at 102–03.) In support of its argument, AHP cites to the testimony of Dr. Lipicky, a witness for the Center, who relied upon an exhibit identified as G–70 in his testimony on this point. (See Lipicky, Tr. Vol. IV at 74–82, 97–104.)

The record indicates that the Center performed at least eight different analyses in its review of the five-center study, with exhibit G–70 being one of the Center's analyses. (Lipicky, Tr. Vol. IV at 75.) Dr. Lipicky testified that in Exhibit G–70, the Center looked at the data in the same way as did AHP in its reanalysis. (Lipicky, Tr. Vol. IV at 76.) Baseline walking distances were computed by averaging a given patient's test measurements at the third and fourth visits. (Lipicky, Tr. Vol. IV at 98.) However, I note that Exhibit G–70 was stricken from evidence by the ALJ on motion of AHP. (Tr. Vol. V at 6.) Therefore, I find any issues pertaining to Dr. Lipicky's testimony regarding this evidence to be moot.

AHP also asks if the ALJ considered whether the study results would have been any different if maximum values had been used rather than average values. (AHP Exceptions at 103.) The ALJ is not required to perform such calculations. More importantly, the fact is that AHP's calculation of the treadmill values using average values was yet one more protocol violation in a study with other protocol violations.

AHP raises the additional argument that the ALJ rejected the five-center study solely on the basis of AHP's use of average treadmill values instead of the maximum values required by the protocol. (AHP Exceptions at 103.) This is a misstatement of the ALJ's opinion. The ALJ rejected the reanalysis because AHP ''provided no good reason'' for analyzing only the first half of the data from this study. (I.D. at 30) Therefore, I find AHP's argument to have no merit.

d. *Variability among centers.* AHP next objects to the ALJ's ruling that the results of the various centers within the five-center study are so inconsistent as to make any finding of a significant drug effect questionable. (AHP Exceptions at 105, citing I.D. at 31.) In its arguments, AHP raises the broad questions of when it is appropriate to ''break open'' a multicenter study and review the results of individual centers, and what it is that the ALJ should examine in such a review. (AHP Exceptions at 107–08.)

By statutory mandate, FDA is charged with reviewing all DESI drugs for efficacy and to withdraw approval for any NDA where ''substantial evidence'' of the drug's effectiveness is lacking (21 U.S.C. 355(e)(3)). Among the considerations to be weighed in the FDA's review are the validity of the methodology used in a particular study, and the determination of whether substantial evidence of efficacy has been proved. (*Warner-Lambert,* 787 F.2d at 153.)

To this end, a thorough review of the studies submitted by a manufacturer to the FDA as proof of a drug's efficacy is always appropriate. All aspects of the data are proper subjects for review. When the study is a multicenter trial, the methodology and data from each participating center may be evaluated and reviewed. I therefore find that the ALJ did not err when he ''broke open'' the multicenter trial and reviewed the outcome at each of the centers.

AHP next argues that the ALJ ignored the pooled results of the five-center study. (AHP Exceptions at 107.) I find that the ALJ did weigh the pooled data but that he concluded that the data failed to meet the requirements of an adequate and well-controlled study. (See generally Commissioner's Decision on Phenformin Hydrochloride (44 FR 20967 at 20970, April 6, 1979) (Commissioner ruled that ALJ did not disregard specified evidence but instead was found to have considered the overall evidence.))

AHP next challenges the ALJ's finding that ''the results of the five-center study are so inconsistent as to make a significant drug effect questionable.'' (AHP Exceptions at 105, quoting I.D. at 31.) I find that the ALJ's ruling is supported by the evidence. Regarding the reanalysis, Dr. Schneiderman, a witness for the Center, testified that there were substantial differences among the five centers in the study. (Schneiderman, Tr. Vol. VII at 8.) On this point, Dr. Schneiderman testified:

> Oh, I think there's a substantial difference among the institutions that tested the patients. One institution shows substantial improvements in the average among the patients, much of that improvement being contributed by one patient who was in one of the inclusions—included once and excluded once—thereby, the selection criteria become of considerable importance in that one institution.
>
> In the four other institutions, two of them show some minor effects for the drug, slightly better than placebo; two of them show some minor effects for placebo, slightly better than the drug. So it seems to me there was a substantial difference among the institutions.

(Schneiderman, Tr. Vol. VII at 8.)

Additionally, another Center witness, Dr. Lipicky, testified that results of the various investigators differed to an extent that made the pooled data difficult to accept as accurate. (Lipicky, G–61 at 19.) Dr. Lipicky reported that two of the five centers found the placebo to be numerically superior to Cyclospasmol®, and that it was the Reich Center which found the largest numerical difference between drug and placebo. Dr. Lipicky further testified, ''Within the study, replication is poor and this remains a major problem. In fact at one point in time AHP used this argument to argue the results of the multicenter study could not be pooled.'' (Lipicky, G–61 at 19.)

e. *Adequacy of the five-center study.* In sum, I find that the five-center study was not adequate and well-controlled. In making this determination, I have considered the aggregate effect of the protocol violations. As I previously discussed: (1) AHP's reanalysis of the five-center study cannot be relied upon as substantial evidence of efficacy from an adequate and well-controlled clinical trial; (2) reconsideration of the inclusion/exclusion decisions called into question the reliability of the reanalysis; (3) calculation of treadmill distances were not performed according to the protocol; and (4) the evidence indicated that results of the various centers differed to an extent that made the pooled data difficult to accept as accurate.

D. *The Senile Dementia Disease Indication*

The labeling for Cyclospasmol® originally identified ''selected cases of ischemic cerebral-vascular disease,'' as being one of Cyclospasmol®'s indications. (G–33.2 at 7; see also A–89 at 4–6; G–57 at 4–7.) However, AHP has modified this proposed labeled indication to that of treatment for cognitive dysfunction in patients

suffering from senile dementia of the multiinfarct or Alzheimer's type. (See AHP Post-Hearing Brief at 1; AHP Exceptions at 111.)

Senile dementia is a clinical term used to describe a series of conditions in which elderly individuals have memory loss and cognitive impairment. (Thal, G–63 at 3.) There are various etiologies which can result in the clinical syndrome of senile dementia. (Thal, G–63 at 3.) Multiinfarcts and Alzheimer's disease are two such etiologies. Other diseases and conditions which can cause dementia include psychiatric problems masquerading as dementia, metabolic disorders, such as hyperthyroidism or Vitamin B–12 deficiency, diseases of the central nervous system, and systemic illnesses that affect the function of the central nervous system, such as diseases of the heart, lungs, liver, kidneys, endocrine and hematologic organ systems. (Thal, G–63 at 3; Leber, G–64 at 5.)

Cognitive dysfunction is a symptom of senile dementia. (Zung, Tr. Vol. III at 43.) Cognitive dysfunction can include a lack of mental alertness, confusion, inattentiveness, memory problems, and disorientation. (Goodman, A–123 at 4; Klerman, A–118 at 6.) Emotional or motivational disturbances are also sometimes associated with cognitive dysfunction. (Klerman, A–118 at 7.)

AHP submitted two studies in support of the dementia indication—the Rao study and the Yesavage study. Each study will be reviewed in turn.

1. The Rao Study

The Rao study was a placebo-controlled, parallel group study conducted from December 1975 through June 1976 at Oak Forest Hospital, Illinois, by Drs. Dodda B. Rao, Emile L. Georgiev, P.D. Paul, and A.B. Guzman. (I.D. at 32.) The stated objective of the study was ''to evaluate the efficacy of Cyclospasmol® in alleviating symptoms of senescence commonly associated with cerebral vascular insufficiency.'' (G–28.8 at 314.)

Patients in the drug group were given 1,600 mg of Cyclospasmol® per day for 12 weeks, while patients in the control group received a placebo. (G–28.8 at 314.) Seventy patients were enrolled in the study. However, nine patients dropped out and three patients were later excluded from the statistical analysis, leaving 58 patients whose results were included in the final analysis. (I.D. at 32.)

Patients in the Rao study were rated by using the Sandoz Clinical Assessment—Geriatric (SCAG), and the Nurses Observation Scale—Inpatient Evaluation (NOSIE). (G–14.2 at 242–43.) Also, a global evaluation of each patient's clinical improvement was made at final visit. (G–14.2 at 243–44.)

With the SCAG measurement, a physician rated each patient based on a list of 19 items, or symptoms, associated with dementia. (G–3.1 at 97.) These items included attributes such as ''confusion,'' ''bothersomeness,'' ''appetite,'' and ''anxiety.'' (G–3.1 at 98.) Each Item in the SCAG was rated on a scale from 1 to 7, with 1 indicating that the symptom was ''not present,'' and 7 indicating that the symptom was ''severe.'' (G–3.1 at 97; see, e.g., G–14.2 at 6–8.)

Eighteen of the SCAG items were then grouped into five factors for patient rating. (G–3.1 at 97; see also G–11.1 at 69–71 (Dr. Yesavage discussing SCAG in the Yesavage study).) The five factors for the SCAG included: (1) Cognitive dysfunction, (2) interpersonal relationships, (3) affect, (4) apathy, and (5) somatic dysfunction. The 19th item, a physician's overall assessment of the patient, was rated separately and was not grouped into a factor. (G–3.1 at 97; see also G–11.1 at 70 n.7 (Dr. Yesavage discussing SCAG in the Yesavage study).)

The NOSIE rated the frequency of 30 specific behaviors, employing a scale from ''1'' for ''never,'' to ''5'' for ''always.'' (See, e.g., G–14.2 at 10.) Among the rated behaviors were such items as ''is sloppy,'' ''sleeps, unless directed into activity,'' and ''has trouble remembering.'' (See, e.g., G–14.2 at 10.)

For the final, global evaluation, the patient's physician rated the patient's overall clinical condition during the study as being either ''worsened,'' ''unchanged,'' ''minimal improvement,'' ''moderate improvement,'' or ''marked improvement.'' (See, e.g., 14.2 at 25.)

Regarding the SCAG ratings, Dr. Rao reported a statistically significant change from baseline in favor of Cyclospasmol® on four of the five SCAG Factors, but not on the separate SCAG Item 19. (G–3.1 at 97–98.)

As for the NOSIE results, the Rao study grouped the 30 items on the NOSIE into 5 factors, identified as: (1) Social competence, (2) social interest, (3) personal neatness, (4) irritability, and (5) retardation. (G–3.1 at 98.) The specific grouping into factors was not discussed in the report on the Rao study. (See G–3.1 at 96–99.) However, it was reported that for three of the five NOSIE factors, the test and control arms were not comparable at baseline. (G–3.1 at 98.) For the remaining two NOSIE factors, which were found to have been comparable at baseline, it was reported that statistical significance was not shown for Cyclospasmol®. (G–3.1 at 98.)

As for the physicians' global evaluations, Dr. Rao reported a statistically significant difference in favor of Cyclospasmol®. (G–3.1 at 98, 99.)

The ALJ ruled that the Rao study cannot be considered an adequate and well-controlled study because he found that the study was conducted ''so poorly that the results cannot be relied on with any degree of certainty.'' (I.D. at 42.) Both AHP and the Center raise objections pertaining to rulings made by the ALJ regarding the Rao study.

a. *Admissibility of the reanalysis.* AHP argues that the ALJ erred in refusing to admit AHP's reanalysis of the Rao study into evidence. (AHP Exceptions at 117–21; I.D. at 9.) In denying the admission of the reanalysis into evidence, the ALJ ruled that the reanalysis was not timely filed as required under FDA regulations. (I.D. at 9; ALJ Order of 5/29/85, Exhibit Vol. 89; § 12.85 (21 CFR 12.85.)) The ALJ further ruled that AHP failed to demonstrate, as was required per the regulations, that AHP could not have submitted the reanalysis sooner, and that the value of the reanalysis to the evidentiary record would justify potential delay resulting from the document's late submission. (I.D. at 9; see § 12.85(c).)

The circumstances preceding the submission of the reanalysis are not in dispute. Following the publication in the Federal Register on May 25, 1979, of a Notice of an Opportunity for a Hearing regarding Cyclospasmol® (44 FR 30443), AHP made a request for a hearing and submitted in support of Cyclospasmol®'s efficacy a four page article published by Dr. Dodda B. Rao discussing this study. (Center Exceptions at 34.) Subsequently, FDA asked AHP for the Rao study's case report forms, but AHP advised FDA that only 3 of the 58 forms could be located. (Center's Narrative, G–57 at 5.) In July of 1984, representatives of FDA visited Oak Forest Hospital and were able to locate and review the hospital records for 56 of the 58 subjects in the Rao study. (Center Exceptions at 35, citing Center's Allegations of Fact Nos. 58–62; Center's Narrative, G–57 at 5.)

In October of 1984, the Center filed its Narrative Statement in which the Center criticized the Rao study for failing to exclude certain patients who had been given concomitant medications during the study and for other violations of the protocol's exclusionary requirements. (Center Exceptions at 35; see Center's Narrative, G–57 at 1–8.) On December 17, 1984, AHP filed with the administrative record copies of AHP's

documentary data and other information relied upon, as required under FDA regulations. (§ 12.85.) The reanalysis of the Rao study was not included with AHP's prehearing submission.

On May 6, 1985, a reanalysis of the Rao study was submitted as an attachment to the deposition testimony of Mr. Danny Chaing. (A–125, Attachment E.) In this reanalysis, AHP excluded 14 patients from the analysis because of concomitant medication violations or concomitant diseases and conditions. (AHP Exceptions at 118.) The results of the reanalysis, using 44 patients of the 58 patients originally analyzed, were reported as showing statistical significance in favor of Cyclospasmol®. (AHP Exceptions at 119.)

The Center moved to strike the reanalysis on the grounds that it was a late submission and that there was no justification for its delayed filing. (Center Motion to Strike 5/13/85, Exhibit Vol. 88 at p. 12–13.) The Center argued that the reanalysis should have been submitted to the FDA in either the NDA for Cyclospasmol® or in the prehearing submissions required under FDA regulations. (§ 12.85.)

FDA regulations require that within 60 days of the publication of the notice of hearing, each participant in the hearing shall submit to the docket all data and information relied upon. (§ 12.85(b).) The regulations further provide that such submissions may be supplemented later in the proceeding, with the approval of the presiding officer, upon a showing that the material contained in the supplement ''was not reasonably known or available when the submission was made or that the relevance of the material contained in the supplement could not reasonably have been foreseen.'' (§ 12.85(c).)

If written evidence is not submitted as required under the regulations, the ALJ may exclude the evidence as inadmissible. (§ 12.94 (21 CFR 12.94(c)(1)(iii)).) Under the regulations, the ALJ in the present case excluded the Rao reanalysis, inasmuch as the submission was neither timely filed, nor was a motion to supplement AHP's submissions made offering an explanation for the lateness of the submission.

In support of its submission, AHP argues that the reanalysis was ''highly relevant,'' and that the reanalysis was the appropriate response to the Center's criticisms of the Rao study. (AHP Exceptions at 120.) AHP also argues that the ALJ's ruling prevented AHP from demonstrating that even if certain patients were excluded from the statistical analysis, the Rao study still resulted in a statistically significant result. (AHP Exceptions at 121.) I find that these arguments merely beg the question and do not address the fact that AHP made no attempt to offer a motion with explanation to the ALJ to supplement AHP's submissions for the Rao study, as stipulated in the regulations. (§§ 12.85(c) and 12.94(c)(1)(iii).) (By contrast, I note that AHP made such a motion, which was granted by the ALJ, to supplement its submissions in connection with the five-center study. (See I.D. at 8–9.))

The reanalysis submitted by AHP entailed a reconsideration of the exclusionary decisions made regarding the study subjects and a recalculation of statistical significance. As was ruled in the Commissioner's Decision on the drug Cothyrobal, ''(I)t is not the function of a hearing to consider new evidence, i.e., evidence that was not available to the agency at the time it initially denied the NDA.'' (Commissioner's Decision on Cothyrobal, 42 FR 28602 at 28616, June 3, 1977), aff'd *Edison Pharmaceutical Co.* v. *FDA*, 600 F.2d 831 (1979); see also *Warner-Lambert,* 787 F.2d at 162 (ALJ has ''the power to make reasonable, nonarbitrary decision regarding the admission or exclusion of evidence for procedural reasons.'').)

Similar decisions pertaining to administrative hearings before other Federal agencies have been affirmed by the courts. For example, in *Michigan Consolidated Gas Co.* v. *Federal Energy Regulatory Comm'n*, 883 F.2d 117, 124–25 (D.C. Cir. 1989), the circuit court ruled, ''When a party is on reasonable notice as to the dates and times for hearings and for filings in an administrative proceeding, we are hard pressed to hold that the administering agency acted arbitrarily or capriciously in denying admission of materials untimely filed.'' (See also *Irving Bank Corp.* v. *Board of Governors of Fed. Reserve System*, 845 F.2d 1035, 1039 n.5 (1988) (Board of Governors of Federal Reserve System had discretion over extent to which it was required to consider late-submitted evidence); *Pittsburgh & Lake Erie R.R. Co.* v. *Interstate Commerce Comm'n*, 796 F.2d 1534, 1544–45 (D.C. Cir. 1986) (Carrier challenging cancellation of several joint rates was not entitled to admission of certain rebuttal evidence which the carrier submitted at a stage in the administrative proceedings when the opposing party would not have had an opportunity to respond.))

In challenging an evidentiary ruling such as this, the objecting party has the burden to make a ''strong showing'' that the ALJ abused his or her discretion. (*Warner-Lambert,* 787 F.2d at 162.) I do not find that AHP has made the necessary strong showing that such an abuse of discretion occurred on the part of the ALJ. Therefore, I find that the ALJ did not err in granting the Center's motion to strike the reanalysis.

b. *Labeling and patient selection.* AHP next argues that the ALJ erred in concluding that the Rao study was not adequate and well-controlled because the claimed indications for Cyclospasmol® went beyond those of the patient group which was originally said to have been studied. (AHP Exceptions at 121; I.D. at 34, 42, 56.) The ALJ had noted that while AHP was now seeking to label Cyclospasmol® for indications in patients with dementia resulting from both Alzheimer's disease and from multiinfarcts, Dr. Rao, in his published account of the study, stated that he had excluded patients with ''a history of Alzheimer's disease.'' (I.D. at 56; G–3.1 at 97.)

As stated in the protocol, the objective of the Rao study was ''to evaluate the efficacy of Cyclospasmol® in alleviating symptoms of senescence commonly associated with cerebral vascular insufficiency.'' (G–28.8 at 314.) The protocol also required, among other things, that patients ''whose symptoms of senescence occurred prior to age fifty'' be excluded. (G–28.8 at 314.)

Dr. Rao, in his subsequently published article, indicated that the focus of the study was the treatment of cerebrovascular insufficiency. (G–3.1 at 96.) Dr. Rao noted ''that in the past vasodilators have too often been prescribed indiscriminately, without proper selection of patients.'' (G–3.1 at 97.) Dr. Rao then went on to describe the patient population for his study as follows:

> Sixty geriatric patients (men and women aged 65 or older) were selected initially for the study. We excluded those with a history of Alzheimer's disease; stroke; psychiatric illness; traumatic, neoplastic or infective brain damage; and other relevant disorders. We attempted to identify patients with clearly evident symptoms of senility, but excluded those who were so severely debilitated as to make the possibility of significant improvement unlikely.

(G–3.1 at 97.)

Notwithstanding Dr. Rao's article reporting that he had excluded patients with Alzheimer's disease, AHP argues that Dr. Rao's exclusions did not prevent the study population from including patients with dementia due to Alzheimer's disease. (AHP Exceptions at 123.) AHP argues that the definition of Alzheimer's disease has changed since the time of Dr. Rao's article. AHP argues that in the mid-1970's, when Dr. Rao conducted this study and published his

article, Alzheimer's disease was defined as dementia in a relatively young patient population, i.e., patients under age 65. Dr. Rao, when he purported to be excluding Alzheimer's patients from his study, excluded only dementia patients under age 65. This definition for Alzheimer's disease is today outmoded. (AHP Exceptions at 122; Zung, Tr. Vol. III at 15–16.) AHP argues that today the definition of Alzheimer's disease includes patients over the age of 65, which would include patients in the age group represented in the Rao study.

Citing the change in the definition of Alzheimer's disease, AHP also argues that despite Dr. Rao's claim of excluding Alzheimer's disease patients from the study, Dr. Rao could not possibly have excluded patients with Alzheimer's disease because the only way to differentiate conclusively between multiinfarct dementia and Alzheimer's disease is by an autopsy. (AHP Exceptions at 123, citing Denton, Tr. Vol. VII at 14; Yesavage, Tr. Vol. IV at 27; Yesavage, A–115 at 7.) AHP argues that the patient population represented in the Rao study was the same as would currently be identified as suffering from either multiinfarct dementia or Alzheimer's disease. (AHP Exceptions at 123.) AHP concludes by arguing that Dr. Rao's exclusions did not prevent the Rao study population from including patients with both multiinfarct dementia and dementia due to Alzheimer's disease, notwithstanding Dr. Rao's contrary intention. (AHP Exceptions at 123.) AHP cites to the testimony of three witnesses in support of its position. (AHP Exceptions at 123.)

The first of the witnesses cited by AHP is Dr. Lowell I. Goodman, a witness for AHP, who testified generally about the population suffering from dementia. Dr. Goodman stated, ''Almost certainly subsequent epidemiological studies and further research into this population have revealed that approximately two-thirds of such patients, diagnosed as having senile dementia, were of the Alzheimer type and approximately a third were either multiinfarct dementia or a mixture of the two.'' (Goodman, Tr. Vol. V at 82.)

AHP also cited to the testimony of Dr. Gerald L. Klerman, also an AHP witness, who testified:

> Our current thinking is that cerebral arteriosclerosis plays relatively little role in most cases of senile dementia and that they are either of the Alzheimer's type or what is called multi-infarct dementia. The Rao and the Yesavage study by current standards would be primarily cases with Alzheimer's disorder and some with a mixture of previous strokes.

(Klerman, Tr. Vol. III at 69.)

The third witness cited by AHP is Dr. Leon J. Thal, a witness for the Center. I have reviewed Dr. Thal's testimony, however, and I do not find it to support the point being advanced by AHP. When Dr. Thal was asked whether it was likely that the patient population chosen under the Rao protocol, i.e., patients having ''symptoms of senescence commonly associated with cerebral vascular insufficiency,'' would today be the same as a population consisting of Alzheimer's patients and multiinfarcts dementia patients, Dr. Thal responded in the negative. Contrary to the position which AHP is arguing, Dr. Thal testified, ''No, that's not correct because, in addition to multi-infarct dementia and Alzheimer's disease, there are many other causes of dementia. The patients in the Rao study were not systematically examined for other causes of dementia.'' (Thal, Tr. Vol. VI at 38.) Dr. Thal went on to add that even if Alzheimer's disease patients and multiinfarct patients were counted as one group, still it was likely that approximately 20 percent of the patients included in the Rao study had other causes of dementia. (Thal, Tr. Vol. VI at 38.)

FDA regulations require that ''(t)he method of selection of subjects provides adequate assurance that they have the disease or condition being studied * * *.'' (§ 314.126(b)(3).) Towards this end, the Commissioner's Decision on Mysteclin, relying upon this section of the regulations, stated:

> It is essential, therefore, that the most accurate diagnostic techniques available be used in order to provide as much assurance as possible that the results are credible. See Lutrexin; Withdrawal of Approval of New Drug Application, 41 Fed. Reg. 14406, 14419 (1976). Because patients often are treated on the basis of preliminary diagnoses that suggest, without confirmation, a disease's etiology, the diagnostic criteria used by physicians when treating patients are not always applicable in the context of a drug investigation.

(Commissioner's Decision on Mysteclin, slip op. at 36–37, FDA Docket No. 82N–0153 (FDA February 8, 1988) (some citations omitted), opinion denying review sub nom. *E.R. Squibb & Sons, Inc.*, v. *Bowen*, 870 F.2d 678 (D.C. Cir. 1989) (hereinafter cited as Commissioner's Decision on Mysteclin).)

Leaving aside the question of Dr. Rao's intent, I turn instead to the evidence that Alzheimer's and/or multiinfarct patients were included in the Rao study, and that patients with other causes of dementia were excluded. The evidence argued by AHP basically consists of the facts that: (1) The patients in the study exhibited dementia, and (2) the patients were in the typical age group for patients having Alzheimer's or multiinfarct.

I find that evidence about dementia in general in the geriatric population, such as that evidence offered by Drs. Goodman and Klerman, does not provide adequate assurance that the subjects of the Rao study had Alzheimer's disease. As Dr. Thal, the third witness cited by AHP, testified, dementia can be caused by various conditions or diseases. (Thal, Tr. Vol. VI at 38.) Included among these other diseases or conditions are hypothyroidism, vitamin B_{12} deficiency, hydrocephalus, psychiatric problems (pseudodementia), chronic alcoholism, Parkinson's disease, severe diabetes, neurological disease, infection in the central nervous system, and brain tumors. (Zung, Tr. Vol. III at 17–18; 23–24, 32, 50; Goodman, Tr. Vol. V at 82–83; Goodman, A–123 at 23.) Despite this fact, the evidence does not show that the patients in the Rao study were examined for other causes of dementia. (Thal, Tr. Vol. VI at 38.)

AHP argues that it did perform a physical examination to screen for other neurological causes of dementia. (AHP Post- Hearing Brief at 88; see Goodman, A–123 at 21–23; Goodman, Tr. Vol. V at 82–83; Zung, A–117 at 30.) This examination was said to consist of an evaluation of each patient's gait, muscle strength, balance, deep-tendon reflexes, level of consciousness, attention and understanding, cooperation and intelligence, and visual, auditory and other special senses. (Goodman, A–123 at 21.) However, none of the results of these tests were in evidence, nor were the results available for review by the Center. In the absence of evidence of the results of such tests, AHP's argument that it did perform certain diagnostic tests is not persuasive and has no probative value. (Commissioner's Decision on Cothyrobal, 42 FR 28602 at 28608 (Where a particular condition can be caused by many factors, evidence must be provided regarding diagnostic criteria and the confirmatory laboratory tests.))

AHP further argues that, because most of the patients entered into the study had been under the close supervision of the study's physicians for years and were familiar to the physicians before the study began, further diagnostic testing was not necessary to screen for other causes of dementia. (AHP Post-Hearing Brief at 88; see Klerman. A–118 at 28–29; Goodman, A–123 at 21–23; Goodman, Tr. Vol. V at 82–83; Zung, A–117 at 30.) I am not persuaded by this argument. By statutory mandate, a

drug's efficacy must be proved by substantial evidence from adequate and well-controlled clinical trials. (21 U.S.C. 355(d).) It is established that the burden of proving the adequacy of a study is on the proponent for the drug. (*Hynson*, 412 U.S. at 617, citing 21 U.S.C. 355(e)(3).) Under agency regulations, the method of selecting subjects for a study must provide adequate assurance that the subjects have the disease or condition being studied. (§ 314.126(3).) In the Rao study, I do not find the undocumented, prestudy experience of the physicians with the study patients to be acceptable as substantial evidence of the patients' conditions.

As for the change in the definition of Alzheimer's disease, I find this equally unpersuasive as a basis for supporting an indication for Alzheimer's disease. As I previously stated, general observations about the geriatric, senile population at large do not provide adequate assurance that the subjects of the Rao study had Alzheimer's disease.

Moreover, as AHP concedes, Alzheimer's disease and multiinfarct dementia are distinct diseases with different etiologies. AHP argues that etiology does not matter because AHP does not have to prove the mechanism of action for Cyclospasmol®. While it is true that the regulations do not require proof of mechanism of action, this is beside the point now at issue. The issue is diagnosis of the disease, not mechanism of action for the drug. In an adequate and well-controlled study, it is not acceptable to group persons having similar symptoms but distinct diseases together into one study without identifying which patient has which disease (as was done in the Rao study). If this practice were permitted, it would be impossible to assess a drug's effectiveness on a particular disease. (Cf. Commissioner's Decision on Lutrexin, 41 FR 14406 at 14422 (In a study of premature labor, results were incapable of scientific interpretation because patients with different conditions were evaluated together without distinguishing between the conditions.); see also Commissioner's Decision on Cothyrobal, 42 FR 28602 at 28608 (Where a particular condition can be caused by many factors, evidence must be provided regarding diagnostic criteria and the confirmatory laboratory tests.))

Difficulty in diagnosis is not a justification for a less than adequate and well-controlled study. (Commissioner's Decision on Cothyrobal, 42 FR 28602 at 28608.) While Alzheimer's disease may not be positively diagnosed until an autopsy is performed, evidence indicated that it was possible to make a differential diagnosis on the basis of patient history by ruling out other causes of dementia. On this point, Dr. William Zung, a witness for AHP, testified that in order to make a differential diagnosis, one must consider the history of the patient. Dr. Zung testified that with Alzheimer's disease, ''the signs and symptoms are progressive. They are of a slow onset.'' (Zung, Tr. Vol. III at 14.) However, for multiinfarct dementia, Dr. Zung testified, ''the symptomatology would come on fairly rapidly * * *.'' (Zung, Tr. Vol. III at 14.) Dr. Zung further testified:

> (Y)ou can tell a differential diagnosis between senile dementia of the Alzheimer type and the multi-infarct because patients who have multi-infarct dementia have focal signs. That is to say, specifically where that part of the brain has been affected by lack of the oxygen and by death of the cells, say, if it's in the motor part of the brain, then that patient would have a decrease in their motor function.

(Zung, Tr. Vol. III at 15.)

I find that for an adequate and well-controlled study, merely selecting an elderly population which has dementia is not sufficient to assure that the study will demonstrate the effectiveness of a drug for patients with Alzheimer's disease. While the ''gold standard'' for diagnosing Alzheimer's disease lies in autopsies, nonetheless, there was evidence indicating that antemortem diagnosis can be made by the process of eliminating other possible causes of dementia. Identification of dementia caused by other conditions must be made and patients with other causes for their dementia excluded from the study. Alternatively, if patients with other causes of dementia, such as multiinfarct dementia, are to be included, then all patients' diagnoses should be identified.[4]

As was ruled in the Commissioner's Decision on Lutrexin, ''The evidence made clear that although existing diagnostic techniques do not permit certainty in the matter, they do allow physicians to make a valid judgment * * *. That the judgment will sometimes prove to be incorrect does not mean that diagnosis * * * is impossible, only that it is inherently uncertain.'' (41 FR 14406 at 14414.) Similarly, in the Commissioner's Decision on Cothyrobal, it was ruled that where a disease or condition can be caused by many factors, a study must give the patients' diagnoses and must also provide sufficient information to substantiate the diagnoses, notwithstanding the fact that a particular disease may be difficult to diagnose. (42 FR 28602 at 28608.)

While AHP argues that difficulties in making a diagnosis are what prevented the Rao study from distinguishing Alzheimer's patients from others, the fact remains that the Rao study was neither looking for nor attempting to identify Alzheimer's patients as that disease is currently defined, i.e., including patients with an onset of dementia over the age of 50. Rather, the Rao study primarily used an age cut off to identify Alzheimer's patients under the old definition. To retrospectively identify Alzheimer's patients under the current definition for Alzheimer's disease would require adequate information in the patient records which could be used to support the diagnoses. This information is not available in the Rao study records.

As was stated in the Commissioner's Decision on Lutrexin, ''(T)he law is clear that the applicant must provide substantial evidence of a drug's effectiveness under its labeled conditions of use, not those under which an investigator chooses to test it.'' (41 FR 14406 at 14419). Therefore, for all of the aforementioned reasons, I find that the Rao study was not adequate and well-controlled in that it failed to show that Cyclospasmol® was tested in Alzheimer's patients.

c. *Concomitant diseases and conditions.* AHP further argues that the ALJ erred in ruling that the Rao study was not adequate and well-controlled because the ALJ found that patients with strokes, histories of alcoholism, severe diabetes, and Parkinson's disease were admitted to the study, although these patients were to have been excluded under the protocol. (AHP Exceptions 125–26, citing I.D. at 42, 56.) In all, the Center identified 18 patients with concomitant diseases or conditions, including 3 patients with multiple conditions, whom they claim should have been excluded. (Center Exceptions at 5–6; Center Post-Hearing Brief at 53–62, & Attachment A.)

AHP concedes that protocol violations occurred, but argues that inclusion of most of these patients resulted in mere technical violations of the protocol and did not confound the results of the study. (AHP Exceptions at 126–28.) AHP further states that the Rao protocol was overly rigid, and that it was a question of medical judgment and expertise as to whether these protocol violations affected the study results. (AHP Post-Hearing Brief at 90, 93.)

The stated objective of the Rao study was ''to evaluate the efficacy of Cyclospasmol®'' in alleviating symptoms of senescence commonly

[4] I note that this was done in the Yesavage study. (See Yesavage, Tr. Vol. IV at 27.)

associated with cerebral vascular insufficiency.'' (G–28.8 at 314.) Towards this end, the protocol provided for the exclusion of patients with dementia caused by other conditions. In relevant part, the protocol's exclusionary criteria read as follows:

> Patients exhibiting any one of the following will be excluded from the study:
> 1. Those with a history of CVA (cerebral vascular accident, i.e., stroke (See A–121 at 28)).
> 2. Those who, upon physical examination, demonstrate neurological evidence of a past CVA.
> * * * * *
> 8. Those with severe diabetes mellitus which requires insuli(n) therapy, or with evidence of glycosuria on urinalysis or who exhibit complication of diabetes.
> * * * * *
> 10. Those with any other severe disease: e.g. significant hematologic disorders; history of malignant disease within one (1) year; recent (4 months) major surgical procedure; pulmonary embolism within one (1) year; severe chronic infection; severe renal, hepatic or neurological disorder, except the one being studied herein * * *.
> * * * * *
> 12. Those whose symptoms of senescence occurred prior to age fifty (50).
> 13. Those with a history of alcohol or other drug abuse, except that patients with a history of alcoholism prior to age 45, with no recurrence after that age, may be entered if the investigator feels that the patient's alcoholism did not contribute to his present symptoms.
> 14. Those with a history of major psychiatric illness.

(G–28.8 at 315–16.)

Relying upon the protocol, the Center identifies numerous patients whom it contends were admitted in violation of the exclusion provisions. I will address each type of alleged violation in turn.

i. *Strokes.* The Center first specifies seven patients, identified as Numbers 3, 12, 15, 21, 31, 45 and 64, as having histories of strokes and therefore subject to exclusion. (Mohs, G–62 at 8–9; Thal, G–63 at 6; Leber, G–64 at 10–15; Leber, G–64, Attachment B at 2; Denton, A–121 at 25, 27–28, 74, 76, 77, 79, 83, 85; Denton Tr. Vol. VII at 16–17; G–14.6 at 351.)

AHP concedes that Patient Nos. 12 and 64 should be excluded (AHP Post-Hearing Brief at 91; Denton, A–121 at 28), but argues against excluding the other five patients, on the grounds that the protocol was overly rigid because it excluded patients whose strokes occurred 2 to 3 years prior to the start of the Rao study. (AHP Post-Hearing Brief at 93.)

In support of its position that these stroke patients need not be excluded, AHP cites to the testimony of Dr. Clarence Denton, a witness for AHP, who testified as follows:

> Generally, there is no need to exclude patients on the basis of a stroke which occurred more than two to three years prior to the onset of the study. Strokes which occurred shortly before the onset of the study should be excluded, however, because the natural recovery process which occurs soon after a stroke is suffered could make it appear that a drug (or placebo) was having a favorable action. Ordinarily, normal recovery from a stroke would occur within six months to one year of the occurrence of the stroke. From a practical standpoint, therefore, it is perfectly reasonable to include patients whose strokes occurred many years prior to the onset of the study, as long as dementia is still present.

(Denton, A–121 at 26.)

It is beyond cavil that patients having a history of strokes were to be excluded under the protocol. Inclusion of these patients was a clear protocol violation. The question now is what effect do these protocol violations have on the validity of the study.

I begin my review of these protocol violations by noting that some protocol violations may be inadvertent or unavoidable on the part of those conducting the study, such as occurs with the failure of a study subject to follow the study's drug regimen. However, other protocol violations may reflect a lack of attention to the requirements of the protocol by those conducting the study. (Commissioner's Decision on Benylin, 44 FR 51512 at 51531 (The inclusion of subjects who did not meet the entrance criteria of the study ''suggests inattention to detail'' and can ''be considered in deciding whether the study was adequate and well-controlled.'').) Failure to follow inclusion/exclusion criteria, such as occurred in the Rao study, can be an indication of such inattention to the details of a study's protocol.

Even violations which by themselves may not warrant rejection of a study can be considered in the aggregate in determining whether a study is adequate and well-controlled. (Commissioner's Decision on Benylin, 44 FR 51512 at 51531.) Evidence of any protocol violation, even if inadvertent or unavoidable, is relevant to the issue of whether the study is adequate and well-controlled. Therefore, I rule that inclusion of the seven stroke patients, both the two patients whom AHP concedes should be excluded and the five whom AHP disputes, properly can be considered as protocol violations and weighed in the review of the Rao study.

ii. *Alcoholism.* The Center further argues that five subjects—Patient Nos. 16, 22, 32, 54, and 63—should have been excluded because they were suffering from alcoholism. (Mohs, G–62 at 9; Thal G–63 at 6; Leber, G–64 at 10–12; Denton, A–121 at 28–29, 42, 77, 79, 84, 85; Denton, Tr. Vol. VII at 22–24; A–126 at 17–20, 22–25.)

AHP makes an argument only against the exclusion of Patient No. 16. (AHP Post-Hearing Brief at 93; AHP Exceptions at 129.) AHP cites to the testimony of Dr. Denton, who testified that Patient No. 16 had consumed no alcohol for 3½ years before the start of the study, and that the initial psychiatric consultation diagnosed both cerebral arteriosclerosis and chronic alcoholism. (Denton, A–121 at 28–29.) Because of the diagnosis of cerebral arteriosclerosis, Dr. Denton suggested that it is unlikely that alcoholism is the primary cause of the dementia in Patient No. 16. (*Id.* at 29.)

Although in the practice of medicine it is expected that a physician may be called upon to treat patients with concomitant illnesses, in clinical drug trials it is necessary to exclude patients with any concomitant conditions that may confound the results of the study. Aside from the fact that Dr. Denton offers no facts to support his position regarding Patient No. 16, I conclude that, at the very least, alcoholism was a confounding factor with this patient. It is clear that Patient No. 16 should have been excluded, as should the other four patients (Nos. 22, 32, 54, and 63) who also had alcoholism.

iii. *Severe diabetes.* The Center next argues that three subjects—Patient Nos. 23, 29, and 32—had severe diabetes, a basis for exclusion under the protocol. (Mohs, G–62 at 9; Thal, G–63 at 6; Leber, G–64 at 13; Denton, A–121 at 32, 80; A–126 at 21.)

AHP takes issue with only the exclusion of Patient No. 32. (AHP Post-Hearing Brief at 92; AHP Exceptions at 130.) AHP argues that it was not necessary to exclude Patient No. 32 because this patient's diabetes was not severe enough to be insulin dependent. (AHP Exceptions at 130; Denton, A–121 at 32.) I find AHP's arguments with regard to this patient to be moot, since AHP has already conceded that Patient No. 32 should be excluded for alcoholism. (See section I.D.1.c.(2). of this document.)

iv. *Severe diseases, Parkinson's disease, psychiatric illness, and other diseases.* The Center argues that three other patients—Nos. 20, 31 and 59—had severe, chronic infections, which was a basis for exclusion under the protocol. (Center Post-Hearing Brief at 56–57; see G–28.8 at 315–16.) The Center first argues that Patient No. 20 should have been excluded because this patient had active pulmonary tuberculosis. (Center

Exceptions at 7–8, citing Mohs, G–62 at 9; Leber, G–64 at 11–12.) Regarding Patient No. 20, Dr. Leber, a Center witness, testified that ''(a)dequate treatment of his condition rather than treatment with Cyclospasmol® may easily have accounted for the patient's 3.0 improvement on Item 19 of the SCAG.'' (Leber, G–64 at 15.)

AHP argues that the diagnosis of severe pulmonary tuberculosis was incorrect for Patient No. 20, and cites to the testimony of Dr. Denton, an AHP witness, who undertook a post-study review of records for the Rao study. (AHP Reply to Center Exceptions at B–6, citing Denton, Tr. Vol. VII at 28–33; AHP Post-Hearing Brief at 91.) In his testimony, Dr. Denton agreed that the patient records showed that Patient No. 20 was treated with anti-tuberculous drugs (see G–14.6 at 77), and further agreed that the records reflect that this patient was diagnosed during the study as having pulmonary tuberculosis with chronic brain syndrome (see G–14.6 at 53, 55), but nevertheless disputes the diagnosis. Dr. Denton based his challenge to the diagnosis on the absence in the patient records of the actual X-ray report and the absence of the sputum examination. (Denton, Tr. Vol. VII at 30.)

I am not persuaded by Dr. Denton's testimony on this point. I find that there is sufficient evidence in Patient No. 20's records to support a conclusion that this patient did have severe pulmonary tuberculosis. There are several notations in this patients' records which state that this patient had pulmonary tuberculosis. (See, e.g., G–14.6 at 53, 55.) Under the protocol, this patient appropriately should have been excluded.

The Center also argues that Patient Nos. 31 and 59 should have been excluded because these patients had severe, chronic infections. (Center Post-Hearing Brief at Attachment A, citing Thal, G–63 at 6.) However, the Center does not identify the types of chronic infections which these two patients were said to have had. I reviewed the extant patient records, but these records were not always legible and I was unable to determine what type of infections these patients had. Therefore, in absence of more specific evidence, I rule that Patient Nos. 31 and 59 should not be excluded.

The Center further argues that two subjects, Patient Nos. 56 and 63, had Parkinson's disease. (Thal, G–63 at 6–7; Leber, G–64 at 14.) AHP concedes that both of these patients should be excluded, and I accept AHP's concession on this matter. (AHP Exceptions at 130; Denton, A–121 at 29, 35, 84–85.)

The Center also argues that Patient No. 9 should have been excluded because this patient had a major psychiatric illness, i.e., hysterical personality. (Leber, G–64 at Attachment B, p.2.) AHP similarly concedes that this patient should have been excluded, and I also accept this concession. (Denton, A–121 at 33, 75.)

The Center next argues that Patient No. 32 had grand mal epilepsy and should have been excluded for this reason. (G–14.7 at 9; A–126 at 21; Denton, Tr. Vol. VII at 20–21.) I need not reach the merits of this argument because AHP has already conceded that Patient No. 32 should be excluded for alcoholism. (See section I.D.1.c.(2). of this document.)

d. *Concomitant Medications.* AHP further argues that the ALJ erred in ruling that the widespread administration of concomitant medications precluded any meaningful analysis of the effects of Cyclospasmol® in the Rao study. (AHP Exceptions at 132, citing I.D. at 37, 42, 56.) In support of its argument, AHP cites to a previous Commissioner's Decision pertaining to the human drug, Oral Proteolytic Enzymes (OPE), in which it was ruled that a study may be used to demonstrate efficacy ''if the identity, quantity, strength, frequency, and length of administration of the concomitant medication is known and if the confounding effect of the concomitant medication has been analyzed so that the effect of the test drug can be determined.'' (Commissioner's Decision on OPE, slip op. at 52–53 (footnote omitted).) AHP argues that under the OPE decision, the ALJ failed to analyze sufficiently whether the concomitant medications had any effect on the study results.

In the Commissioner's OPE decision, it was noted that ''(t)he uncontrolled use of concomitant medication violates several of the most basic scientific principles governing clinical investigations.'' (Commissioner's Decision on OPE, slip op. at 47.) Three such scientific principles, all of which have been incorporated into FDA regulations, were cited by the Commissioner's Decision on OPE.

The first of these principles, as articulated in the regulations, requires that ''(t)he 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 * * * use of drugs or therapy other than the test drug.'' (§ 314.126(b)(4) (At the time of the Commissioner's Decision on OPE, the citation for the comparable regulation was 21 CFR 314.111(a)(5)(ii)(a)(2)(iii)).) The objective of this requirement is to limit, before the study has begun, the extraneous factors which could be responsible for a difference between groups. (Commissioner's Decision on OPE, slip op. at 47–48.) If the assignment of patients is biased, this can skew the study's results.

The second relevant principle, also incorporated into agency regulations, is a requirement that ''(t)he study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect.'' (§ 314.126(b)(2) (The comparable numbered section of the regulations at the time of the Commissioner's Decision on OPE was § 314.111(a)(5)(ii)(a)(4)).) The use of concomitant medication can make it impossible to state with accuracy whether the results of a study were due to the test drug under study or were due to the use of concomitant medication. (Commissioner's Decision on OPE, slip op. at 48–50.)

Thirdly, the Commissioner's Decision on OPE ruled that concomitant medication use must be sufficiently documented so that a scientific evaluation of the use of concomitant medication can be done. (Commissioner's Decision on OPE, slip op. at 50–53.) If a study lacks sufficient documentation of concomitant medication use, the study cannot be considered as part of the basis for approval of effectiveness claims. (Id.) This requirement is expressed in the regulatory requirement that the report of a study ''provide sufficient details of study design, conduct, and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present.'' (§ 314.126(a) (The comparable numbered section of the regulations at the time of the Commissioner's Decision on OPE was 21 CFR 314.200(d)(2)).)

Regarding the review of concomitant medication, I note that the Commissioner's Decision on OPE further states that the use of concomitant medication must be considered as ''a fatal flaw'' in the absence of detailed records which would permit evaluation of the effect of the concomitant medication on the results of the study. (Commissioner's Decision on OPE, slip op. at 52.) The burden is on the proponent of the drug to supply detailed records demonstrating the effects of the concomitant medication on the results of the study. (Commissioner's Decision on OPE, slip op. at 134, 144, 203–04.)

As for the Rao study, I have reviewed the ALJ's decision, and I find that the ALJ considered each instance of concomitant medication use. (See I.D. at A–1 to A–5.) Contrary to AHP's claim, the ALJ did not base his decision solely upon the number of patients who were given concomitant medication. As was observed in the Commissioner's OPE decision, ''the use of more than one concomitant medication increases the difficulty of the evaluation of the (study drug's) effect.'' (Commissioner's Decision on OPE, slip op. at 56 (footnote omitted).) While the number of patients given concomitant medication was one factor which properly was considered by the ALJ (Commissioner's Decision on OPE, slip op. at 57), a review of the ALJ's complete decision reveals that the ALJ also considered the identity, quantity, strength, frequency, and length of administration of the various concomitant medications. (See I.D. at A–1 to A–5.) The ALJ took the cited portion of the Commissioner's Decision on OPE into consideration when the ALJ ruled that the concomitant medications ''were so numerous and so pervasive in the Rao study as to preclude any meaningful analysis of the test drug.'' (I.D. at 37.)

AHP also made arguments regarding the individual patients' concomitant drug use. (AHP Post-Hearing Brief at 96–99.) The Center, based upon a review of the hospital records, identified 16 different concomitant medications used by 21 patients in the Rao study,[5] including Patient No. 1 (Valium, Compazine), Patient No. 2 (Mellaril), Patient No. 6 (Valium), Patient No. 9 (Haldol, Benadryl), Patient No. 10 (Valium), Patient No. 14 (Valium), Patient No. 17 (Valium, Mellaril), Patient No. 22 (Mellaril), Patient No. 23 (Seconal), Patient No. 24 (Aldomet), Patient No. 28 (Hydergine), Patient No. 29 (Mellaril, Insulin, Doxepin), Patient No. 32 (Phenobarbital, Dilantin), Patient No. 36 (Haldol, Seconal, Meprobamate), Patient No. 42 (Seconal), Patient No. 43 (Seconal, Peritrate), Patient No. 45 (Mellaril, Peritrate), Patient No. 51 (Mellaril), Patient No. 56 (Valium, Sinemet), Patient No. 57 (Compazine), and Patient No. 68 (Thorazine). The Center argued that the confounding effect of the concomitant medications used by these patients made the Rao study results unreliable. (Center Post-Hearing Brief at 65.)

I note, however, that of these 21 patients, AHP has already conceded that 9 patients (Patient Nos. 9, 22, 23, 29, 32, 36, 43, 56, 68) should be excluded for violations of the inclusion/exclusion criteria. (See section I.D.1.c. of this document.) Additionally, Dr. Denton, a witness for AHP, conceded that Patient No. 36 should be excluded because this patient was taking the concomitant medication, Seconal, a psychoactive drug, and Haldol, a major tranquilizer, at the time of final evaluation. (Denton, A–121 at 81–82.) Remaining after these nine conceded exclusions are 12 patients who received 7 different drugs, including Patient No. 1 (Valium, Compazine), Patient No. 2 (Mellaril), Patient No. 6 (Valium), Patient No. 10 (Valium), Patient No. 14 (Valium), Patient No. 17 (Valium, Mellaril), Patient No. 24 (Aldomet), Patient No. 28 (Hydergine), Patient No. 42 (Seconal), Patient No. 45 (Mellaril, Peritrate), Patient No. 51 (Mellaril), and Patient No. 57 (Compazine). I will address the issues concerning these remaining, contested exclusions.

However, before I address the specific records for each patient, I will make some general observations regarding all the patient records in evidence from the Rao study. First, it must be noted that the contents and status of the patient records in evidence is not consistent from patient to patient. Most records appear to contain only excerpts from the original records. Some records include numerous pages from the physician order sheets, medication records, nursing care record sheets, and patient progress notes. (See, e.g., Patient No. 24, G–14.6 at 175–209.) Other patient records contain only a single page. (See, e.g., Patient No. 18, G–14.6 at 30.) Then again, other records contain a few pages of various sections from the original patient records. (See, e.g., Patient No. 2, G–14.5 at 51–62.)

In addition to the difficulty presented by the inconsistent content of the patient records, another problem is legibility of records. In some instances, although records are in evidence, portions of those records are printed so faintly as to be illegible. (See, e.g, Patient No. 1, G–14.5 at 32, 34, 39, 41; Patient No. 42, G–14. 7 at 245–264; Patient No. 45, G–14.7 at 320.)

Another problem I have found with the records in evidence is the difficulty in identifying the dates on which the patient was evaluated during the study. The protocol provided that ''(e)ach patient will be observed four (4) times. These observations will be made at the initial evaluation and at weeks 4, 8, 12.'' (G- 14.2 at 241.) The dates of these evaluations are important to a review of concomitant medication use because the protocol also provided that ''no major tranquilizer should be administered within the four (4) days immediately proceeding (sic) any evaluation.'' (G–14.2 at 243.)

In reviewing the patient records, I noted that, despite the requirements of the protocol, in a number of patient records the dates on which the patient received the study drug and the dates of the patient evaluations are not consistent with the specifications of the protocol. For example, in the physician order sheets and in the medication records for Patient No. 1, evidence indicates that this patient began to receive the study drug on December 17, 1975, and continued to receive this drug until March 19, 1976. (G–14.5 at 13–16, 21, 23, 25, 27.) However, other documents in evidence indicate that this patient was initially evaluated on January 14, 1976, 1 month after the patient began to receive the study drug. (G–14.5 at 10.) Additional documents in evidence also point to a delayed evaluation occurring in January. For example, one document lists a date of February 25, 1976, and states, ''Mental Status: Second evaluation during the fourth week.'' (G–14.5 at 9.) Another document lists the date of May 11, 1976, as the date of the third evaluation. (G–14.5 at 8.)

It is difficult to fathom why the initial evaluation would have occurred a month after the study had begun, but the dates in the records of a number of other patients clearly support this conclusion. (See also Patient No. 6, G–14.5 at 153, 154; Patient No. 17, G–14.6 at 14, 18.) I further noted that this 1 month difference in dates is not found consistently in all patient records. (See, e.g., Patient No. 57, G–14.8 at 132, 135 (initial evaluation and start of study drug occurred on same date.)) Of course, an initial evaluation that occurred 1 month after the start of the study drug would be a protocol violation and would not be the proper procedures for an adequate and well-controlled study. An initial evaluation of the patient should be taken before the patient has been randomized in the study.

I also noted that while most patient records in evidence contained a page from a psychological evaluation which was captioned at the top ''Final Evaluation,'' I found that the date of this evaluation in many instances appeared to be from the middle of the study, often closer to week 8 than to the actual time of final evaluation at week 12. (See, e.g.,

[5] The Center also argues that Patient No. 2 in the Rao study should be excluded because this patient had been given Elavil, which was a violation of the protocol. The Center further argues that Patient No. 24 had received Serax, and Patient No. 34 had received Phenergan in violation of the protocol. However, my review of the records reveals that it was Patient Nos. 2, 24, and 34 in the Yesavage study, not the Rao study, who had taken these drugs. Accordingly, these issues will be addressed in the discussion of the Yesavage study.

Patient No. 25, G–14.6 at 210–213; Patient No. 26, G–14.6 at 234–237.) However, not all patient records follow this pattern. In some cases, the date on the ''Final Evaluation'' document does appear to have occurred 12 weeks after the patient started on the study drug. (See, e.g., Patient No. 45, G–14.7 at 310, 312.) Therefore, I did not find the date on the document entitled ''Final Evaluation'' to be a reliable means of establishing the dates of the patients' final evaluations in many instances.

Also, I have found several records in which the physician order sheets or medication records indicate that the patient had been receiving the test drug for a month before the recorded date of the patient's initial evaluation. (See, e.g., Patient No. 1, G–14.5 at 10, 13; Patient No. 3, G–14.5 at 68, 73; Patient No. 26, G–14.6 at 235, 239.)

Nevertheless, despite these flaws I have given the patient records full consideration. These records were closely scrutinized for pertinent dates and schedules of relevant medication use. However, AHP, as sponsor of these studies, bears the responsibility of providing adequate records for review. For this reason, any failure of the records to document concomitant medication use can be weighed against finding the Rao study adequate. (Commissioner's Decision on OPE, slip op. at 50–53.) With this as background, I turn now to the specifics of each use of concomitant medication now at issue.

The Rao protocol's requirements regarding concomitant medications were as follows:

> No vasodilating agents, psychoactive drugs, narcotics, reserpine derivatives or steroids other than estrogen will be permitted during the study, except for an h.s. (*hora somni,* i.e., at bedtime) hypnotic, which may be either Noludar or chloral hydrate, or an occasional dose of a major tranquilizer (phenothiazines, haloperidol, etc.) deemed necessary for the patient's welfare. However, any patient who receives more than sixteen (16) doses of a major tranquilizer during the entire course of the study, or more than three (3) doses in any one week, will be dropped from the study. Also, no major tranquilizer should be administered during the four (4) days immediately proceeding (sic) any evaluation. Other routine drugs (e.g. digitalis, diuretics, oral hypoglycemics, non-narcotic analgesics, antibiotics, etc.) required by the patient may be administered, but every effort should be made to maintain a consistent dosage schedule. Patients who have been receiving agents not permitted during the study should have them discontinued 21 days prior to entry.

(G–28.8 at 318.)

Regarding the use of concomitant medication, the Center first argues that Patient No. 1 should be excluded because this patient received both Valium and Compazine during the course of the study. (Center Post-Hearing Brief at 64 and Attachment B; G–14.5 at 20–28; Thal, G–63 at 7.) Valium, a benzodiazepine, is a psychoactive drug, given to reduce anxiety; this drug can cause drowsiness, and affect attention and alertness. (Leber, G–64 at 14; Zung, Tr. Vol. III at 38; Denton, Tr. Vol. VII at 25–26.) Compazine, also a psychoactive drug, may impair mental and physical abilities. (Denton, Tr. Vol. VII at 39.)

The frequency of administration of Valium given to Patient No. 1 is particularly troubling. According to the testimony of Dr. Denton, this patient was given 23 doses of Valium during the study. (Denton, A–121 at 72; see also G–14.5 at 20–28; I.D. at A–1.) Specifically, this patient received Valium 11 times between December 18 to December 23, 1975, 5 times between January 24 to January 31, 1976, 8 times between February 14 to February 22, 1976, and 4 times between March 2 to March 5, 1976. (Denton, A–121 at 72; I.D. at A–2; G–14.5 at 13–49.) In addition, at least 5 doses of Valium were given during the prestudy washout period. (I.D. at A–2; G–14.5 at 13–28.) Moreover, the time of administration of the Valium is not always clearly indicated in the record. This is a clear violation of the protocol, which provided that no psychoactive drugs, except for a bedtime dose of Noludar or chloral hydrate, were permitted. (G–28.8 at 318.) Accordingly, I am in agreement with the ALJ in finding that this is no mere technical violation of the protocol, and that Patient No. 1 should be excluded.

The Center also argues that Patient No. 6 should be excluded for receiving Valium during the study. (Center Post-Hearing Brief at 64 & Attachment B.) The ALJ ruled that this patient should have been excluded because medication records appeared to indicate that this patient had received Valium throughout the course of the study. (I.D. at A–1.) The ALJ cited to the fact that the copy of the medication records in evidence shows a line drawn across all dates in the chart entry for Valium. (I.D. at A–1, citing G–14.5 at 154.) AHP challenges the ALJ's interpretation of the medication records, arguing that the referenced markings on Patient No. 6's chart do not support a finding that the patient was given Valium on those days. (AHP Post-Hearing Brief at 97.)

I have reviewed the cited portion of the medication records for Patient No. 6, and I find that the medication chart in question does show an arrow drawn across all dates in the chart. (G–14.5 at 154.) There are also notations in the margins next to this Valium entry which read, ''Start 12/31,'' ''Valium 10 mg. 'IM' daily,'' ''q 8°,'' and ''Stop 3/19,'' or it may be ''Stop 5/19,'' the writing is not clear. (G–14.5 at 154.) However, my interpretation of this entry is that this particular chart was begun on December 31, and the arrow across the chart was intended to delete the earlier days in the month of December, and was not meant to reflect dosages on those earlier dates. Therefore, I find that the ALJ was in error in his interpretation of this particular chart.

Notwithstanding my ruling with regard to the previously mentioned chart, I find that other records in evidence do support a finding that Patient No. 6 was receiving regular doses of Valium at later dates throughout the study. Aside from the aforementioned chart entries, there are several other chart entries which state that 10 mg of Valium was to be given intramuscularly every 8 hours, commencing on December 31, 1975, and running through March 9, 1976. (G–14.5 at 154, 155, 156, 157.) During this same time, Patient No. 6 was receiving the study drug. (G–14.5 at 154, 155, 156, 157.) The extent of Valium administration was a clear violation of the protocol's general prohibition on the use of psychoactive drugs except for bedtime doses of Noludar or chloral hydrate. (G–28.8 at 318.) Therefore, I affirm the ALJ's ruling in excluding Patient No. 6.

As for Patient No. 17, the physician order sheet states that Patient No. 17 was to receive chloral hydrate PRN (*pro re nata*, as occasion arises) during the study (G–14.6 at 19, 21), and evidence indicates that the patient received this drug on several occasions. (Mohs, G–62 at 9–10.) I note, however, that chloral hydrate at bedtime was permitted under the protocol, and I do not find this to be a basis for excluding this patient. (G–28.8 at 318.)

The Center also argues that Patient No. 17 received both Valium and Mellaril on several occasions, and that this is a basis for excluding this patient. (Center Post-Hearing Brief at Attachment B; Mohs, G–62 at 9–10.) As previously discussed, Valium is a psychoactive drug. The use of psychoactive drugs was generally prohibited except for bedtime doses of Noludar or chloral hydrate. (G–28.8 at 318.) Mellaril, on the other hand, would fall under the category of a major tranquilizer under the protocol, of which occasional doses were permitted if necessary for the patient's welfare. (G–28.8 at 318.)

I have reviewed the extant charts for Patient No. 17, and I have found that the

physician order sheets contain a notation, dated December 18, 1975, to run through February 18, 1976, which reads, ''Valium 10 mg I.M. (intramuscularly) PRN.'' (G–14.6 at 17.) Another entry in the physician order sheets, dated February 18, 1976, directed that the Valium order be continued through April 19, 1976. (G–14.6 at 20.) Entries on the nursing care records, which are illegible in sections, indicate that Patient No. 17 received 10 mg of Valium intramuscularly on at least five occasions. (G–14.6 at 23–25.) The record indicates administration of Valium on December 16 and 21, 1975, and on January 1, January 9, and January 14, 1976. It also appears from the record that this patient began receiving the study drug on December 19, 1975. (G–14.6 at 18.)

The physician order sheets further show that on December 18, 1975, orders were given for Patient No. 17 to receive 25 mg of Mellaril, an antipsychotic drug, ''t.i.d.'' (*ter in die*, three times a day), beginning during the final 2 days of the washout period. (G–14.6 at 17; see also Leber, G–64 at 11; Mohs, G–62 at 9–10.) However, another chart entry, dated December 19, 1975, ordered the Mellaril discontinued. (G–14.6 at 18.) The nursing care records do not record the administration of Mellaril.

With regard to the dates of evaluation of Patient No. 17, I note that there are significant inconsistencies in this patient's records. While the physician's order sheets indicate that Patient No. 17 was started on the study drug on December 19, 1975 (G–14.6 at 18), another document in the record indicates that this patient's initial evaluation occurred on January 19, 1976 (G–14.6 at 14), 1 month after the patient had been on the study drug. This January date for the initial evaluation is consistent with another record entry, which lists the date for the ''(s)econd evaluation during the fourth week'' as being on February 25, 1976. (G–14.6 at 13.) But in apparent contradiction to the January date, yet another record item, this one found in the patient progress notes, dated January 23, 1976, states that the patient ''is on vasodilator drug Cyclospasmol® for another month.'' (G–14.6 at 15.) This would place this patient's initial evaluation at sometime in November 1975, and final evaluation in February 1976.

These inconsistencies, along with the illegibilities and obvious incompleteness of the record (there are large gaps of at least two months duration between dates in the patient progress records), make the records of Patient No. 17 inadequate for proper review. Therefore, I find that this patient should be excluded. (Commissioner's Decision on OPE, slip op. at 50–53.)

Regarding Patient No. 24, Dr. Paul Leber, a witness for the Center, testified that there were several interruptions in treatment with Cyclospasmol® between the dates of February 18, and February 22, 1976, during the study. (Leber, G–64 at 12.) I have reviewed the physician's order sheet for this patient, and I have found that the records do show that Cyclospasmol® was discontinued on February 18, but was started again on February 22, 1976. (G–14.6 at 182, 183.) I note Patient No. 24's records indicate that this patient's initial evaluation was on January 26, 1976, and the patient's final evaluation was on May 7, 1976. (G–14.6 at 175, 177.) In view of the brevity of the interruption, and the fact that it did not occur close to the time of either the initial or the final evaluation, I do not find this a basis to exclude Patient No. 24.

Dr. Leber also testified that Patient No. 24 received Aldomet, an antihypertensive medication which can affect mood and cognition. (Leber, G–64 at 13.) Dr. Leber testified that ''the protocol (was) unclear as to whether such patients could or could not have been admitted, but discontinuation of this medication (Aldomet) might affect a patient's mental status.'' (Leber, G–64 at 13.)

In considering the administration of Aldomet to Patient No. 24, I note that the protocol provided that ''routine drugs (e.g., digitalis, diuretics, oral hypoglycemics, non-narcotic analgesics, antibiotics, etc.) required by the patient may be administered, but every effort should be made to maintain a consistent dosage schedule.'' (G–14.2 at 243.) I would place Aldomet in the category of routine drugs for the purposes of the Rao study. As for the schedule of administration of Aldomet to Patient No. 24, the physician's order sheets indicate that this patient was receiving 250 mg of Aldomet four times a day from November 14, 1975 (G–14.6 at 186), until February 16, 1976. (G–14.6 at 184.) As I previously noted, this patient's initial evaluation was on January 26, 1976, and the final evaluation was on May 7, 1976. (G–14.6 at 175, 177.) Thus, this patient was receiving Aldomet throughout the washout period and continuing through several weeks of the study.

Having considered Patient No. 24's use of Aldomet, I find that this is not a basis to exclude this patient. At the time of initial evaluation, this patient was well-established on the regimen of Aldomet, which could mean that any initial drowsiness which the patient might have experienced may have passed. As for the withdrawal of Aldomet during the study, I do not find the evidence of any negative effects on the patient to be sufficient to exclude this patient. Therefore, I uphold the ALJ's decision to include Patient No. 24 in the Rao study. (I.D. at A–2.)

The Center next argues that Patient No. 28 should be excluded for receiving Hydergine during the study. (Center Post- Hearing Brief at 64 & Attachment B.) Evidence indicates that this patient received Hydergine three times a day during the first week of the study. (Denton, A–121 at 80; Thal, G–63 at 7; G–14.6 at 261–62.) Regarding the effect of this drug, Dr. Denton testified, ''Hydergine is an agent which helps to relieve some of the cognitive aspects of dementia through an unknown mechanism of action.'' (Denton, A–121 at 39; see also Zung, Tr. Vol. III at 64.) However, Dr. Denton suggested that Patient No. 28 did not have to be excluded because Hydergine was administered during the first week of the study in December 1975, and this should not have affected the final evaluation made in March 1976. (Denton, A–121 at 40.)

I have reviewed the records in evidence for Patient No. 28, and I found that the physician order sheets indicate that this patient was receiving Hydergine for at least two months prior to the start of the Rao study. (G–14.6 at 261, 262, 265.) To the extent that Hydergine is effective, then Patient No. 28's baseline might have been higher than it would have been otherwise. The withdrawal of Hydergine could have caused a worsening in the patient's condition over the course of the 12-week study. I therefore find that the possible confounding effect of Hydergine must be considered, and that for this reason, Patient No. 28 should be excluded.

Regarding Patient No. 42, Dr. Denton testified that this patient received Seconal at bedtime during the final week of the study, from March 27 to April 2, 1976. (Denton, A–121 at 82.) As Dr. Denton acknowledged, Seconal is a psychoactive medication, and, as such, its use was generally prohibited under the protocol. (Denton, A–121 at 81 (discussing Patient No. 36); G–28.8 at 318.) Nevertheless, Dr. Denton takes the position that this is not a reason to exclude Patient No. 42, notwithstanding the fact that the medication was given at the time of final evaluation. (Denton, A–121 at 82.)

First, I note that this patient's use of Seconal does not appear to be documented in the patient records in evidence; however, I also note that

many of this patient's records are not legible. (G–14.7 at 219–264.) The question of documentation was not raised by the Center; rather, the Center's arguments are based on the violation of the concomitant medication restrictions in the protocol.

Because the averred level of use of Seconal was that of a bedtime hypnotic, I find that, while Patient No. 42's concomitant medication use violated the protocol's general prohibition on psychoactive drugs except for bedtime doses of Noludar or chloral hydrate (G–28.8 at 318), this level of use is not cause for excluding Patient No. 42. Nevertheless, I note that AHP's failure to provide documentation for the administration of Seconal can be considered as a flaw in the Rao study and can be weighed in evaluating the adequacy of this study. (Commissioner's Decision on OPE, slip op. at slip op. at 52–53.) Additionally, the fact of this protocol violation can also be considered in evaluating this study.

Regarding Patient No. 45, evidence indicated that this patient received 20 mg of Peritrate, a vasodilator, twice a day during the study, from March 23 to March 31, 1976. (G–14.7 at 314; Denton, A–121 at 39, 82–83; Mohs, G–62 at 11.) Patient No. 45's records do not indicate the date of initial evaluation, but, from an entry on the physician's order sheet, it appears that this patient had been receiving the study drug since January 5, 1976. (G–14.7 at 312.) Another entry in this patient's progress notes states that, as of March 7, 1976, this patient had been on Cyclospasmol® for 2 months, which would be consistent with an initial date of January 5, 1976. (G–14.7 at 318.) Final evaluation of this patient apparently was on April 8, 1976. (G–14.7 at 310.) Evidence also indicates that Patient No. 45 was receiving an unspecified level of Mellaril during the washout period. (Denton, A–121 at 83.) The Center argues that because of these concomitant medications, Patient No. 45 should be excluded. (Center's Post-Hearing Brief at 64.)

In Dr. Denton's written review of Patient No. 45, Dr. Denton wrote that Mellaril was given prior to the study, but was discontinued on December 26, 1975, about 10 days before the study drug was started. (Denton, A–121 at 83.) Regarding the Peritrate, Dr. Denton concluded that the use of this drug for a period of one week was ''irrelevant.'' (Denton, A–121 at 83.)

I have reviewed the records in evidence for Patient No. 45, but these records, which are illegible in parts, do not appear to contain the chart of administration of Mellaril. (See G–14.7 at 310–333.) While the absence of complete records can be considered a ''fatal flaw'' for the adequacy of a study (Commissioner's Decision on OPE, slip op. at 52–53), nevertheless, because the issue is the washout period, in this instance I will accept Dr. Denton's testimony regarding the administration of Mellaril. Specifically, I will accept that Mellaril was discontinued 10 days prior to the commencement of the Rao study. I find that this is probably sufficient for the purposes of including this patient in the study, although the protocol required a 21-day washout period. (See G–14.2 at 243.)

Notwithstanding my finding regarding the inclusion of Patient No. 45 despite this patient's use of Mellaril, I note both the violation of the protocol's 21-day washout period, and the incompleteness of the records regarding Patient No. 45's use of Mellaril can be considered in evaluating the adequacy of the Rao study.

As for the administration of Peritrate to Patient No. 45, I note that the administration of this vasodilating agent was a violation of specific prohibitions of the protocol against the use of vasodilating agents other than Cyclospasmol®. (G–28.8 at 318.) However, because Peritrate was not administered near the time of either the initial evaluation, on January 5, or the final evaluation, on April 8, I will accept Dr. Denton's estimation that this level of Peritrate was not a basis to exclude this patient, although I do not accept his characterization of the use of this drug as ''irrelevant.'' Therefore, I find that this patient could be included in the analysis of the Rao study. Nevertheless, this is a clear protocol violation, and the possible confounding effect of Peritrate should be weighed in reviewing the adequacy of the Rao study.

Regarding Patient No. 57, Dr. Denton testified that this patient received Compazine for 2 days during the course of the study. (Denton, A–121 at 84.) However, I have reviewed the records for this patient, and I found that the physician's order sheet indicates that Compazine, 10 mg PRN, was ordered on January 30, 1976, with the order running through February 20, 1976. (G–14.8 at 135.) A second order to discontinue the Compazine was entered on February 20, 1976. (G–14.8 at 136.) There were no medication records tracking actual administration of Compazine. I note that this patient's initial evaluation was on January 30 (G–14.8 at 132), and the patient's final evaluation was on May 11, 1976. (G–14.8 at 131.)

The Center's argument pertaining to Patient No. 57's concomitant medication use is based on Dr. Denton's testimony that this patient received Compazine twice during the study. Because this was the focus of the Center's argument, I will address my ruling to the Center's argument, rather than considering the standing order for Compazine reflected in the patient's records. On this basis, I do not find that Patient No. 57 needed to be excluded.

Notwithstanding my ruling regarding Patient No. 57's receiving Compazine, I nevertheless note that AHP's failure to provide documentation of the administration of Compazine can be considered as a flaw in the Rao study. (Commissioner's Decision on OPE, slip op. at 52–53.) While Dr. Denton testified that Compazine was only administered twice, the physician's order sheets for this patient suggest that this drug might have been administered more frequently. Because of the absence of adequate records, this patient's concomitant medication use can not be fully reviewed, and this fact can be considered in weighing the adequacy of this study.

The Center also argues that several patients were in violation of the protocol's 21-day, prestudy washout requirement. (Center Post-Hearing Brief at Attachment B.) It is alleged that a number of patients received major tranquilizers during the washout period. However, before I review the records of each of the patients which the Center cites, I note that administration of occasional doses of a major tranquilizer during the study were permitted by the protocol. (G–28.8 at 318). Because occasional doses were permitted during the study, by extension, I find that occasional administration of a major tranquilizer might be said to have been permitted during the prestudy washout period. However, I also find that the same restrictions on the level of the dose and the timing of administration, i.e., not within 4 days of an evaluation, would still apply during the washout period.

Turning now to the Center's arguments, first, the Center argues that Patient No. 2 received Mellaril during the washout period. (Denton, A–121 at 72–74.) The problem with assessing Patient No. 2's use of Mellaril is that this patient's records reveal only that Mellaril, dose unspecified, was discontinued at the same time that Cyclospasmol® was begun. (G–14.5 at 55.) The record of Mellaril use during the washout period is not included in the evidentiary record.

Dr. Leber, a witness for the Center, had testified regarding the effects of Mellaril. Dr. Leber testified that Mellaril, an anticholinergic,

antipsychotic drug, has a great potential to adversely affect cognition, learning, and memory. (Leber, Tr. Vol. I at 68–69.) Patients who are receiving Mellaril can have their cognitive performance appear worse than it actually would have been, absent Mellaril. When the patient is withdrawn from Mellaril, the patient's cognitive performance may improve due to the withdrawal of Mellaril. (Leber, Tr. Vol. I at 69.) Moreover, Mellaril is a drug with a ''very long half-life.'' (Leber, Tr. Vol. I at 70.) That is to say, it can accumulate in the body. (Leber, Tr. Vol. I at 70.)

As for the administration of Mellaril to Patient No. 2, I find this to be an apparent violation of the protocol's restriction against giving a patient a major tranquilizer within 4 days of an evaluation, in this instance the initial evaluation. (G–28.8 at 318.) I use the word ''apparent,'' since the necessary records of Mellaril use are not in evidence. However, as was held in the Commissioner's Decision on OPE, the use of concomitant medication can be considered as ''a fatal flaw'' in the absence of detailed records which would permit evaluation of the effect of the concomitant medication on the results of the study. (Commissioner's Decision on OPE, slip op. at 52–53.) Without the necessary records regarding Patient No. 2, I find that this patient should have been excluded from the Rao study.

The Center next argues that Patient No. 51 also received Mellaril during the washout period. (Center Post-Hearing Brief at Attachment B.) I have reviewed this patient's medication charts, and I have found that these records indicate that this patient received Mellaril, 25 mg four times a day, from December 4, 1975, to January 31, 1976, a time period which included the entire washout period. (G–14.8 at 40, 41.) This patient began receiving the study drug on January 30, 1976. (G–14.8 at 40; Leber, G–64 at 14.) Dr. Denton, in his review of this patient's records, wrote, ''There is no practical necessity of the 3 week washout, when the final evaluation is done 3 months after the start of the study.'' (Denton, A–121 at 83.) Dr. Denton, however, did not address himself to the fact that the initial evaluation of this patient may have been affected by the frequent and regular use of Mellaril.

The level of Mellaril used by Patient No. 51 was a violation of two provisions of the protocol. Specifically, this patient received more than three doses of a major tranquilizer in 1 week, and received a major tranquilizer within 4 days of initial evaluation. (G–28.8 at 318.) In fact, records support a finding that Mellaril was administered four times a day even on the day of initial evaluation. I find this level of Mellaril use by Patient No. 51 at the time of initial evaluation to be a basis for excluding this patient from the study.

Patient No. 10 received Valium during the washout period. (Denton, A–121 at 75.) In my review of this patient's records, I found that the physician order sheets contained a notation which read, ''Valium 5 mg at 8 PM,'' with the further notation that the medication was to start on December 11, 1975, and continue until January 19, 1976. (G–14.5 at 233.) However, a later notation indicated that Valium was discontinued on December 23, 1975, two weeks after it had been initiated. (G–14.5 at 234.) This patient had begun to receive the study drug on December 18, 1975. (G–14.5 at 233.) The administration of Valium to this patient violated the protocol's general prohibition against the use of psychoactive drugs except for bedtime use of Noludar or chloral hydrate. (G–28.8 at 318.) However, I do not find this level of use of Valium to be cause to exclude this patient. Nevertheless, I note the fact that this protocol violation can be weighed in evaluating the adequacy of the Rao study.

Patient No. 14 received Valium, 2 mg twice a day, beginning on December 15, 1975. (G–14.5 at 334; Denton, A–121 at 77.) This patient started on the study drug on December 19, 1975; Valium was discontinued on December 23, 1975. (G–14.5 at 334.) As with the previously discussed patient, the administration of Valium to Patient No. 14 violated the protocol's general prohibition against the use of psychoactive drugs except for bedtime use of Noludar or chloral hydrate. (G–28.8 at 318.) Nevertheless, I do not find this level of use of Valium to be cause to exclude this patient, but I note the fact of this protocol violation can be weighed in evaluating the adequacy of the Rao study.

Also cited by the Center for receiving medications during the washout period, in addition to the Center's claims of concomitant medication use during the study by these particular patients, were Patients No. 22 for receiving Mellaril (Leber, G–64 at 12), Patient No. 29 for receiving both Doxepin, an antidepressant, and Mellaril (Leber, G–64 at 13), and Patient No. 56 for receiving Valium (Leber, G–64 at 14) during the washout period. I need not discuss these three patients because AHP has conceded that these patients should be excluded for violations of the inclusion/exclusion criteria. (See sections I.D.1.c.2. (regarding Patient No. 22), I.D.1.c.3. (regarding Patient No. 29), and I.D.1.c.4. (regarding Patient No. 56).)

In summary, the Center had alleged concomitant medication use in violation of the protocol by 21 of the 58 patients in the Rao study. Of these 21 patients, AHP has already conceded that 9 patients (Patient Nos. 9, 22, 23, 29, 32, 36, 43, 56, 68) should be excluded for violation of the inclusion/exclusion criteria. Additionally, it was conceded by Dr. Denton, AHP's witness reviewing the Rao study, that Patient No. 36 should be excluded for the concomitant use of Seconal at the time of final evaluation.

After these conceded exclusions, there remained 12 other patients cited by the Center for concomitant medication use, but whose exclusion AHP contests. Of these patients, I have found that Patient Nos. 1, 2, 6, 17, 28, and 51 should be excluded for concomitant medication use. I further find that Patient Nos. 10, 14, 42, 45 and 57 can be included, but that for the various reasons previously discussed, the inclusion of these patients can be weighed against problems with the records for these patients, and with the fact that protocol violations were found in connection with these patients. I note that even protocol violations which individually may not warrant rejection of a study can be considered in the aggregate in determining whether a study is adequate and well-controlled. (See Commissioner's Decision on Benylin, 44 FR 51512 at 51531.) Lastly, I find that Patient No. 24 can be included.

e. Case Report Forms. AHP further makes a general challenge to the ALJ's consideration of the lack of case report forms for 55 out of the 58 patients as another factor to be weighed in reviewing the adequacy of the Rao study. (AHP Exceptions at 137–39, citing I.D. at 40, 42.) AHP argues that the case report forms were not needed because hospital records (see G–14.5; G–14.6; G–14.7; G–14.8) and computer printouts (see G–11.2) regarding most of the patients were available. (AHP Exceptions at 139.)

The Center argues that the case report forms were needed for several reasons. (Center Response to AHP Exceptions at 53; Center Post-Hearing Brief at 60–62, 65–66, 68–74.) The Center argues that for most of the patients, there are no results for the neurological examination required by the protocol, the absence of which undermines any assurances by AHP that the patients did not have a neurological cause for their senility. (Center Post-Hearing Brief at 61–62.) Additionally, there were no hospital records available for two of the

patients—Nos. 7 and 48—included in the analysis. (Center Post-Hearing Brief at 65–66.) For these reasons, it was impossible to determine whether these patients were given concomitant medications to any extent. (Center Post-Hearing Brief at 65–66.)

Regarding the computer printouts, the Center argues that these documents are inadequate because they do not contain necessary information such as the results of the physical examination, the neurological examination, and the laboratory tests. (Center Post-Hearing Brief at 70–72.) Moreover, the Center argues that computer printouts are not an adequate supplement because the printouts do not record any of the subjects' medical histories, concomitant medication use, the SCAG evaluations for ten of the placebo patients, nor the identities of investigators who made each patient's SCAG evaluation. (*Id.* at 70–73.)

Dr. Mohs, a witness for the Center, explained the reasons for needing the case report forms as follows:

> (I)t makes it very difficult to evaluate the study when the original data forms are not available. It is difficult to determine how well the records were kept and whether or not there were errors made in taking the data from the original case report forms to the analysis system. In other words, it makes it impossible to verify whether the protocol was followed and whether the results, which were eventually reported in the published article, accurately reflect the data that were collected.

(Mohs, G–62 at 8.)

Similar testimony was given by Dr. Leber, a witness for the Center, who testified in part, ''The documentation supplied by the sponsor (makes) it impossible to determine whether or not certain requirements of the protocol were actually carried out.'' (Leber, G–64 at 16.)

The act requires that a new drug application include ''full reports of investigations'' which have been made to show whether such drug is effective in use. (21 U.S.C. 355(b)(1).) This statutory requirement was extensively discussed in the Commissioner's Decision on OPE. In that decision, it was noted that neither the statute nor agency regulations imposes a per se requirement that in every instance raw data be submitted in support of a new drug application. (Commissioner's Decision on OPE, slip op. at 66.) The Commissioner's decision on OPE went on to note that while raw data are not required in support of all NDAs, this does not mean, however, that the submission of raw data may never be required by the agency. The ''full reports'' requirement can be met without access to the raw data only when the report of the study: (1) Is published in the scientific literature, (2) is reliable, and (3) describes an adequate and well-controlled study. (Commissioner's Decision on OPE, slip op. at 67.)

Additionally, it should be noted that publication alone does not negate the necessity for raw data from a study to be supplied to the agency. Regarding published studies, the Commissioner's Decision on OPE ruled:

> (P)ublished studies can be considered reliable and can be accepted without supporting raw data *only if the reports of the studies contain details adequate to support a scientific determination that the study is an adequate and well-controlled clinical investigation*. The determination of whether the report is adequate (and raw data unneeded) is a discretionary determination made on the basis of the quality of the published data. Among the factors that determine whether a published report is sufficient are whether the protocol, the results, and the manner by which the study meets each of the requirements of (FDA regulations) are described in detail.

(Commissioner's Decision on OPE, slip op. at 70–71 (citations omitted, emphasis added).)

Turning now to the Rao study, I note that while the Rao study was published in the *Journal of the American Geriatrics Society*, the article, which was four pages in length, failed to provide any details regarding the patient selection process, and completely failed to discuss concomitant medication use, and further failed to discuss concomitant diseases or conditions which the patients had during the course of the study. (A–80 at 1–4.) The computer printouts which AHP cites are not sufficient to make up this deficit because the printouts do not contain information such as the results of the neurological examination required by the protocol, nor do the printouts identify which doctor performed which SCAG evaluation. (I.D. at 39.) The hospital records, which do not contain SCAG or NOSIE scores but which do contain information regarding concomitant medication use, are missing for two of the patients included in the analysis. (Center Post-Hearing Brief at 65.)

I find that Dr. Rao's published report fails to contain details adequate to support the scientific determination necessary to find that the Rao study is an adequate and well-controlled clinical investigation. Therefore, I find that the unavailability of the raw data was a matter properly considered by the ALJ. I conclude that the omission of the raw data can be weighed in determining whether the Rao study was adequate and well-controlled.

f. *Blinding and bias.* Regarding the matter of bias, the Center argues that Dr. Rao did not remain blinded throughout the clinical trial and for this reason was biased in his observations. (Center Post-Hearing Brief at 75; Center Response to AHP Exceptions at 53–54.) AHP argues that the evidence fails to support the Center's claims. (AHP Post-Hearing Brief at 99–104; AHP Exceptions at 142–47.) While the ALJ discussed the issues of bias and blinding in the Initial Decision, the ALJ made no ruling regarding this matter. (I.D. at 41–42, 43.)

Dr. Rao had died prior to the commencement of the administrative hearing, so there was no direct testimony from him on this point. The underlying basis for the Center's claims lies in the fact that of the 16 Cyclospasmol®-treated subjects assigned to Dr. Rao, Dr. Rao rated 10 of these subjects as ''markedly improved,'' whereas the three other investigators in the same study (Drs. Georgiev, Guzman and Paul), who together rated 16 Cyclospasmol®-treated subjects, only rated one subject as ''markedly improved.'' (Mohs, G–62 at 12–13; Thal, G–63 at 8, citing (G)-11.2 at 72–73 & (G)-14.2 at 254; Leber, G–64 at 18.) The Center argues that this disparity in ratings among the four evaluators indicates that adequate measures were not taken to minimize bias on the part of the observers and analysts of the data. (Center Response to AHP Exceptions at 53–54.)

In support of its argument on the blindness issue, the Center cites to the testimony of three of its witnesses—Drs. Leber, Thal, and Mohs. (Center Post-Hearing Brief at 75.) Each of these witnesses raised questions about the credibility of Dr. Rao's ratings as compared with that of the three other investigators in the Rao study.

On this issue, Dr. Leber, a witness for the Center, testified that there was ''a marked inconsistency between (Dr.) Rao's findings and those of his three co-investigators.'' (G–64 at 18.) Dr. Leber noted that of the 32 patients collectively assigned to the four investigators in the Cyclospasmol® arm, 12 of the 13 patients reported to have shown the largest improvements from baseline on SCAG Item 19 were in Dr. Rao's group. (G–64 at 18.) Additionally, Dr. Leber testified that on the physician's final global evaluation of each patient, a ''marked improvement,'' the highest level of improvement, was reported by all investigators for 11 of the 32 patients in the Cyclospasmol® arm, with 10 of these 11 ''marked improvements'' being reported by Dr. Rao. (G–64 at 18.) Dr.

Leber added that the hospital records often failed to support the marked improvements which Dr. Rao reported. (G–64 at 20.) Dr. Leber expressed the view that ''at best, Dr. Rao's use of the SCAG represents a sort of 'grade inflation.' That is, patients who have either had only trivial or minimal changes are rated as having very large improvements.'' (G–64 at 20.)

Dr. Leber also cited numerous specific examples of patient evaluations which he found to be questionable. (G–64 at 20–22.) Among the patients cited by Dr. Leber were Patient Nos. 15, 17, 20, 29, and 63. All of these patients were reported by Dr. Rao to have had a 3.0 change on SCAG Item 19, yet the clinical psychologist reports for the Rao study indicated that these patients worsened during the study. (G–64 at 20–22.) Other patients, including Patient Nos. 16, 22, 24, 52, and 56 were also reported by Dr. Rao to have had an improvement in their SCAG scores by 3.0 points, and, in one instance, a 4.0 improvement, yet the clinical psychologist evaluation reported no change in these patients or, in the case of the patient with the reported 4.0 change, minimal improvement. (Leber, G–64 at 21–22.)

Dr. Thal, another witness for the Center, similarly expressed the view that there were a number of items that suggested a ''credibility gap'' in the Rao study. (Thal, G–63 at 8.) On this point, Dr. Thal testified:

> First, although 4 different investigators rated the patients, only Dr. Rao found a large number of markedly improved patients. * * * The second problem is that Dr. Rao's global improvement evaluation of marked improvement in the 10 patients is not substantiated by other observers (including NOSIE scores, clinical psychology notes, nursing notes, and doctors' progress notes.) Overall, the discrepancies noted raise questions about the credibility of the data.

(Thal, G–63 at 8.)

Regarding this issue, Dr. Richard C. Mohs similarly testified:

> Since (Dr. Rao) evaluated only 16 patients in this group (the Cyclospasmol® arm) Dr. Rao rated 62% of his Cyclospasmol® patients as markedly improved while the other three physicians together only rated 1 of 16 patients as markedly improved (6%). This is very unlikely to have occurred by chance and suggests that Dr. Rao may not have been blind to the drug conditions of the patients.

(Mohs, G–62 at 13.)

I have reviewed the evidence cited by the Center in support of its argument, but I do not find the evidence sufficient to support the serious charge that Dr. Rao became unblinded during the clinical trial and failed to report becoming unblinded. While the evidence does seem to indicate a sort of ''grade inflation'' on Dr. Rao's part, as was suggested by Dr. Leber in his testimony, nevertheless the evidence is inconclusive regarding the question of Dr. Rao's blinding. There is no evidence which I find which is dispositive of the Center's claim of unblinding by Dr. Rao. Moreover, there is no evidence which indicates that Dr. Rao's patients were randomized between placebo and Cyclospasmol® arms in a way different from that of the patients in other investigators' groups, which might have revealed the patient's status to Dr. Rao. I find that while the disparity in ratings among the investigators was an issue properly raised by the Center, nevertheless I find the evidence ambiguous and not sufficient to support the Center's claim. Therefore, I rule in favor of AHP on the issues of blinding and bias.

g. *Adequacy of the Rao study.* In sum, I find that the Rao study was not adequate and well-controlled. In making this determination, I have considered the aggregate effect of the protocol violations. As I previously discussed: (1) The study failed to show that patients were examined for other causes of dementia, and therefore the study did not adequately show that Alzheimer's disease patients were included in the study; (2) patients with concomitant diseases and conditions, including strokes, histories of alcoholism, severe diabetes, Parkinson's disease, and other serious diseases were admitted to the study, although these patients were to have been excluded under the protocol; and (3) the widespread administration of concomitant medications precluded any meaningful analysis of the effects of Cyclospasmol® in the study. Also, I find that Dr. Rao's published report failed to contain details adequate to support the scientific determination that the Rao study is an adequate and well-controlled clinical investigation; the unavailability of the raw data was a matter properly considered by the ALJ, and the omission of the raw data can be weighed in determining whether the Rao study was adequate and well-controlled. I further find that the ALJ did not err in refusing to admit AHP's reanalysis of the Rao study, since the reanalysis was not timely filed and AHP did not make a motion justifying the potential delay resulting from the document's late submission. I did rule in favor of AHP on the issue of the blinding and bias of Dr. Rao. However, the favorable ruling on this issue is not enough to counteract the aggregate effect of the other deficiencies of the Rao study.

2. The Yesavage Study

The Yesavage study was originally planned as a multicenter study combining the results of three investigators at three different sites. However, the results of one of these investigators were dropped at the request of FDA because of certain questions about that portion of the study. (I.D. at 43; see also G–10.2 at 1–2.) The results of the second investigator were not submitted by AHP, for reasons which are disputed by the Center but which are not at issue in this appeal. (I.D. at 43- 44.) In any case, only the results of Dr. Yesavage's group were submitted as proof of efficacy for Cyclospasmol®. Hereinafter, the results of Dr. Yesavage's group will be referred to as the Yesavage study.

The Yesavage study was a placebo-controlled, parallel group study with the stated objective of evaluating ''the efficacy of Cyclospasmol® compared to placebo in improving symptoms usually associated with impaired brain function in the elderly, whether due to cerebral arterial disease or diffuse cellular dysfunction.'' (G–9.2 at 32.) Twenty-eight patients were enrolled at the start of the study. (I.D. at 43, citing G–9.2 at 32; G–11.1 at 10, 17.)

Under the protocol, patients selected for the Yesavage study were to be ''residing in a retirement, intermediate care facility, convalescent, nursing or other home for the aged and who exhibit mild to moderate deterioration of brain function as manifested by their behavior or symptoms * * *.'' (G–9.2 at 32.) Accordingly, the patients selected for the study were drawn from one of three nursing homes and from an intermediate care facility (Lincoln Glen Manor, Empress Convalescent Hospital, Skyline Convalescent Hospital, or Lincoln Glen Intermediate Care Facility). (I.D. at 43, citing Yesavage, Tr. IV at 43–44.) However, a few patients lived at home with relatives. (I.D. at 43, 46; Yesavage, Tr. Vol. IV at 43–44.)

Subjects in the study were assessed on the basis of 28 outcome measures. These measures included the Nurses Observation Scale—Inpatient Evaluation (NOSIE), which, in contrast to the NOSIE in the Rao study, was used to give a single measure for each patient, the Hamilton Depression Scale, the Buschke Memory Test (BMT), the physician's clinical global impression score, and the 24 measures—5 factors plus 19 items—on the Sandoz Clinical Assessment—Geriatric (SCAG). (G–9.2 at 45.)

At time of final analysis, the results of 23 of the 28 patients in the study were analyzed on the basis of measurements

taken at Weeks 3, 6, 9, and 12. (I.D. at 43, citing G–64 at 24; see also G–11.1 at 17.) However, additional and variable numbers of patients were excluded from the final analysis for which the patients' baselines were compared with their outcomes at Week 16, which was the final week of the study. (G–11.1 at 20–37.) For the SCAG rating, 20 patients, including 12 Cyclospasmol® and 8 placebo patients, were used. (G–11.1 at 29–31.) For the BMT, the results of 17 patients, including 10 Cyclospasmol® and 7 placebo patients, were analyzed. (G–11.1 at 32.) For the Clinical Global Impression, the measures of 22 patients, of which 13 were Cyclospasmol® patients and 9 were placebo patients, were used. (G–11.1 at 33.) For the NOSIE scale, 15 patients, including 10 Cyclospasmol® and 5 placebo patients, were used. (G–11.1 at 34–36.) For the Hamilton Depression Scale, 21 patients, including 13 Cyclospasmol® and 8 placebo patients, were analyzed. (G–11.1 at 37.) AHP's reasons for analyzing different numbers of patients for each outcome measure were not discussed in the final analysis of the Yesavage study. (See G–11.1 at 5- 45.)

Based upon the results of the 20 patients whose outcomes were included in the final analysis of the SCAG Factors, AHP reported a statistically significant difference in favor of Cyclospasmol® on SCAG Factor 1 (''cognitive dysfunction''), and SCAG Item 19 (''overall impression of patient functional capacity''). (G–11.1 at 19–20, 29, 78; Thal, G–63 at 16–17; Chaing, Tr. Vol. I at 52–53; Overall, A–116 at 6.)

The ALJ ruled that the Yesavage study cannot be considered an adequate and well-controlled study, in part, because: (1) Patients who did not meet the entrance criteria were included in the study, (2) concomitant medication use confounded the study, and (3) clinical significance was not demonstrated. AHP and the Center make the following arguments challenging the ALJ's decision.

a. *Selection of patients.*—(i) *Parkinson's Disease.* AHP first argues that the ALJ erred in ruling that two of the patients in the study—Patient Nos. 34 and 37—had Parkinson's disease and should have been excluded. (AHP Exceptions at 149, citing I.D. at 53, 57.) AHP argues that this ruling is an error because the protocol for the Yesavage study did not exclude patients with Parkinson's disease. (AHP Exceptions at 149.)

The Center argues that these two patients should properly be excluded because Parkinson's disease itself causes dementia, which could confound the results of the study. (Center Response to AHP Exceptions at 55–57.) The Center additionally argues that Parkinson's disease is a type of organic brain syndrome (Denton, Tr. Vol. VII at 38), and that patients with organic brain syndrome were to have been excluded under the Yesavage protocol's exclusionary criteria. (Center Response to AHP Exceptions at 56 n.26, citing G–9.2 at 34.)

Whether the inclusion or exclusion of a particular patient is consistent with the protocol is one factor which can be considered in reviewing a study, for it goes towards proving whether the study was adequate and well-controlled. However, conformance to a study's protocol is not an ironclad guarantee that the study will be found to be adequate and well-controlled.

The burden of designing and conducting an adequate and well-controlled study lies with the proponent of the drug. (Commissioner's Decision on Mysteclin, slip op. at 11; see generally § 314.126.) Protocols can be found to be inadequate. If a protocol is flawed, it does not matter if the protocol was perfectly adhered to in its execution. (Cf. Commissioner's Decision on Cothyrobal, 42 FR 28602 at 28604 and 28606 (Study found not to be adequate and well-controlled because design of study did not include test arms for all components of a combination drug.).) Moreover, FDA cannot be estopped in its review of safety and effectiveness issues. (*United States* v. *Articles of Drug * * * Hormonin*, 498 F. Supp. 424, 437 (D.N.J. 1980), aff'd 672 F.2d 904 (3d Cir. 1981).)

Turning now to the evidence regarding the Yesavage study, the record shows that Dr. Leon Thal, a witness for the Center, testified that Parkinson's disease can cause dementia. (Thal, G–63 at 12.) Specifically, Dr. Thal testified, ''Patients with Parkinson's disease do have dementia, however, the dementia may not be secondary to Alzheimer's disease but due to a dementia associated with Parkinson's disease which has a different pathological basis.'' (Thal, G–63 at 12.)

FDA regulations require that a protocol for an adequate and well-controlled study have a ''method of selection of subjects (that) provides adequate assurance that they have the disease or condition being studied * * *.'' (§ 314.126(b)(3).) In the Commissioner's Decision on Lutrexin it was ruled, under an earlier edition of the regulations, that it is necessary to use ''the most accurate diagnostic techniques available'' to assure that patients who do not have the condition under study are identified and excluded from the study; the failure to do so ''undermin(es) the validity of the results.'' (41 FR 14406 at 14419.)

Having reviewed the Yesavage study, I find that the ALJ was correct in ruling that Parkinson's disease, though not specifically excluded by the protocol, would make it more difficult to characterize the improvement of a demented patient. (I.D. at 45.) I conclude that because dementia caused by Parkinson's disease is not a labeled indication for Cyclospasmol®, Patient Nos. 34 and 37, who had Parkinson's disease, should have been excluded from the study to prevent confounding of the study's results.

The record also supports a finding that Patient No. 18 had Parkinson's disease. Patient No. 18's case record states that this patient had ''Parkinsonian tremor.'' (G–12.4 at 108.) Additionally, testimony indicates that this patient received the drug, Sinemet, during the study. Sinemet is used in the treatment of Parkinson's disease. (Denton, A–121 at 54.)

While the ALJ noted that the evidence indicated that Patient No. 18 had Parkinson's disease, the ALJ declined to rule that this patient should have been excluded for having Parkinson's disease because the Center failed to make this argument. (I.D. at B–2.) In view of the ALJ's ruling on this matter, I, too, will refrain from ruling that Patient No. 18 should be excluded despite the evidence of Parkinson's disease. Nevertheless, I rule that AHP's failure to address this patient's apparent concurrent condition can be considered in the weighing of the Yesavage study.

ii. *Outpatients.* AHP further argues that the ALJ erred in ruling that three other patients—Patients Nos. 14, 16, and 18—should have been excluded from the study because these patients lived at home with their families, rather than in a nursing home as required by the protocol. (AHP Exceptions at 152, citing I.D. at 46.) AHP argues that the inclusion of these patients represented mere technical violations of the protocol, and that these patients need not have been excluded.

The relevant section of the Yesavage study protocol provided that subjects for the study shall be ''(p)atients who are residing in a retirement, intermediate care facility, convalescent, nursing home or other home for the aged * * *.'' (G–9.2 at 32.) While the purpose for this requirement is not stated in the protocol, the ALJ, after hearing all the evidence, concluded that the purpose of this requirement was to assure that patients were taking the study medication as directed, and to assure that the use of concomitant medication would be monitored. (I.D. at

46; AHP Exceptions at 152; see generally Porter, Tr. Vol. IV at 43–46.) The ALJ's conclusions on this point are not in dispute.

While the ALJ made a ruling regarding three of the study subjects, I note that testimony from Dr. Clarence Denton, an AHP witness, indicates that five patients—Patient Nos. 14, 15, 16, 17, and 18—were outpatients. (Denton, A–121 at 48.) However, the evidence in the record does not include the case reports for Patient Nos. 15 and 17. Perhaps for this reason, the ALJ mentions only Patient Nos. 14, 16, and 18 in his decision. (See I.D. at 46.) However, I conclude that the testimonial evidence of Dr. Denton is a sufficient basis for reviewing the status of all five of the outpatients.

Dr. Yesavage testified that the patients who lived at home were seen by Dr. William Garcia in the latter's private office, although Dr. Yesavage was listed on the case report forms as the patients' doctor. (Yesavage, Tr. Vol. IV at 43, 46.) Dr. Yesavage testified that Dr. Garcia was not required by the protocol to record concomitant medications into the case report forms. (Yesavage, Tr. Vol. IV at 45.) For nursing home patients, concomitant medications were noted on the patient order sheets; regarding outpatients, Dr. Yesavage testified that he ''presume(d)'' that Dr. Garcia made notes in his private files regarding concomitant medications for the outpatients. (Yesavage, Tr. Vol. IV at 44–46.)

The responsibility of recording all subjects' concomitant medications, including that of the outpatients, onto the case report forms was given to Mr. Michael Adey, Dr. Yesavage's assistant. (Yesavage, Tr. Vol. IV at 45–46.) For the nursing home patients, it was Mr. Adey's responsibility to review the order sheets, identify concomitant medications, and record these into the case report forms. (Yesavage, Tr. Vol. IV at 47.) For the outpatients, Mr. Adey was similarly to review the medical records from Dr. Garcia, identify concomitant medications, and record this information into the case report forms. (Yesavage, Tr. Vol. IV. at 48.)

The Center argues that the outpatients should properly be excluded because there is no evidence to show that the families of the outpatients kept careful records of any concomitant medications given at home, nor does the evidence show that Mr. Adey recorded in the case report forms concomitant medications given at home. (Center Response to AHP Exceptions at 59.) Additionally, the Center argues that there is no evidence that the outpatients' families kept careful records regarding the administration of the test drug. (Center Response to AHP Exceptions at 59.)

FDA regulations require that a study use a design ''that permits a valid comparison with a control to provide a quantitative assessment of drug effect.'' (§ 314.126(b)(2).) The regulations also require that ''(t)he method of assigning patients to treatment and control groups minimize bias and * * * assure comparability of the groups with respect to pertinent variables such as * * * use of drugs or therapy other than the test drug.'' (§ 314.126(b)(4).) Monitoring a patient's medications during the course of a study is an important factor in the design of an adequate and well-controlled study and is necessary for a valid comparison between a test article and a control. (See generally Commissioner's Decision on OPE, slip op. at 47–53.)

While restricting the Yesavage study to patients who were in a nursing home and under constant medical supervision is one way to monitor concomitant medications, this restriction is not perforce required to monitor concomitant medications. Although the evidence indicated that there were problems with recording of concomitant medications [6] and with concomitant medication use (the latter of which will be discussed in section I.D.2.d. of this document), these problems do not appear to be unique to the outpatients in the Yesavage study. For these reasons, I will accept AHP's argument that the inclusion of outpatients was a technical violation of the protocol and was not grounds by itself to exclude these patients.

Nevertheless, as I previously noted, even protocol violations which by themselves may not warrant rejection of a study can be considered in the aggregate in determining whether a study is adequate and well-controlled. (See Commissioner's Decision on Benylin, 44 FR 51512 at 51531.) Failure to follow inclusion/exclusion criteria can be an indication of an inattention to detail and can be considered in deciding whether the study was adequate and well-controlled.

Therefore, I find with respect to the Yesavage study that the inclusion of outpatients in violation of the study's protocol may be considered in evaluating the adequacy of the Yesavage study.

b. *Distribution of patients with strokes.* Unlike the Rao study's protocol, which planned to exclude patients with strokes, the Yesavage study's protocol did not propose to exclude stroke patients. This difference between the two studies' protocols was not an issue at the administrative hearing.

AHP argues that the ALJ erred in holding that seven patients in the Yesavage study had medical histories indicating strokes, and that these patients should have been proportionately distributed between the drug and placebo groups. (AHP Exceptions at 154, citing I.D. at 53, 57.) The Center, citing to the testimony of Dr. Thal, argues that AHP's failure to identify patients with stroke histories and to see that such patients were proportionately assigned between the Cyclospasmol® and the placebo groups meant that the two groups cannot be found to be comparable. (Center Response to AHP Exceptions at 60–61.) I find the Center's argument to have merit.

Turning first to the testimony of Dr. Thal, a witness for the Center, this witness testified:

> There are some problems with the protocol in that the protocol does not attempt to separate out patients who have Alzheimer's disease from those who had multiple strokes. *A problem with lumping together two groups of patients is that if they are unequally distributed, the treatment effect seen may be due to an effect on the treatment on one disorder and not the other.* For example, if a large number of patients with multiple strokes are in the treatment group, the effect of the drug would then be licensed for the treatment of both patients with multi-infarct dementia and Alzheimer's disease when in fact the drug may be totally non-effective in patients with Alzheimer's disease. In reviewing the case report forms for these patients, I found (7) patients with a history or an examination compatible with stroke (patients 9, 25, 28, 29, 33, 34, 35). If these patients are removed from the statistical analysis, it is perfectly possible that all statistical significance would be lost in the remaining patients.

(Thal, G–63 at 11 (emphasis added).)

I have reviewed the records for all patients in this study, and I have found that Dr. Thal was correct with regard to six of the seven patients which Dr. Thal identified as having histories of strokes. I was unable to verify the diagnosis of a stroke with regard to Patient No. 25, as there are no records in evidence for this patient. However, regarding the remaining six patients, the records support Dr. Thal's testimony. Patient No. 9's records show a clinical diagnosis of a stroke, specifically a cerebral

[6] Dr. Yesavage testified that his research assistant may not have included all sleeping medications in the case report records of concomitant medications. (Yesavage, Tr. Vol. IV at 42.) Dr. Yesavage explained that his research assistant was permitted to ''use some judgment'' in deciding which medications to include on the case report forms because it was not felt that it was important to include all concomitant medications regardless of their indications. (Yesavage, Tr. Vol. IV at 42.)

vascular accident with left hemiplegia. (G–12.2 at 106, 109.) Patient No. 28's records show a diagnosis of a stroke. (G–12.6 at 309, 312–13.) Patient No. 29's records show a diagnosis of a stroke, specifically a cerebral vascular accident with right hemiplegia. (G–12.7 at 4, 7–8.) Patient No. 33's records show a diagnosis of a stroke, specifically a cerebral vascular accident with left hemiplegia. (G–12.7 at 107, 110–11.) Patient No. 34's records show a diagnosis of a stroke with left hemiparesis. (G–12.7 at 210, 215–16.) Patient No. 35's records indicate a diagnosis of stroke. (G–12.8 at 9.) Additionally, Patient No. 7's records indicate a diagnosis of a stroke (G–12.2 at 5), although this patient was not identified by the Center in its brief as a stroke patient.

What the records do not reveal, either in the patient records or in the analysis of the Yesavage study, is to which group (Cyclospasmol® or placebo) these, or indeed any, of the patients were assigned. (See G–12.1 through 12.8; G–11.1.) While AHP faults the ALJ's decision for failing to make a finding as to how the stroke patients were distributed, AHP offers no information in this regard. (AHP Exceptions at 155.)

Based upon the evidence in the record, it cannot be ascertained whether both arms of the clinical trial included stroke patients. For this reason, I find that, strictly speaking, proportional distribution of stroke patients is not the crux of this issue; rather, it is the failure to show that stroke patients were included in both the Cyclospasmol® arm and the placebo arm of the clinical trial.

As I previously ruled (see section I.D.1.b. of this document), in an adequate and well-controlled study, it is not acceptable to group persons having similar symptoms but distinct diseases together into one study without identifying which patient has which disease, otherwise, as in the Yesavage study, it will be impossible to assess a drug's effectiveness on a particular disease. (Cf. Commissioner's Decision on Lutrexin, 41 FR 14406 at 14422 (In a study of premature labor, results were ruled incapable of scientific interpretation because women with different conditions were evaluated together.)) It is, of course, essential to show that a drug is tested on the population for which it is labeled. As was ruled in the Commissioner's Decision on Cothyrobal, ''Clearly, a study * * * must be conducted in patients who have one of the labeled indications if that study is to be used as proof of effectiveness for those indications.'' (42 FR 28602 at 28610.) Similarly, in the Commissioner's Decision on Lutrexin, it was ruled, ''(T)he law is clear that the applicant must provide substantial evidence of a drug's effectiveness under its labeled conditions of use, not those under which an investigator chooses to test it.'' (41 FR 14406 at 14419.)

The Center cites to the regulation requiring that the method of assigning subjects must assure comparability of the groups with respect to pertinent variables, including severity and duration of disease. (Center Response to AHP Exceptions, citing § 314.126(b)(4); see also Commissioner's Decision on Lutrexin, 41 FR 14406 at 14414.) Necessarily, the group assignments must be comparable with respect to the disease itself. I therefore find that the failure to show that stroke patients were included in both the drug and the placebo arms of the clinical trial can be considered as a flaw in the Yesavage study, and can be weighed in determining if the study was adequate and well-controlled.

c. *Baseline comparability.* AHP next argues that the ALJ erred in finding that the lack of comparability between the drug and placebo groups at baseline for the Buschke Memory Test (BMT) weighed against finding the Yesavage study adequate and well-controlled. (AHP Exceptions at 156–57, citing I.D. at 48, 53, 57.) The average BMT score at baseline for the Cyclospasmol® group was ''7.2'' out of a possible score of ''15.0,'' but was ''3.6'' for the placebo group, a difference between the two groups which was statistically significant. (Schneiderman, G–65 at 10; Thal, G–63 at 13.)

AHP argues that the BMT measured only a narrow parameter of cognitive functioning, and that the results of other tests at baseline should have been weighed more heavily. Specifically, AHP cites to the baseline measures for SCAG Factor 1 (''cognitive dysfunction''), SCAG Item 3 (''impaired recent memory''), SCAG Item 19 (''overall impression of patient functional capacity''), the Hamilton Depression Scale, and the NOSIE, which were comparable at baseline for the drug and placebo groups. (AHP Exceptions at 158; I.D. at 48.)

The Center concedes that the BMT measures a narrower parameter of cognitive dysfunction, specifically, recent memory dysfunction, but argues that impaired recent memory is the core of cognitive dysfunction and is, therefore, a critical parameter. (Center Post-Hearing Brief at 86, citing Thal, Vol. VI at 45.) The Center further argues that the BMT's baseline values carry more weight than the SCAG's baseline values because the BMT is an objective, quantitative test of recent memory dysfunction. (Center Response to AHP Exceptions at 63.) By contrast, the SCAG is a subjective, observer-rated test. (Center Post-Hearing Brief at 86.) The Center argues that for this reason, the BMT is more telling of baseline comparability between the two study groups. The Center further argues that the lack of baseline comparability on the BMT rendered the Yesavage study not adequate and well-controlled. (Center Reply to AHP Exceptions at 63.)

Before discussing the merits of this issue, the relevant parameters of the SCAG and the BMT need to be described. The SCAG required the physician to rate the patient from a list of 19 Items. Each Item in the SCAG was rated on a scale from ''1'' to ''7,'' with ''1'' indicating that the symptom was ''not present,'' and ''7'' indicating that the symptom was ''severe.'' (G–3.1 at 97; see, e.g., G–14.2 at 6–8.) Eighteen of these Items were then grouped into five Factors for rating the patient. (G–11.1 at 70.) The 19th Item, the Physician's Overall Assessment of the patient, was rated separately. (G–11.1 at 70 n.7.) The Factor upon which AHP now relies, Factor 1, Cognitive Dysfunction, was defined as including the following Items: (1) Confusion, (2) impaired mental alertness, (3) impaired recent memory, and (4) disorientation. (G–11.1 at 70–71, 75.)

The BMT, on the other hand, was described by Dr. Yesavage, an AHP witness, as ''a memory performance test in which subjects are required to remember and repeat words from a stimulus list of 15 objects.'' (G–11.1 at 21.)

Regarding the differences between the SCAG and the BMT, Dr. Thal, a Center witness, testified:

> The SCAG is a subjective measure based on an interviewer rating scale. The rating scale is such that it is neither objective nor as accurate as the type of data that one would generate on the Buschke memory test. Additionally, and more importantly, the SCAG measures many factors other than memory such as sociability, mood, etc. Only a small number of the SCAG items deal directly with memory.

(Thal, G–63 at 14.)

The main disagreement between AHP's witnesses and the Center's witnesses lies in which test the witnesses think should be given more weight. Dr. Thal testified that he would recommend relying upon the BMT as an indicator as to whether the two populations were similar, especially for indications of cognitive dysfunction or memory problems. (Thal, G–63 at 14.) By contrast, Dr. Klerman, an AHP

witness, testified that he would give greater weight to the SCAG. (Klerman, Tr. Vol. III at 87.)

Under FDA regulations, for a clinical trial to be considered adequate and well-controlled, assignment of patients must be accomplished by a method that minimizes bias and ''assur(es) comparability of the groups with respect to pertinent variables such as * * * severity of disease * * *.'' (§ 314.126(4).) With regard to the Yesavage study, short-term memory loss is one of the characteristics of senile dementia. Therefore, the severity of the impairment of recent memory functioning is a pertinent variable in the evaluation of senile dementia.

While SCAG Item 3 includes impaired recent memory as a characteristic to be evaluated, SCAG Item 3 is, nevertheless, a subjective measure. The BMT quantifies the severity of the recent memory impairment through an objective test of short-term memory. As such, the BMT is an indicator of the severity of this aspect of senile dementia. A statistically significant difference between the treatment and the placebo groups on this measure, with the placebo group being worse, does indicate a lack of comparability between the treatment and placebo groups on one of the hallmarks of senile dementia.

Therefore, I find that the statistically significant difference between the two groups at baseline was a proper consideration to be weighed in determining whether the Yesavage study was adequate and well-controlled.

d. *Concomitant medications.* The law regarding concomitant medications was discussed in a previous section of this decision, and I will not repeat it here. (See section I.D.1.d. of this document.)

The Yesavage study protocol contains an extensive section pertaining to concomitant medications, which in full reads:

> Treatment with vasodilating, anti-convulsive, psychoactive, or narcotic agents, ergot or reserpine derivatives or steroids (other than estrogen) will not be allowed during this study. The patient may have chloral hydrate as a hypnotic. Occasional doses of thioridazine or diazepam may be used if deemed necessary; however, no more than 16 doses of one of these agents may be taken per study and there should be no more than three doses in any week. Other medication, which is considered necessary for the patient's welfare and which will not interfere with the study medication, may be continued at the discretion of the investigator, but no new drug, other than those previously stated, should be started during the course of this study, except that medication required for an acute purpose which would not disqualify the patient (e.g., an analgesic, an antibiotic, etc.). If the investigator feels it is necessary to start or change a *chronic* medication during the course of the study, he will contact the Ives Medical Monitor to determine whether the patient may continue in the program. However, if during the course of the study the investigator feels it is necessary to start the patient on digoxin and/or diuretic therapy because of congestive heart failure he may do so, without consulting the Ives Medical Monitor, unless the severity of the congestive heart failure interferes with the administration of the study drugs or creates a major change in the patient's mental state. In either of the latter situations, the patient should be dropped from the study.
>
> Administration of *all* concomitant medication must be reported on the case report form, supplied by the sponsor, including the name of the drug, dose, reason for use and date started.

(G–9.2 at 34–35 (emphasis in original).)

Regarding concomitant medications, the Center identified 12 patients who received 11 different concomitant medications with possible confounding effects. The patients identified by the Center and the medications which these patients were said to have taken included Patient No. 2 (Aldomet, Inderal, Elavil), Patient No. 5 (Inderal, Valium), Patient No. 7 (Inderal), Patient No. 9 (Dalmane), Patient No. 16 (Sinemet), Patient No. 18 (Sinemet), Patient No. 21 (Mellaril), Patient No. 24 (Inderal, Serax), Patient No. 33 (Elavil), Patient No. 34 (Benadryl, Phenergan), Patient No. 35 (Haldol), and Patient No. 37 (Elavil, Sinemet). (See Center Post-Hearing Brief at Attachment D.) The ALJ also identified a 12th concomitant medication, Librium, which was given to Patient No. 16, who received 10 mg of this drug. (I.D. at B–2; Denton, A–121 at 52.) AHP does not concede that any of these patients should be excluded. (AHP Post-Hearing Brief at 108; AHP Exceptions at 163.) The concomitant medication use of each of these patients will be discussed in turn.

Patient No. 2, who was in the Cyclospasmol® group, received three concomitant drugs during the study, specifically Aldomet, Inderal, and Elavil. (I.D. at B–1.) Regarding Aldomet, an antihypertensive drug, Patient No. 2 received 250 mg of this drug three times a day throughout the study. (G–12.1 at 11, 29, 42, 57, 60, 63, 70.) Aldomet can affect mood and cognition. (Leber, G–64 at 13.)

Additionally, according to the testimony of Dr. Denton, a witness for AHP, Patient No. 2 received 40 mg of Inderal twice a day throughout the study. (Denton, A–121 at 52–53.) This patient's case records do not document the administration of Inderal to this patient. (See G–12.1 at 4–105.) Regarding Inderal, Dr. Denton testified that Inderal in ''a large dose, perhaps more than 80 mg/day, might make patients confused or depressed.'' (Denton, A–121 at 53.) Other possible side effects of Inderal include disorientation, short term memory loss, clouded sensorium, and decreased performance on neuropsychometric tests. (Denton, Tr. Vol. VII at 34–35.) As for the effect of Inderal on Patient No. 2, Dr. Denton testified that he believed the dosage to be ''too small to influence cognitive functioning in any manner.'' (Denton, A–121 at 53.)

The administration of Elavil to Patient No. 2 deserves particular attention because of the frequency of this drug's administration. Elavil is a psychoactive drug used in the treatment of depression. (Zung, Tr. Vol. III at 51.) While the case records in evidence for Patient No. 2 do not record the administration of Elavil, the testimony of Dr. Denton, a witness for AHP, indicates that Patient No. 2 received 25 mg of Elavil at night before sleep, but that this medication was stopped during the last 7 weeks of the study. (Denton, A–121 at 52.) Since patients were in the Yesavage study for 19 weeks—3 weeks of prestudy washout followed by 16 weeks in the clinical trial (G–9.2 at 32)—this would mean that Patient No. 2 was receiving Elavil nightly for the first 12 weeks of the 19 week study.

Despite Patient No. 2's extended use of a psychoactive drug, Dr. Denton testified that he did not believe that this patient should have been excluded. (Denton A–121 at 52.) Dr. Denton testified that, while a ''strict interpretation of the protocol might have eliminated'' Patient No. 2 for the concomitant Elavil use, Dr. Denton nonetheless concluded that this patient need not be excluded because the administration of Elavil was stopped during the last two evaluations, ''the crucial ones from an efficacy standpoint.'' (Denton, A–121 at 52.)

In considering this evidence, the ALJ was not persuaded by Dr. Denton's explanation for failing to exclude Patient No. 2. The ALJ found that the question remained as to whether Elavil use during the beginning of the study could have caused a SCAG score that was worse than it would have been without the drug. (I.D. at B–1.) When the Elavil administration was ceased during the final two evaluations, this alone may have caused any improvement in this Patient's SCAG score. (I.D. at B–1.) I agree with the ALJ's analysis of this issue, and I conclude that the concomitant medication use of Elavil by Patient No. 2 was grounds to exclude this patient.

For the next patient, Patient No. 5, a Cyclospasmol® patient, the case records indicate that this patient received Valium (diazepam) ''occasionally for nervousness,'' and Inderal ''q.i.d.'' (*quater in die,* four times a day). (G–12.1 at 212; Denton, A–121 at 51, 53–54.) The case records for this patient do not reveal the dosage for these drugs, nor is there a contemporaneous medication record tracking the days or times at which either of these medications were administered. (See G–12.1 at 206–308.)

Regarding the administration of Inderal, Patient No. 5's case records do not indicate the dose given, but Dr. Denton testified that this patient received 10 mg of Inderal four times a day. (Denton, A–121 at 53.) As was previously stated, Dr. Denton also testified that Inderal in ''a large dose, perhaps more than 80 mg/day, might make patients confused or depressed.'' (Denton, A–121 at 53.) Other possible side effects include disorientation, short term memory loss, clouded sensorium, and decreased performance on neuropsychometric tests. (Denton, Tr. Vol. VII at 34–35.)

As for the administration of Valium to Patient No. 5, Dr. Denton's testified as follows:

> The hospital records reveal that the Valium was ordered on a prn (*pro re nata,* as occasion arises) basis, which suggest that it was used infrequently, and her referring physician told me by telephone that it was used 0–2 times per week. There were no medication sheets on this patient's record.

(Denton, A–121 at 51–52.)

It should be emphasized that Dr. Denton's estimation of the ''infrequency'' of the administration of Valium to Patient No. 5 is only speculation, in view of the fact that there were no medication records for Dr. Denton's review, nor is there evidence that this patient's referring physician based his or her statements on any such medication records.

I further note that even if Dr. Denton is correct in estimating the administration of Valium to Patient No. 5 to be as much as 2 times per week during the 19 week study, that amount of Valium—as much as 38 doses during the study—is a clear violation of the protocol, which specifies, ''Occasional doses of thioridazine (Mellaril) or diazepam (Valium) may be used if deemed necessary; however, no more than 16 doses of one of these agents may be taken per study * * * .'' (G–9.2 at 34.)

The absence of detailed records tracking the administration of Valium and Inderal to Patient No. 5 makes it impossible to fully evaluate the effect of these concomitant medications. The inadequate records are a ''fatal flaw'' which can weighed against finding the Yesavage study to be adequate and well-controlled. (Commissioner's Decision on OPE, slip op. at 52.)

Patient No. 16, an outpatient and a Cyclospasmol® subject, received 10 mg of Librium, a benzodiazepine, ''only rarely,'' according to the testimony offered by Dr. Denton. (A–121 at 52.) However, Dr. Denton gave no specific information regarding the dosage, or dates and times of administration of Librium, and the records in evidence for Patient No. 16 contain no information at all pertaining to this patient's use of Librium. (G–12.4 at 1–100.) The administration of Librium could have had a confounding effect on the results of this study, and the absence of medication records is, as with the previous patient, a ''fatal flaw'' that can be weighed against finding the Yesavage study adequate and well-controlled. (Commissioner's Decision on OPE, slip op. at 52.)

Regarding Patient No. 18, a Cyclospasmol® subject, Dr. Denton testified that this patient had been given Sinemet (carbidopa/levodopa), a drug used in the treatment of Parkinson's disease, between the ratings taken at weeks 7 and 8. (Denton, A–121 at 50, 54–55.) The final rating was taken at week nine. (See G–12.4 at 190–201.) Dr. Denton acknowledged that Sinemet can have a ''positive effect on cognition.'' (Denton, A–121 at 54; see generally Leber, G–64 at 14 (Sinemet use in Rao study).) Nevertheless, Dr. Denton testified that he believed that if Sinemet had any effect on Patient No. 18, it was only to make this patient worse. (Denton, A–121 at 54.) Dr. Denton based his conclusion on the SCAG scores for Patient No. 18. (Denton, A–121 at 54.) Dr. Denton stated that at baseline this patient's SCAG score was 49, and that at visit 7 the score had improved to 43 (a lower score being a better score), but that at visit 9 the score was again 49. (Denton, A–121 at 54.)

I find Dr. Denton's proffered explanation that Sinemet made Patient No. 18's SCAG score worse to be based on mere speculation. Aside from the fact that Dr. Denton's explanation was inconsistent with his other testimony, in which he testified that Sinemet can have a positive effect on cognition, I note that another possible explanation not addressed by Dr. Denton is that Patient No. 18's SCAG score might have deteriorated even further had it not been for the Sinemet. Additionally, as Dr. Zung, a witness for AHP, testified, there are instances where patients with Parkinson's disease have a period of remission or spontaneous improvement with the disease, which could have a confounding effect on the results of a study. (Zung, Tr. Vol. III at 23.) However, these explanations, too, are speculative.

I note also that, as with the previously discussed Yesavage patients, the records in evidence pertaining to Patient No. 18 contain no information regarding this patient's concomitant medications. (G–12.4 at 101–201.) Once again, I state that the absence of such records is a fact which can be weighed against finding the study to be adequate and well-controlled. (Commissioner's Decision on OPE, slip op. at 52.)

Patient No. 24, a Cyclospasmol® subject, received both Inderal and Serax. Dr. Denton testified that this patient received 20 mg of Inderal three times a day, subsequently reduced to 20 mg, twice a day. (Denton, A–121 at 53.) Dr. Denton did not specify when this change in dosing schedule was made. However, this patient's clinical records contain a notation that this patient was on Inderal 20 mg, twice a day, as of the first visit, which was on January 10, 1982, and the patient continued this medication throughout the study. (G–12.6 at 12, 28, 41, 56, 59, 62, 71, 78, 87, 94.) As previously discussed, Inderal can cause side effects such as confusion and depression (Denton, A–121 at 53), disorientation, short term memory loss, clouded sensorium, and decreased performance on neuropsychometric tests. (Denton, Tr. Vol. VII at 34–35.)

As for the administration of Serax, a benzodiazepine, to Patient No. 24, Dr. Denton testified that 10 mg of Serax was given to Patient No. 24 at bedtime as a sedative. (Denton, A–121 at 52.) This patient's clinical records contain no mention of this medication or the frequency and dosages given. (G–12.6 at 2–104.) This level of administration of a benzodiazepine certainly violates the intent of the protocol's concomitant medication restriction, which permits ''(o)ccasional doses of thioridazine or diazepam,'' but no more than 16 doses per study per patient, and no more than 3 doses per week. (G–9.2 at 34.) For this reason, Patient No. 24 should have been excluded. Additionally, the absence of written records tracking the strength, frequency, and length of administration of this drug can be weighed against finding the Yesavage study to be adequate and well-controlled. (OPE, slip op. at 52–53.)

Patient No. 34 and Patient No. 37 both had Parkinson's disease. (G–12.7 at 210 (Patient No. 34); G–12.8 at 109, 113 (Patient No. 37); Mohs, G–62 at 16; Thal, G–63 at 12.) Patient No. 34, a Cyclospasmol® subject, received 25 mg of Benadryl twice a day. (G–12.7 at 217; Mohs, G–62 at 16; Thal, G–63 at 12.)

Benadryl is a drug which has indications for use for patients with Parkinson's disease. (Zung, Tr. Vol. III at 52; see also G–12.7 at 217.) The side effects of Benadryl can include diminished mental alertness, sedation, sleepiness, dizziness, and confusion. (Zung, Tr. Vol. III at 52.) Phenergan, an antiemetic, was also given to this patient. (Denton, A–121 at 52.)

Patient No. 37, also a Cyclospasmol® subject, received Sinemet 25/100 (25 mg carbidopa/100 mg levodopa) every four hours to control symptoms of Parkinson's disease. (Mohs, G–62 at 16; Thal, G–63 at 12; Denton, A–121 at 54.) This patient also received 25 mg of Elavil twice a day. (G–12.8 at 114.) The frequency of administration of Elavil, a psychoactive drug (Zung, Tr. Vol. III at 51), warranted the exclusion of Patient No. 37.

Additionally, as I ruled in a previous discussion, both Patient 34 and Patient 37 should have been excluded because of their concomitant Parkinson's disease. (See section I.D.2.a. of this document.) Moreover, I rule that the concomitant medication use by these patients can be weighed against finding the Yesavage study to be adequate and well-controlled because the effect of the concomitant drugs may have confounded the results now attributed to Cyclospasmol®.

Patient No. 7, a placebo patient, received Inderal twice a day during the study. (G–12.2 at 7.) The case records for this patient do not record the dose for this drug. However, Dr. Denton testified that Patient No. 7 received 10 mg of Inderal twice a day. (Denton, A–121 at 53.) Inderal can affect cognition. While this level of Inderal use may not itself be reason to exclude this patient, nevertheless, the possible confounding effect of this drug's side effects can be taken into consideration. Additionally, the failure of the case records to document Patient No. 7's concomitant medication use can be considered in evaluating the Yesavage study. (Commissioner's Decision on OPE, slip op. at 52–53.)

Regarding Patient No. 9, a placebo patient, Dr. Denton testified that orders were given for this patient to receive 15 mg of Dalmane at bedtime ''PRN.'' Dr. Denton conceded that Dalmane, a benzodiazepine, ''might be considered a contraindicated medication.'' (Denton, A–121 at 56.) However, Dr. Denton testified that Patient No. 9 was only given Dalmane once during the study—on September 14, 1981—and for this reason Dr. Denton did not believe this medication confounded the study. (Denton, A–121 at 56.) The final evaluation of this patient occurred on September 17, 1981.

The clinical documents in evidence contain no record of Patient No. 9 being administered Dalmane. (G–12.2 at 104–205.) A single administration of a benzodiazepine would not appear to be confounding to this study. Nonetheless, the actual administration of Dalmane is not corroborated in this patient's case records. The failure of the case records to document the actual administration of Dalmane can be weighed against finding the Yesavage study to be adequate and well-controlled. (OPE, slip op. at 52–53.)

Patient No. 21, also a placebo patient, received 25 mg of Mellaril (thioridazine hydrochloride) twice a day throughout the study. (Denton, A–121 at 55–56.) This patient's clinical records now in evidence contain no record of Patient No. 21 having received Mellaril. (G–12.5 at 105–208.) Mellaril can affect cognitive performance and cause a patient to perform worse on cognitive tests than he or she might have but for the Mellaril. (Leber, Tr. Vol. I at 69.) Administration of Mellaril at this frequency was clearly a violation of the protocol, which restricted thioridazine to occasional doses. (G–9.2 at 34.) This patient should have been excluded.

Regarding Patient No. 33, the Center had argued that this patient should have been excluded on the basis that this patient received the concomitant medication of Elavil during the study. (Center Post-Hearing Brief at 81 & Attachment D.) This patient's records do not reveal whether this patient was a placebo patient or a Cyclospasmol® patient, and Patient No. 33's medication use was not discussed by Dr. Denton in his testimony.

Regarding Patient No. 33's concomitant medication use, a notation in this patient's records of the prestudy evaluation indicates that this patient had received 25 mg of Elavil twice a day from January 4, 1979, through May 18, 1982. There are no medication records in evidence but, based upon this notation in the prestudy evaluation, it appears that the administration of Elavil was reported to have been stopped 2 weeks before Patient No. 33 was accepted into the Yesavage study. (G–12.7 at 112.)

Other patient records in evidence indicate that this patient's first visit during the study occurred on August 2, 1982. (G–12.7 at 128.) According to the protocol, at the first visit the patient was to enter into a single-blind washout period. (G–9.2 at 36, 38.) This washout period was to last until the patient's second visit, at which point the patient entered the double-blind medication phase of the study. (G–9.2 at 168.) A further notation in this patient's records from this patient's second evaluation, which occurred on August 24, 1982, states, ''Elavil still discontinued for length of study.'' (G–12.7 at 143.)

Although daily medication records are not in evidence for Patient No. 33, I nevertheless rule, based upon the records which are in evidence, that Patient No. 33 properly was included in the study. Based upon the evidence, it does not appear that this patient was receiving the concomitant medication of Elavil during the study.

Patient No. 35, a placebo patient, received Haldol during the study. (Denton, A–121 at 56.) This patient's clinical documents in evidence contain no record of this patient's receiving this medication. (G–12.8 at 104–205.) Nonetheless, Dr. Denton testified that Patient No. 35 received a single, 1 mg dose of Haldol, 9½ weeks before final evaluation. (Denton, A–121 at 56.) However, Dr. Denton's testimony appears inconsistent on this point, because he also testified that Patient No. 35 received Haldol ''b.i.d.,'' that is, *bis in die*, or twice a day.

Additionally, I note that Patient No. 35's clinical records indicate that this patient received 10 mg of Isordil, a vasodilator, four times a day throughout the study. (G–12.8 at 11, 40, 56, 59, 62, 71, 78, 87, 94.) This could have caused a confounding effect. Neither the Center nor AHP address this part of the patient's record, nor does the ALJ discuss the apparent concomitant Isordil use. Although there is sufficient evidence for me to conclude that Isordil was administered concomitantly, I will, in view of the fact that no party addressed this issue, instead weigh this evidence as a deficiency in the clinical records for the Yesavage study. (Commissioner's Decision on OPE, slip op. at 52–53.)

To summarize, a pervasive problem with the Yesavage study is the failure to adequately document concomitant medication use. In many instances, the case records do not even mention the concomitant medication at issue. In other instances, the medication is listed but the dosage is not, nor is the schedule of administration for the drug.

The use of concomitant medications is an important matter. Uncontrolled use of concomitant medications defeats the scientific value of a study. (Commissioner's Decision on OPE, slip op. at 204.) Vague or incomplete records of concomitant medications are ''fatal flaws'' which weigh heavily against finding a study adequate and well-controlled. (*Id*. at 53.) Also, the number of various concomitant medications

increases the difficulty of evaluating Cyclospasmol®'s effect. (*Id*. at 56.) Additionally, the proportionately large number of patients receiving concomitant medications—12 out of 23 patients in the final analysis—weighs against finding the Yesavage study adequate and well-controlled. (*Id*. at 57.)

I conclude by ruling that, based upon both the patient case records and testimonial evidence, Patient Nos. 2, 24, 37, and 21 should have been excluded for concomitant medication use. Regarding Patient Nos. 5, 16, and 35, their concomitant medication use could not be properly evaluated because of incomplete case records. The testimony offered by Dr. Denton regarding Patient Nos. 5, 16, and 35 was vague and was not sufficient to evaluate these subjects. This absence of documentation of concomitant medication use can be weighed against finding the Yesavage study to be adequate and well-controlled.

As for Patient Nos. 7 and 9, assuming for the purposes of this discussion that Dr. Denton's testimony completely and accurately described these patients' concomitant medication use, then these two patients were possibly properly included. However, the medication regimens for Patient Nos. 7 and 9 were not corroborated in their case records, which weighs against finding the Yesavage study to be adequate and well-controlled.

Regarding Patient Nos. 34 and 37, I previously ruled that these patients should have been excluded for Parkinson's disease. I note that I have additionally found that Patient No. 37 should have been excluded for concomitant medication use.

As for Patient No. 18, if concomitant medication use alone is considered, and, assuming that Dr. Denton's testimony completely and accurately describes this patient's concomitant medication use, then this patient may properly have been included. However, the failure of the case records to document this patient's concomitant medication use weighs against finding the Yesavage study to be adequate and well-controlled. Furthermore, I previously found that Patient No. 18's case records seem to indicate that this patient had Parkinson's disease. AHP's failure to address this patient's apparent concurrent Parkinson's disease can be weighed against finding the Yesavage study to be adequate and well-controlled.

Regarding Patient No. 33, it appears from the records in evidence that this patient was not receiving the concomitant medication of Elavil during the study.

Overall, I find that the uncontrolled use of concomitant medication and the poor documentation of concomitant medication use weighs against finding the Yesavage study to be adequate and well-controlled.

e. *Small sample size.* AHP argues that the ALJ erred in ruling that in view of the small sample size in the Yesavage study—12 Cyclospasmol® patients and 8 placebo patients at week 16—it was ''inappropriate to generalize the results.'' (AHP Exceptions at 166, quoting I.D. at 57.) On this point, the ALJ also had noted that earlier in the study, at week 12 when 14 Cyclospasmol® patients and 9 placebo patients were tested, there was no statistically significant drug effect. (I.D. at 52.) However, at week 16, when three patients had been dropped from the study, statistical significance was reported. (I.D. at 52, citing Thal, G–63 at 17.) While the ALJ found that there had been no showing that the dropping of the three patients resulted in statistical significance, the ALJ nevertheless observed, ''The problem with such a small sample size is that the omission of one or two patients can change the results rather dramatically.'' (I.D. at 52.) AHP objects to the ALJ's opinion on these points.

In support of its argument, AHP cites the testimony of Dr. Mantel, a statistician and witness for AHP, who, in connection with his testimony pertaining to the MDS–96 study, testified as follows regarding small studies:

> As to Dr. Reich's comment that ''most often a larger sample provides more convincing conclusions than a small one,'' Dr. Reich is correct. If I wished to have my study provide more convincing conclusions, I would conduct a larger study employing a larger sample. But once a study is completed that argument is no longer relevant. A significant result from a small study is, nevertheless, a significant result. And a significant result from a small study would betoken an important effect. Large studies would very likely yield statistical significance if the true effect were important. But with a very large study even a minor treatment effect would lead to a statistically significant outcome. It is recognized that the hypothesis of absolutely no treatment effect is almost never exactly true—thus, statistical significance could reflect large study size yet only a very minor treatment effect. * * * As indicated above, statistical significance despite limited study size would betoken an important treatment effect.

(Mantel, A–127 at 7–8.)

AHP also cites the testimony of two other of its witnesses, Mr. Danny S. Chaing and Dr. John E. Overall, who testified regarding statistical power and sample size in the Yesavage study. On this matter, Mr. Chaing testified, ''(The) Yesavage sample is large enough to produce reliable and generalizable conclusions * * *. (T)here's no single minimum required sample size.'' (Chaing, Tr. Vol. I at 22–23.) Dr. Overall testified, ''There's no merit in the criticism that a sample is too small from an appropriately designed and conducted study which has produced statistically significant results.'' (Overall, Tr. Vol. II at 55.)

AHP further argues that if a small study yields a result that is statistically significant, this suggests that the drug effect is ''large'' because ''the variability of human response would make it unlikely that statistical significance would be achieved in a small study if the drug effect were small.'' (AHP Exceptions at 167.) The Center counters that AHP is confusing the size of the drug effect with the variability inherent in a small sample. (Center Response to AHP Exceptions at 69.) The Center further argues that in a small study, regardless of the size of the drug effect, the results from only one or two subjects can completely alter the study's results. (Center Response to AHP Exceptions at 69.) I find the Center's arguments to have merit.

Small samples have larger standard errors, i.e., the uncertainty in the results encompasses a greater range of values by which the mean of the population may vary. The size of the standard error from a study is a measure of the degree to which the study's results reflect the true value which would have been found in the population-at-large having the disease or condition. In studies based on small samples, results may differ greatly from one study to the next because the results of only a few subjects can greatly affect the outcome of the study.

While a small sample study can indicate a statistically significant result, I note that the problem with a small sample is that its larger standard error can make it difficult to identify, with a useful degree of precision, the true value or result which would be found in the larger population having the disease or condition under study. This concern was expressed in the testimony of Dr. Thal, a witness for the Center, who testified, ''(A)s the number of patients in a study decreases, the chance variation or the variability introduced by a single one or two patients grows.'' (Thal, Tr. Vol. VI at 48–49.)

Because of the larger standard error with a small sample, the results from a study conducted on a small sample may not reflect the true value which would have been obtained from the population-at-large having the disease

or condition under study. Evidence of effectiveness can be drawn from small samples, but for the evidence to be reliable the sample needs to be carefully selected beforehand. The sample must be representative of the larger population having the disease or condition under study.

The problems of generalizing results from a small study were also at issue in the Commissioner's Decision on OPE, which stated:

> (A) statistically significant result, when based on a sample size of only five subjects, does introduce the strong likelihood that the subjects were not representative of the larger population from which the sample was drawn, and that there may be an inadvertent lack of comparability in the test and control groups, contrary to the requirements of (the regulations).

(Commissioner's Decision on OPE, slip op. at 117; cf. Commissioner's Decision on Lutrexin, 41 FR 14406 at 14419 (In a study with a total of 32 patients, the small size of the sample was identified as a factor which ''aggravated'' the problems arising from the unreliability of the diagnostic criteria used in the study.))

For the above discussed reasons, I therefore find that the ALJ was correct in observing that the omission of one or two patients can change the results of a small sample study (I.D. at 52), and was correct in questioning whether it was appropriate to generalize the results of the Yesavage study. (I.D. at 57.)

As for AHP's argument that a statistically significant result in a small sample indicates that the drug effect is ''large,'' I find this statement to be inaccurate and misleading. (See AHP Exceptions at 167, citing Mantel, A–127 at 7–8.) AHP seems to be implying that a statistically significant result in a small study necessarily means that the test drug had a significant clinical effect. This implication is incorrect.

Statistical significance is not the same as clinical significance. (Commissioner's Decision on Benylin, 44 FR 51512 at 51521.) Statistical significance is an expression of the probability that an observed difference between the mean outcome of the test drug group and the mean outcome of the control drug group occurred by chance. (Commissioner's Decision on Benylin, 44 FR 51512 at 51520.) A clinically significant effect, however, is an expression of the degree of benefit which was observed in the study's patients and which may be expected in future patients. (Commissioner's Decision on Benylin, 44 FR 51512 at 51520.)

As has been noted in previous Commissioner's decisions, it is possible to achieve a statistically significant difference between treatment and control groups in a clinical trial, yet the test drug may be found not to have had a clinically significant effect, i.e., the effect on the patient is not beneficial either in degree or type of effect. (Commissioner's Decision on Lutrexin, 41 FR 14406 at 14419; Commissioner's Decision on Benylin, 44 FR 51512 at 51520 and 51521; Commissioner's Decision on Mysteclin, slip op. at 24–29.) Estimates of clinical significance take into consideration other matters beyond a finding of statistical significance, such as identifying which parameters were said to have shown statistical significance and deciding whether those parameters are important in a clinical setting. These considerations are further discussed in the next section of this decision. (See section I.D.2.f. of this document.)

Therefore, for the foregoing reasons, I find that the ALJ was correct in considering the small sample size as a factor to be considered in reviewing the results of the Yesavage study.

f. *Clinical significance.* AHP next argues that the ALJ erred in finding that the improvement on SCAG Factor 1 was not clinically significant. (AHP Exceptions at 169, citing I.D. at 54, 57.) As was previously described (see section I.D.2.c. of this document), SCAG Factor 1, ''cognitive dysfunction,'' included the following four items: (1) Confusion, (2) impaired mental alertness, (3) impaired recent memory, and (4) disorientation. (G–11.1 at 70.) AHP argues that the outcome on SCAG Factor 1 was clinically significant because dementia is a progressive disease, and that any small improvement would be important to both the patient and the physician. (AHP Exceptions at 170.)

The ALJ's finding was based on the testimony of two witnesses for the Center, Drs. Mohs and Thal. These witnesses both testified that the absolute magnitude of change from baseline for SCAG Factor 1 was very small, approximately 1.9 change on a scale on which patients in the study had been shown to have a baseline value of 14.1. (Mohs, G–62 at 18; Thal, G–63 at 15–16.) Drs. Mohs and Thal testified that this degree of change—a 14 percent improvement on one SCAG Factor—would not be evident to most observers. (Mohs, G–62 at 18; Thal, G–63 at 15–16.) It should be noted that the lowest/best score on SCAG Factor 1 would be a 4; the highest/worst score would be a 28. (See, e.g., G–12.1 at 38.) This would mean that from a baseline score of 14.1, the score on SCAG Factor 1 had lowered/improved to approximately 12.2.

On the other hand, three witnesses for AHP—Drs. Overall, Zung and Klerman—testified that because dementia has no known cure and because this disease is a progressive one, a 14 percent improvement on one SCAG factor is, in their opinions, clinically significant. (Overall, Tr. Vol. II at 49; Zung, Tr. Vol. III at 7; Klerman, Tr. Vol. III at 70–71.) Based on the testimony of these witnesses, AHP essentially is arguing that any statistically significant result on any one of the several tests used in the Yesavage study is necessarily clinically significant because there is no known cure for dementia. I do not find this argument to be persuasive.

In the United States Supreme Court decision of *United States* v. *Rutherford*, 442 U.S. 544 (1979), the Court recognized that the statutory requirement of proof of effectiveness necessarily required a showing of some clinical benefit to the patient. In relevant part, the Court stated, ''(I)n the treatment of any illness, terminal or otherwise, a drug is effective if it fulfills, by objective indices, its sponsor's claim of prolonged life, improved physical condition, or reduced pain.'' (442 U.S. at 555.) Consistent with the *Rutherford* decision, the United States Court of Appeals for the Third Circuit has ruled that it is within the purview of the FDA to decide whether a drug has clinical significance. (*Warner-Lambert*, 787 F.2d at 154–56; see also Commissioner's Decision on Mysteclin, slip op. at 24.)

To reiterate some of the discussion of the previous section (see section I.D.2.e. of this document) regarding the difference between statistical and clinical significance, a drug can have a statistically significant effect without having a clinically significant effect. Statistical significance is an expression of the probability that an observed difference between the test drug and the control drug occurred by chance. Clinical significance, on the other hand, is an evaluation of whether the test drug offers a therapeutic benefit to the patient. (Commissioner's Decision on Mysteclin, slip op. at 25; Commissioner's Decision on Benylin, 44 FR 51512 at 51520 and 51521; Commissioner's Decision on Lutrexin, 41 FR 14406 at 14419.) Proof of statistical significance is insufficient without proof of clinical significance. (Commissioner's Decision on OPE, slip op. at 60–62.) As the Court in *Warner-Lambert* noted:

> The fact that the drug, not chance, can be assumed to have contributed to (the finding of statistical significance for) the factor measured does not necessarily establish that patients will receive a benefit from the drug.

The Commissioner has consistently required a showing of some benefit as an element of the statutory requirement of effectiveness.

(Warner-Lambert, 787 F.2d at 155 (citation omitted).)

Turning now back to the evidence at hand, AHP's argument in favor of finding clinical effectiveness for Cyclospasmol® was expressed in the testimony of Dr. Zung, an AHP witness, who testified as follows:

I would say that first of all, we are dealing with an illness, which is the dementias, where we know that there has been no drug available for the treatment of this disease so that there has been no improvement whatsoever on any drug that's known. So here we're talking about an illness with progressive deterioration so, therefore, in fact any treatment that would either arrest the development of the illness or in fact improve the illness would definitely be significant. Factor 1 of the SCAG then, in fact, is specific to measure the cognitive dysfunction that's associated with the dementia and that, of course, has been the indication for which the drug has been studied.

(Zung, Tr. Vol. III at 7–8.)

In contradistinction to Dr. Zung's testimony, the testimony offered by Dr. Mohs, a witness for the Center, was as follows:

The absolute magnitude of change was very small for the cognitive factor in the SCAG, approximately 1.9 on a scale that had a baseline value of 14.1. This change would not be evident to most observers. Also, there was no corroboration even as a trend on the other measures, such as, the NOSIE, the Buschke memory test or the clinical global evaluation. Finally, there is a discrepancy between the overall item, item 19 on the SCAG, and (the) clinical global item completed by the investigator at the end of the study. The overall item on the SCAG did tend to show an improvement for the Cyclospasmol® group, whereas the clinical global item completed at the end of the study did not show any significant effect and these items presumably should be highly cor(r)elated. Because the effect claimed is so small, not corroborated by other tests, and in fact inconsistent with tests that measure the same effect, I do not find the results to be clinically significant.

(Mohs, G–62 at 18.)

Similar testimony was offered by Dr. Thal, another witness for the Center, who testified with reference to Cyclospasmol®, ''If the drug fails to show a clinically significant improvement on any global or clinical evaluation scale and fails to make a meaningful difference in the way a (patient) lives his or her life, one must seriously question whether that drug should be marketed for a specific indication.'' (Thal, G–63 at 16.)

Having reviewed the evidence, I do not find AHP's argument to be persuasive. There is no indication that the results on SCAG Factor 1 will translate into a clinically meaningful reversal or slowing of the progress of dementia. Moreover, AHP's witnesses failed to address the fact that the statistically significant result on SCAG Factor 1 stands alone and is not corroborated by the other measures.

I further note that when a comparable argument was advanced by the manufacturer in the Commissioner's Decision on Lutrexin, that decision ruled that, notwithstanding the fact that there may be no alternatives for the proposed indication for the drug under review, the act nonetheless requires that the effectiveness of a drug be demonstrated by substantial evidence. The Commissioner's Decision went on to note that this requirement does not result in depriving patients of the only known effective drug therapy for a proposed indication because, absent scientifically reliable evidence, that particular drug is not proven to be effective for that indication. (Commissioner's Decision on Lutrexin, 41 FR 14406 at 14411.)

For these reasons, I do not find that AHP has fulfilled the requirement of proving clinical significance.

g. *Multiple tests.* In the Yesavage study, 28 outcome measures were statistically analyzed, including the Nurses Observation Scale—Inpatient Evaluation (NOSIE) score, the Hamilton Depression Scale, the BMT, the clinical global impression score, and the 24 measures—5 factors plus 19 items—on the Sandoz Clinical Assessment—Geriatric (SCAG) measure. (G–9.2 at 45.) Each of these measures was also assessed for six time periods during the study, including at baseline and at weeks 3, 6, 9, 12, and 16. (G–11.1 at 29–37.) Of these 28 outcome measures, 2 measures—SCAG Factor 1 (''cognitive dysfunction'') and SCAG Item 19 (''overall impression of patient functional capacity'')—showed statistical significance in favor of the Cyclospasmol® group, based upon the results of the 20 patients whose outcomes were included in the final analysis of the SCAG. (G–11.1 at 19–20, 29, 78; Thal, G–63 at 16–17; Chaing, Tr. Vol. I at 52–53; Overall, A–116 at 6.)

AHP argues that the results of SCAG Factor 1 are ''the most relevant and important indicator'' of the efficacy of Cyclospasmol® for senile dementia.[7] (AHP Post-Hearing Brief at 116.) However, the ALJ ruled that because the number of tests and outcome measures for each patient in the Yesavage study were so numerous, it was ''difficult to draw definitive conclusions from the fact that statistical significance was found on one factor (SCAG Factor 1).'' (AHP Exceptions at 172, quoting I.D. at 54.) AHP argues that this was error, and AHP further argues that the fact that multiple outcome measures were used does not lessen the strength of its SCAG Factor 1 finding, nor the SCAG Item 19 finding, which was also reported to have been statistically significant. (AHP Post-Hearing Brief at 117.) AHP additionally argues that because the various outcome measures were specified in the protocol, the multiple statistical analyses were not performed to generate a post hoc hypothesis. (AHP Post-Hearing Brief at 116.)

The Center argues that the ALJ was correct in his ruling, and also argues that the statistically significant results on SCAG Factor 1 and SCAG Item 19 may be due to the multiple statistical tests employed. (Center Post-Hearing Brief at 90–92; see also Mohs, G–62 at 17; Thal G–63 at 16.) The Center argues that cognitive dysfunction is only one aspect of senile dementia, and that senile dementia has many manifestations besides that of cognitive impairment, such as impairments in social functioning, orientation, personality, and the ability to speak (aphasia). (Center Post-Hearing Brief at 91, citing Zung, Tr. Vol. III at 43–44.) The Center points to the fact that AHP did not specify cognitive impairment, either on SCAG Factor 1 or SCAG Item 19, as the parameter of interest in advance of the study. (Center Response to AHP Exceptions at 73.) In support of its argument, the Center quotes from the Yesavage study's protocol as stating more generally that the purpose of the study was to evaluate Cyclospasmol® ''in improving symptoms usually associated with brain function.'' (Center Post-Hearing Brief at 90–91, quoting G–9.2 at 32.)

The Center also cites to the testimony of Dr. Zung, a witness for AHP. (Center Response to AHP Exceptions at 72–73.) When Dr. Zung was asked how corrections for multiple comparisons are performed, he replied that there are two methods for making such corrections. The first is to specify in advance, before the statistical analysis is performed, the parameter of interest. The second method is to employ a statistical correction for the number of multiple comparisons which were made. (Zung, Tr. Vol. III at 62–63.) The Center argues that such corrections should have been

[7] I note that there was a difference between SCAG Factor 1 in the Yesavage study, and SCAG Factor 1 in the Rao study. In the Yesavage study, SCAG Factor 1 was called ''Cognitive Dysfunction,'' and it was comprised of SCAG Items 1 through 4. In the Rao study, SCAG Factor 1 was called ''Mental Dysfunction,'' and it was comprised of SCAG Items 1 through 4 and Item 8. (Chaing, Tr. Vol. I at 47.)

made in the Yesavage study. I find the Center's arguments to have merit.

A comparable issue was adjudicated in the Commissioner's Decision on Mysteclin. Therein, it was ruled, ''(E)ven if the subgroups and multiple endpoints had been identified in the protocol, * * * some downward adjustments in the p values should have been made to correct for the analyses of multiple subgroups and endpoints.'' (Commissioner's Decision on Mysteclin, slip op. at 43; see also Commissioner's Decision on Deprol, 58 FR 50929 at 50933.) Similarly, in the Commissioner's Decision on Deprol, it was noted that, ''if enough pair-wise comparisons are made, some comparisons will be 'statistically significant' by chance alone.'' (Commissioner's Decision on Deprol, 58 FR 50929 at 50933.) When multiple comparisons are made, corrections in the p values are needed to maintain the correct Type I error rate because the likelihood of a Type I error increases with the number of individual comparisons. (Commissioner's Decision on Deprol, 58 FR 50929 at 50933.) In other words, as one great author more expressively observed, ''Fortune brings in some boats that are not steered.'' (Shakespeare, *Cymbeline*, IV, iii, 46.)

For these reasons, I find that in weighing the adequacy of the Yesavage study, it is proper to consider the fact that numerous statistical analyses were employed, and to consider that the particular outcome of interest was not specified in advance, nor were adjustments to the p value made. Accordingly, I find no error in the ALJ's ruling on this point.

h. *Adequacy of the Yesavage study*. In sum, I find that the Yesavage study was not adequate and well-controlled. In making this determination, I have considered the aggregate effect of the protocol violations. I base my ruling upon these findings: (1) That the selection of patients for the study was flawed by the inclusion of patients with the concomitant condition of Parkinson's disease, and by the inclusion of outpatients, who were to be excluded under the protocol; (2) that the failure to show that stroke patients were included in both the drug and the placebo arms of the clinical trial can be considered as a flaw in the study; (3) that the fact that a statistically significant difference between test and control groups existed on the BMT was a proper consideration; (4) that the uncontrolled use of concomitant medication and the poor documentation of concomitant medication use weighs against finding the Yesavage study to be adequate and well-controlled; (5) that the small sample size was a proper factor to be considered in reviewing the results of the study, and can be weighed against the adequacy of the study; (6) that the improvement of patients on SCAG Factor 1 was not clinically significant; and (7) that the fact that numerous statistical analyses were employed and that the particular outcome of interest was not specified in advance, nor were adjustments to the p value made, can be weighed against the adequacy of the study.

II. Conclusion and Order

The foregoing opinion in its entirety constitutes my findings of fact and conclusions of law. Based on the foregoing discussion, findings, and conclusions, I affirm the ALJ's Initial Decision in all respects, except where specifically stated otherwise. I find that there is a lack of substantial evidence that Cyclospasmol® will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling. Accordingly, under 21 U.S.C. 355(e)(3), the NDA for Cyclospasmol® must be withdrawn. I further find that, by reason of the lack of substantial evidence of its effectiveness, Cyclospasmol® is a ''new drug'' within the meaning of 21 U.S.C. 321(p).

Therefore, under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(e), and under authority delegated to me by the Secretary (§ 5.10(a)(1)), the new drug application for Cyclospasmol® and all amendments and supplements thereto, are hereby withdrawn, effective January 2, 1997.

Dated: November 12, 1996.

Michael A. Friedman,

Deputy Commissioner for Operations.

[FR Doc. 96–30648 Filed 12–2–96; 8:45 am]

BILLING CODE 4160–01–P

[Docket No. 96D–0334]

Procedures for Issuance of and Review and Response to Materials Submitted in Response to Clinical Hold for Investigational New Drug (IND) Applications; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of two documents entitled ''Centerwide Policy on Issuance of and Response to Clinical Hold Letters for Investigational New Drug Applications'' (OD–R–8–96, Center for Biologics Evaluation and Research (CBER)) and ''IND Process and Review Procedures'' (MAPP 6030.1, Center for Drug Evaluation and Research (CDER)). The documents specify the procedures for the issuance of and review and response to material submitted in response to a notice of clinical hold. It is intended that these documents will clarify the agency's policy in regard to responses to clinical holds. The documents are made available as part of the agency's commitment to review and respond to data submitted in response to a clinical hold within 30 days of receiving the submission, as stated in the November 1995, Presidential National Performance Review report entitled ''Reinventing the Regulation of Drugs Made from Biotechnology.''

ADDRESSES:

CBER Information: For additional copies of the documents submit written requests to the Manufacturers Assistance and Communication Staff (HFM–42), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448. Send one self-addressed adhesive label to assist that office in processing your requests. The document may also be obtained by mail or FAX by calling the CBER FAX Information System at 1–888–CBER FAX, or 301–827–3844. Persons with access to the Internet may obtain the document using FTP, the World Wide Web (WWW), or bounce-back e-mail. For FTP access, connect to CBER at ''ftp://ftp.fda.gov/CBER/''. For WWW access, connect to CBER at ''http://www.fda.gov/cber/cberftp.html''. For bounce-back e-mail send a message to ''INDHOLD@a1.cber.fda.gov''.

CDER Information: For additional copies of the documents contact the Drug Information Branch (HFD–210), Division of Communications Management, Center for Drug Evaluation and Research (CDER), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–1012. The form may also be obtained by calling the CDER FAX–ON–DEMAND System at 1–800–342–2722, or 1–301–827–0577. An electronic version of the documents is also available via Internet using FTP, Gopher, or the World Wide Web (WWW). For FTP, connect to the CDER anonymous FTP server at cdvs2.cder.fda.gov and change to the ''guidance'' directory. For Gopher, connect to the CDER Gopher server at