DEPARTMENT OF HEALTH AND HUMAN SERVICES

U.S. FOOD AND DRUG ADMINISTRATION

REGULATORY HEARING ON THE PROPOSAL TO DISQUALIFY

PAUL W. BOYLES, M.D.

FROM RECEIVING INVESTIGATIONAL NEW DRUGS

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REPORT OF THE PRESIDING OFFICER

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1. INTRODUCTION

Pursuant to Title 21 of the Code of Federal Regulations ("C.F.R.") Parts 16 and 312, the U.S. Food and Drug Administration ("FDA") conducted a hearing on December 18, 1991, to consider the proposal of the FDA's Center for Drug Evaluation and Research ("Center") to disqualify Paul Weldon Boyles, M.D. from receiving investigational new drugs.[1] The Center contended that Dr. Boyles should be disqualified for the following reasons: (1) submitting false information to the sponsors[2] in required reports, in violation of 21 C.F.R. § 312.70; (2) failing to

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[1] An **investigational new drug** is defined as "a new drug, or biological drug that is used in a clinical investigation." [See 21 C.F.R. § 312.3(b).] A **new drug**, which includes an approved drug that is proposed for a new use, is defined in section 201(p) of the Federal Food, Drug, and Cosmetic Act. [See 21 C.F.R. § 310.3.]

[2] A **sponsor** is "a person who takes responsibility for and initiates a clinical investigation." [21 C.F.R. § 312.3(b).]

obtain initial and continuing Institutional Review Board ("IRB")[3] approval, in violation of 21 C.F.R. § 312.66; (3) failing to maintain adequate and accurate records, in violation of 21 C.F.R. § 312.62; and (4) failing to follow the investigational plan, in violation of 21 C.F.R. § 312.60.

This document constitutes my report on the hearing pursuant to 21 C.F.R. § 16.60(e). This report, along with the parties' comments with respect thereto and the administrative record, will be referred to the FDA Commissioner for a final determination on this matter. [See 21 C.F.R. § 16.95.]

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[3] "**Institutional Review Board** (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research." [21 C.F.R. § 50.20(i) (emphasis added).]

2. BACKGROUND

In 1983, Dr. Boyles[4] conducted a clinical investigation under an Investigational New Drug ("IND")[4] application for the drug manufactured by the [See Boyles Exhibit ("BX") C at 40-50, 53.] In 1987 the FDA audited the clinical study conducted by Dr. Boyles. [See id.; Trans. at 10.] The Center testified that Dr. Boyles had told the FDA investigator during the audit that an IRB which he controlled, i.e., the Boyles Foundation, Inc. ("Boyles Foundation IRB"), reviewed some of the clinical studies. [Trans. at 10.] The Center further testified that at the time of the 1987 audit, the FDA auditor scheduled an inspection of the IRB at a later date. [Id.]

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[4] Prior to his current position as a physician at and Clinical Assistant Professor of Medicine, University of , School of Medicine, , , Dr. Boyles was employed in the following positions: Assistant Director of Medical Research at from 1965-1968, Assistant Director of Clinical Research at from 1968-1972, and Medical Director of a firm called from 1988-1990. [See Curriculum Vitae, Boyles Exhibit ("BX") A, Administrative Record ("AR") Vol. II, Tab A, at 3 and 59.]

[4] 21 C.F.R. § 312.20 requires a sponsor to "submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to 21 C.F.R. § 312.2(a)." A **clinical investigation** is defined as "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects." [See 21 C.F.R. § 312.3(b).]

The Boyles Foundation IRB was then inspected on July 12-29, 1989, by FDA investigator Ms. Barbara Frazier[5] and an FDA investigator-trainee, Ms. Kathleen Workman.[6] [See Center Exhibit ("CX") 27.] The FDA inspectors found that the Boyles Foundation IRB was located in Dr. Boyles' private practice in Cary, North Carolina. [Trans. at 8-9.] Dr. Boyles was President and Chairman of the IRB at the time of the IRB inspection. [CX 27 at 1.] Dr. Boyles had been originally elected as chairman of the Boyles Foundation IRB in November 1980, and he was reelected to this position as recently as January 30, 1989. [Trans. at 9.] Dr. Boyles was the only investigator[7] for whom the IRB reviewed trials, as well as the only physician member of the IRB from 1985 until the 1989 inspection. [CX 27 at 1 and 3.] The IRB had approved twelve clinical studies conducted by Dr. Boyles, starting in 1981. However, it did not review the study. [Trans. at 46 and 151.] Among the other discrepancies noted on the FDA Form 483, certain problems were listed regarding a study of the drug , (sponsored by , conducted by Dr.

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[5] Ms. Frazier, who testified at the hearing, has been an investigator with the FDA for 21 years. At the time of this inspection, Ms. Frazier worked out of the Raleigh resident post of the Atlanta district office. [Trans. at 8.]

[6] Ms. Workman was not present at the hearing and, therefore, did not testify.

[7] An **investigator** is defined as "an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject.)" [21 C.F.R. § 312.3(b).]

Boyles in 1987. [CX 27 at 2-3.]

In response to the findings from the IRB inspection, Frances O. Kelsey, Ph.D., M.D., Director of the Center's Division of Scientific Investigations, Office of Compliance, sent Dr. Boyles a "Notice of Adverse Findings" letter on September 13, 1989, requesting that the IRB terminate all studies subject to 21 C.F.R. Parts 50 and 56, until the Center had received assurances that the IRB had adequately corrected its procedures, to comply with Parts 50 and 56. [CX 28 at 1-2.] The letter stipulated that Dr. Boyles had 30 days to correct the deficiencies in his IRB. [Id. at 2.]

Dr. Boyles then apparently attempted to comply with the IRB requirements (e.g., a voting physician member was added to the IRB; IRB forms were revised), and Dr. Boyles provided assurances that the IRB would improve its record-keeping. [See CX 28 at 3-13.]

From February 7 - March 9, 1990, a follow-up investigation of the Boyles Foundation IRB was conducted that focused on two of Dr. Boyles' studies, a study ( ) and the previously-referenced, study.[8] [Trans. at

[8] Ms. Frazier served as the official FDA investigator for this inspection. Ms. Doralie Segal, who was a physiologist for

26; CX 26.]

The inspection also uncovered numerous problems with both the and clinical studies, listed in an FDA Form 483, of which Dr. Boyles was apprised at an exit interview. [CX 26; Trans. at 150.]

As a result of these findings, on July 10, 1990, Dr. Kelsey sent Dr. Boyles a letter, citing the specific instances of his noncompliance with FDA regulations. [CX 28 at 14-22.] The letter offered him an opportunity to respond to the allegations in writing or at an informal conference, or to enter into a consent agreement that would rescind his eligibility to receive investigational drugs. [Id.] The letter concluded by stating that, in the absence of a consent agreement or a satisfactory response, Dr. Boyles would be offered the opportunity for a regulatory hearing on these matters under 21 C.F.R. Part 16. [Id. at 21.] On October 5, 1990, the Center sent a second letter

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the Clinical Investigations Branch in the Center's Division of Scientific Investigation, Office of Compliance at the time of the inspection, participated in the inspection "as a scientific resource and technical assistance person for Ms. Frazier."

The "for-cause" inspection of Dr. Boyles' and studies in 1990 were conducted in follow up to the previous inspection. Among other reasons, the inspection of the study was conducted because the drug sponsor had submitted Dr. Boyles' study as a pivotal study in support of a New Drug Application ("NDA") for . [Trans. at 53; see also CX 26 at 1.]

to Dr. Boyles, because, as the letter stated, the Center had not received a response to its previous letter. [Id. at 24.] This letter requested that Dr. Boyles call Dr. Kelsey's office prior to October 15, 1990, if he wished to take advantage of the options listed in the July 10, 1990 letter. [Id.] The Center advised Dr. Boyles that if no response was received, the Center would initiate an action that could result in a finding that Dr. Boyles would be ineligible to receive investigational drugs. [Id.]

3. PROCEDURAL HISTORY

By letter dated April 26, 1991, Ronald G. Chesemore, FDA Associate Commissioner for Regulatory Affairs, informed Dr. Boyles of a "Notice of Opportunity for Hearing" ("NOOH")[9] [attached], pursuant to 21 C.F.R. §§ 312.70 and 16.22.[10] [CX 28 at 26-35; Administrative Record ("AR") B at 1-10.] On June 4, 1991, FDA re-sent the NOOH because Dr. Boyles failed to respond

[9] 21 C.F.R. Part 16 provides: "FDA will give to the party requesting the hearing reasonable notice of the matters to be considered at the hearing, including a comprehensive statement of the basis for the decision or action taken or proposed that is the subject of the hearing and a general summary of the information that will be presented by FDA at the hearing in support of the decision or action." [21 C.F.R. § 16.24(f).]

[10] Neither the Center nor Dr. Boyles submitted additional information regarding the concerns raised in the Center's original July 10, 1990, or the October 5, 1990 letters.

to the April 26, 1991 correspondence, and no postal confirmation of delivery had been received by the Agency. [AR B at 11.]

The NOOH informed Dr. Boyles of his opportunity to request a regulatory hearing to determine whether he should be disqualified from receiving investigational new drugs. [CX 28 at 34-5; AR B at 9-10.] On June 21, 1991, Dr. Boyles requested a hearing in a letter addressed to John L. Hauser.[11] [AR C.] On September 23, 1991, a hearing was scheduled for December 18-19, 1991. [AR H.] As Presiding Officer, I provided both the Center and Dr. Boyles with information on Part 16 hearing procedures, as well as copies of 21 C.F.R. Parts 16 and 10 and § 312.70, in a letter dated August 23, 1991. [AR G.] The letter also provided an opportunity for each party to submit information for consideration. [See AR G, J and Mc.] Dr. Boyles was repeatedly advised of his right to retain an attorney for ~~this~~ matter. [AR J and Mc.]

In a letter that I received November 22, 1991, Dr. Boyles requested a postponement of the hearing. He claimed that documents concerning his investigational studies were destroyed as a result of an auction of the clinic building and equipment following Chapter 7 bankruptcy. [AR O at 1.]

[11] Mr. Hauser was a Consumer Safety Officer in the Center's Division of Compliance Policy.

I considered the reason for postponement offered by Dr. Boyles to be insufficient and denied his request in a facsimile followed by a letter, dated December 9, 1991. [AR U.] Dr. Boyles submitted materials by facsimile on December 17, 1991, with a notation that they were in lieu of his appearance at the hearing. [See BX A.] The hearing was held on the scheduled date of December 18, 1991; however, Dr. Boyles did not appear. [AR XYZ.] Shortly after the hearing convened, I closed it to the public, in accordance with 21 C.F.R. § 16.60. [Trans. at 4.]

The Center made the following charges, as described in the NOOH, in support of its proposal that Dr. Boyles be disqualified from receiving investigational new drugs:

I. Dr. Boyles violated 21 C.F.R. § 312.70(a) by submitting false information to the sponsor in required reports.

II. Dr. Boyles violated 21 C.F.R. § 312.66 by failing to obtain initial and continuing IRB review and approval.

III. A. Dr. Boyles violated 21 C.F.R. § 312.62(a) by failing to maintain adequate records of the disposition of investigational drugs.

B. Dr. Boyles violated 21 C.F.R. § 312.62(b) by failing to prepare and maintain adequate case histories for study subjects.

IV. Dr. Boyles violated 21 C.F.R. § 312.60 by failing to follow investigational plans delineated in the and protocols.

The Charges made by the Center against Dr. Boyles were fully described in the NOOH.

To support the charges, the Center presented two witnesses, Ms. Barbara Frazier[5] [Trans. at 8-49.], and Ms. Doralie Segal[8] [Trans. at 50-150.], and the Center submitted 36 exhibits. As stated previously, although Dr. Boyles did not appear at the hearing, he submitted 59 pages of exhibits by facsimile, including his Curriculum Vitae, a history of his litigation with a pharmaceutical manufacturer, and several personal statements.

4. REGULATORY FRAMEWORK

FDA's regulations governing the clinical evaluation of investigational new drugs are set forth in 21 C.F.R. Part 312. Regulations regarding informed consent and IRBs applicable to clinical investigations are set forth in 21 C.F.R. Parts 50 and 56.

Section 312.70 of the regulations provides for the disqualification of investigators. That section provides, as here relevant:

> After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, Part 50, or Part 56, . . . the Commissioner will notify the investigator and the sponsor of any investigation in which the investigator has been named as a participant that the

> investigator is not entitled to receive investigational drugs. The notification will provide a statement of basis for such determination.

[21 C.F.R. § 312.70(b).]

Although many of the events cited in the charges of the NOOH took place prior to the revision of the IND regulations on March 19, 1987, the NOOH referred to the revised IND regulations. However, because the revised regulations are largely consistent with the regulations in place at the time of the events in issue (except as noted in the "Analysis" section), this revision had no effect on the recommended disposition of the charges. Therefore, for purposes of this report, I have used and cited the current form of the regulations for analyzing the Center's charges, unless otherwise noted.

5. ANALYSIS

In preparing my report, I reviewed each charge made by the Center in the NOOH, taking into account the information submitted by the parties and the Center's presentation at the hearing. I provided both the Center and Dr. Boyles 30 days to make post-hearing submissions. However, neither the Center nor Dr. Boyles submitted materials within the 30-day time period. Therefore, I did not consider any post-hearing submissions in arriving at my recommendations.

Charge I. Dr. Boyles violated 21 C.F.R. § 312.70(a) by submitting false information to the sponsor in required reports.

The Center charged that Dr. Boyles submitted false information to his sponsor in required reports, in violation of 21 C.F.R. § 312.70. Section 312.70 provides the following (emphasis added):

> If FDA has information indicating that an investigator has repeatedly or deliberately failed to comply with the requirements of this part, Part 50, or Part 56, **or has submitted to the sponsor false information in any required report**, the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research will furnish the investigator written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered but not accepted by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research, the investigator will be given an opportunity for a regulatory hearing under Part 16 on the question of whether the investigator is entitled to receive investigational new drugs.

Subcharges I.A., I.B., I.C., and I.D.

I.A. IRB approval letters for the clinical studies appeared to be altered copies of prior IRB approval letters.

I.B. The study was terminated twice at meetings by the IRB for which there were no records. The signatures on these termination letters appeared to be photocopies, rather than original signatures.

I.C. The acknowledgement letter from the IRB to sponsor of the study, appeared to have a signature identical to that of prior IRB approval letters and was, therefore, photocopied from a previous letter.

I.D. The approval letter for a past study appeared to be an altered copy of the approval letter of an earlier study). In the letter, the list of people present at the IRB meeting was inconsistent with the names of individuals mentioned in the minutes of the same IRB meeting.

To support **Subcharges I.A, I.B., I.C. and I.D.**, the Center produced several of the documents listed in the Subcharges and presented testimony that Dr. Boyles had generated documents from photocopies of other documents. [CX 29-31, 33; Trans. at 15-23.] However, the Center focused on how the reports submitted by Dr. Boyles to the sponsors were generated and did not address the issue regarding his submission of "**false information** in required reports," i.e., the veracity of the information contained in the documents as that information reflected the factual situation.

The Center focused on how the reports submitted to the drug sponsors were generated by Dr. Boyles ~~and~~ his staff. For example, the Center testified (emphasis added):

> When we started comparing approval letters that we located in Ms. notebook and Dr. Boyles' folder and in the study records, one with another, we were finding that some of the dates -- some of the information on the approval letters appeared to be changed. For example, we found three approval letters for . There were two dated May 10, '87 and December 16, '87 that **appeared to be altered copies** of a May 10, 1984 approval letter. Those two letters listed members as being present for meetings that there were no minutes for. There were no minutes showing there was a meeting on May 10, ~~'87~~ or December 16, '87 . . . .

[Trans. at 16 (emphasis added); see also CX 29.]

During the hearing, the Center presented testimony that Dr. Boyles had admitted that he created documentation for IRB events after the fact. [See Trans. at 23-6.][12] Of these four subcharges, only **Subcharge I.D.** addressed the veracity of a document, namely the IRB approval form for the study [CX 29 at 11.], which listed a member who did not appear on the list of attendees at the minutes of the meeting [CX 30 at 7.]. [Trans. at 16.] However, the minutes of the meeting were illegible[13] and had not been signed by the IRB's secretary. For these reasons, I find that the Center failed to provide sufficient evidence to prove **Subcharge I.D**, and that **Subcharges I.A, I.B, and I.C** fail to support a charge that Dr. Boyles submitted false information to the sponsor.

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[12] The following is an excerpt from such testimony: "It was during this discussion [of the protocols] that he [Dr. Boyles] admitted that he had photocopied old approval letters for us." [Trans. at 25 (testimony of Ms. Frazier).]

[13] The Center testified as to the poor condition of Dr. Boyles' records which had resulted in unreadable photocopies submitted by the Center as exhibits or in the lack of a record altogether, for example: "The laboratory records, the EKG tracings for the study had been stored in a box on the floor in the basement and become [sic] wet and mildewed. So the records were stuck together and part of the tracings were totally obliterated . . . ." [Trans. at 29 (testimony of Ms. Frazier); see also id. at 18 and 64; see also infra.]

The Center asks me to conclude that because the documentation of the IRB review is a photocopied record that was apparently an altered version from an earlier record, IRB review of the and studies did not occur. I can not find that the Center has met its burden.

The Center has the burden of showing that review did not occur. While the state of the record raises significant questions about the care with which the Boyles Foundation IRB generated letters, and whether the close relation between Dr. Boyles and the IRB led to a manner of conducting business that does not comply with professional standards, it does not show that the IRB did not consider the and studies. If the minutes of the IRB meeting at which the study was allegedly discussed were devoid of any mention of it, a persuasive circumstantial showing might have been made. Those minutes, however, are illegible. Therefore, I can not draw the inference that the Center suggests can be drawn from the ragged state of the records, and I find that the Center failed to substantiate **Subcharges I.A., I.B., I.C., and I.D.**

Subcharge I.E.

The signatures of study subjects 806 and 12003 on some consent forms did not appear to match those of these individuals on other records and on forms in office charts. The name of study subject 12007, who was illiterate, was misspelled on his consent form.

For **Subcharge I.E.**, the Center produced as evidence a consent form for study subject 12007, in which the study subject's name was spelled with an "e". [CX 5 at 1.] The Center produced a sample [See CX 5 at 1 and 3.] of the study subject's signature from a Medicare Card, in which the name was spelled with a "u". [See id. at 2-3; Trans. at 30-1.] Although Dr. Boyles did not respond to this charge in writing, the Center alleged in the NOOH that Dr. Boyles had explained that the name was misspelled [with the "e"], because the study subject was illiterate, and his wife usually signed for him. [AR B and attached, at 3.]

To support this Subcharge further, the Center presented additional excerpts from study subjects' files where study subjects' signatures had allegedly been forged on the consent form. [See CX 2, 3, and 14.] The Center, however, was unable to produce expert handwriting testimony, or a certified signature of a study subject, e.g., a signature verified by a Notary Public, to compare to the signatures on the consent forms at the hearing

to support this charge. [See Trans. at 31-5.][14] Moreover, the documents provided at the hearing were photocopies of Dr. Boyles' records, making it even more difficult to judge whether the signatures had been falsified without expert assistance. Therefore, I find that the Center failed to substantiate the allegations in **Subcharge I.E.**

Subcharge I.F.

> **The time to first awareness of angina was changed on the Case Report Form ("CRF") for study subject 12008, which permitted the study subject to meet an eligibility criterion for a subsequent double-blind trial.**

In **Subcharge I.F.** the Center alleged that Dr. Boyles falsified the time to first awareness of angina in the Case Report Form for study subject 12008. The Center presented two versions of the study subject's CRF. [CX 6 at 4-5.] Both CRF's were dated May 12, 1987, and both were labeled as "Page 10 of 27" for this study subject. [Id.] On one CRF, page 10 specified a "7:00" minute time for the "Elapsed TIME From

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[14] When the witnesses were questioned regarding their specific training and expertise to assess handwriting, Ms. Frazier denied expertise in handwriting analysis. [Trans. at 31.] While Ms. Segal claimed some experience, she denied having credentials or specialized training in handwriting analysis. [Trans. at 34.] Although the Center expressed an intent to submit expert testimony at a later date [Trans. at 33.], no such information was received. In fact, the Center testified that the Center had initially contacted a handwriting expert but the expert had told the Center that the Center's copies were "not very good." [Id.]

Beginning of Test to EVENT [first awareness of angina]." [Id. at 4.] On the other CRF, an "8" had been written over the original "7" and appeared to be initialed by Dr. Boyles. [See id. at 5.]

The Center also presented a letter to Dr. Boyles, dated September 18, 1987, from for the Inc., which stated: " With regard to Patient RF [study subject 12008], Study Visit 2, first awareness of angina, Dr. would rather you left the time as it was originally (7:00) unless the tracing actually shows the 8:00 time. You can send me a new page 10 . . . ." [CX 32 at 11.] Based on this letter, it appeared that the CRF page with the altered time (i.e., "8:00") was the form to which Ms. referred, and that she was requesting Dr. Boyles to confirm this change from "7:00" minutes with the subject's actual EKG tracing. [See CX 6 at 4 and 5.] Since there existed a another Page 10 with the "7:00" number, it appeared that Dr. Boyles must have prepared a new page 10 with the time as it was originally, "7:00." [See id.]

The protocol specifically excluded subjects with "greater than +/- 25%" or "+/- 2 minutes difference" in "time to angina" [timed treadmill test done to the point of developing chest pain] or "time to termination" of exercise [timed treadmill test to the point the study subject could no longer tolerate the

exercise] from week to week. [CX 24 at 9.] For study subject 12008, the original seven minute time would have resulted in the exclusion of this study subject from the protocol, whereas the altered eight minute time resulted in eligibility for the protocol. [See **Subcharge IV.F.**, infra.]

Dr. Boyles provided no alternative explanation for why the time would have been changed. Therefore, I find that the Center provided sufficient information to support **Subcharge I.F.** Since the Center met its burden of proof for one of the six subcharges, I find that Dr. Boyles did violate 21 CFR § 312.70(a) and the Center sufficiently demonstrated **Charge I.**

Charge II. **Dr. Boyles violated 21 C.F.R. § 312.66 by failing to obtain initial and continuing IRB review and approval.**

Title 21 C.F.R. Section 312.66 states (emphasis added):
"Assurance of IRB review. An investigator shall assure that an IRB that complies with the requirements set forth in Part 56 will be responsible for the **initial and continuing review and approval** of the proposed clinical study."

To support **Charge II**, the Center cited a number of documents used in support of **Charge I.** [See CX 29-31; 33.] In its testimony, the Center again focused on the issue that the information

supplied in the documents recording IRB protocol approvals or IRB meetings was "false information" and, therefore, could not have constituted "initial and continuing IRB review and approval." As with **Charge I**, the Center's witnesses described how the alleged "altered copies" of documents regarding IRB meetings and approval letters were generated. [See id.; Trans. 9-22.] Specifically, the supporting paragraph for **Charge II** in the NOOH (attached, at 3-4, emphasis added) reads:

> As stated in Part I [**Charge I.**] above, the approval and termination letters for the approval letter for and the letter acknowledging receipt of amendment 250.1 appeared to be altered copies of other letters previously issued by the IRB. **You were unable to provide the FDA investigator with original copies of any of these letters or with any other documentation that the information contained in the letters is accurate.**

The Center asks me to conclude that because the documentation of the IRB review is a photocopied record that was apparently an altered version from earlier record, IRB review of the and studies did not occur. I can not find that the Center has met its burden.

The Center has the burden of showing that review did not occur. As I stated above, while the state of the record raises significant questions about the care with which the Boyles Foundation IRB generated letters, and whether the close relation between Dr. Boyle's and the IRB led to a manner conducting

business that does not comply with professional standards, it does not show that the IRB did not consider the and ; studies. If the minutes of the IRB meeting at which the study was allegedly discussed were devoid of any mention of it, a persuasive circumstantial showing might have been made. Those minutes, however, are illegible. Therefore, I can not draw the inference that the Center suggests can be drawn from the ragged state of the records. In addition, the Center did not point to any requirement that demanded that "original copies" of letters and documents be maintained.

For these reasons, I find that the Center failed to prove that Dr. Boyles did not obtain initial and continuing IRB approval, and, therefore, find that he was not in violation of 21 C.F.R. § 312.66, as alleged in **Charge II.**

Subcharge III.A. **Dr. Boyles violated 21 C.F.R. § 312.62(a) by failing to maintain adequate records of the disposition of investigational drugs.**

Section 312.62(a) of the regulations provides that "[a]n investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects." Since the Center's charge focused on the absence of records kept by Dr. Boyles, the Center presented testimony to that effect. Ms. Frazier testified: "There were no records of

drug accountability showing when he received test articles or when he distributed them, or when he'd return any unused supplies to the drug sponsors." [Trans. at 29.]

Ms. Segal testified: "[T]here were no drug accountability records on site at all, other than what was faxed in by the sponsor. But we had nothing to go on that he provided." [Trans. at 54.] Ms. Segal further testified that since Dr. Boyles' studies were double blind, double dummy, the sponsor had probably prepackaged the drug for specific study subjects and sent the drug to Dr. Boyles to administer to these individuals. Therefore, Dr. Boyles would not know who actually received the drug. [Trans. at 55-6.]

Dr. Boyles had been notified in the NOOH that these matters would be considered at the hearing. However, he did not affirm or deny them prior to the hearing or after he had received the Center's exhibits. Dr. Boyles also failed to address these matters upon receiving the transcript of the hearing. Dr. Boyles had signed the FDA Form 1573, which stated:

> The investigator shall maintain the records of the disposition of the drug and case histories described above for a period of 2 years following the date a new-drug application is approved for the drug; or if the application is not approved, until 2 years after the investigation is discontinued.

From February 7 through March 9, 1990, FDA investigators Frazier

and Segal conducted an inspection of Dr. Boyles' and protocols. [Supra; see also FN 8 at 5.] Because was not approved until January 28, 1991,[15] at the time of this inspection, Dr. Boyles was required to have his records for the study in his possession. Since no information was presented during the hearing to indicate that either a New Drug Application (NDA)[16] had or would soon be filed for or that the IND under which Dr. Boyles had been operating was at any time withdrawn prior to the 1990 inspection, Dr. Boyles should also have had the study records available for the FDA's 1990 inspection.

Dr. Boyles was responsible for insuring that his records were "adequately" maintained, legible, and available for an FDA inspection. [See 21 C.F.R. § 312.62(c).] This he failed to do.

Thus, for the and studies described in the NOOH, I find that Dr. Boyles failed "to maintain adequate records of the disposition of investigational drugs," as required by 21

[15] Listing for in Approved Drug Products with Therapeutic Equivalence Evaluations 12th Edition, U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Management, 1992 at 3-244.

[16] NDAs are submitted to FDA in accordance with 21 C.F.R. Part 314 and under section 505 of the Federal Food, Drug, and Cosmetic Act to market a new drug.

C.F.R. § 312.62(a), as alleged in **Subcharge III.A.**

Charge III.B. **Dr. Boyles violated 21 C.F.R. § 312.62(b) by failing to prepare and maintain adequate and accurate case histories for study subjects.**

Section 312.62(b) of the regulations provides that (emphasis supplied):

> [a]n investigator is required to prepare and maintain adequate and accurate case histories designed to record **all observations and other data pertinent** to the investigation on each individual treated with the investigational drug . . . .

Subcharge III.B.1. **Dr. Boyles failed to keep records of the hypertensive histories of study subjects in the study.**

The Center alleged in **Subcharge III.B.1.** that Dr. Boyles failed to keep records of the hypertensive histories of study subjects in the study. The "hypertensive history" of a subject who was being studied with an antihypertensive investigational agent, e.g., would be part of the case history required under section 312.62(b). [Supra.]

Although the Center did not define the term "hypertensive history" before, during, or after the hearing, it provided several types of information required to be recorded and maintained for the study, which included information

about the study subjects' hypertension, their prior and concomitant medications, and their physical examinations and laboratory parameters (e.g., blood pressures). [See CX 10-23.] For example, the Center's exhibits included a "History" sheet (aka "History and Physical"), which included the study subject's "Present Complaints," medications and allergies [See, e.g., CX 18 at 1.]; the "Progress Notes" (aka "Office Visits"), listing the dates of the office visits and the study subject's weight and blood pressure [See, e.g., id. at 2.]; and the data sheet listing previously prescribed antihypertensive medication, [See, e.g., id. at 3.], as well as other study forms.

In addition, in **Subcharge III.B.2.** [infra] charged that "Dr. Boyles failed to report prior or concomitant therapy . . . ." Such therapy would have included the use of cardioactive drugs that affected the study subjects' blood pressure. A "hypertensive history" would necessarily encompass this information. For this reason, I will defer further discussion of "hypertensive histories" to the next subcharge.

Subcharge III.B.2. **Dr. Boyles failed to report prior or concomitant therapy, as required on case report forms (CRFs) for study subjects 12009 [Subcharge III.B.2.a] and 801 [b], 804 [c], 805 [d], 807 [e] and 808 [f].**

Subcharge III.B.2. alleged that Dr. Boyles failed to report **prior**

or **concomitant** therapy on CRFs for six study subjects. As part of the case history required for each study subject, the recording of concomitant drug use was also considered to be among the "observations and other data pertinent to the investigation on each individual treated with the investigational drug." [See 21 C.F.R. § 312.62(b).]

In addition, the study protocols that were implemented by Dr. Boyles specifically required the recording of **concomitant** drugs. The protocol "required that concomitant drugs, dosages, dates and reason for taking the drug be reported on the CRF." [CX 25 at 15.] The protocol required that the doses and dates of all concomitant medications be recorded on the CRFs. [CX 24 at 6.]

Besides the investigator's records, subjects on the study were required to record and maintain an account of the number of anginal attacks per day and the number of **sublingual nitroglycerin ("NTG") tablets** consumed per day. [CX 24 at 10.] The protocol discussed the use of sublingual NTG. Under the subject selection criteria, it stated: "Patients must have a history of substernal or precordial chest pain, pressure or distress, provoked by exertion, and relieved by rest or by nitroglycerin in sublingual doses of 0.3 or 0.4 mg . . . ." [Id. at 3.]

Subjects would be excluded from the protocol for the following: "Patients who, in the investigator's judgement [sic], need to continue other anti-anginal medication aside from sublingual nitroglycerin, or to continue other cardioactive medications, vasodilators, psychotropic agents, or any drug know to affect the ST segment." [Id. at 4-5.]

With respect to concomitant medications: "Patients may not be given digitalis, or other cardioactive medication other than sublingual nitroglycerin . . . ." [Id. at 6.]

For study subject 12009, the Center presented the subject diary, in which the subject recorded the use of NTG **tablets,** administered **sublingually**, and NTG **patches**, applied to the skin. As discussed above, although the use of **NTG patches** was not explicitly addressed by the protocol, such use would constitute "other cardioactive medication" which was specifically excluded as a **concomitant** medication.

The Center presented a poorly photocopied CRF for study subject 12009 in which the "Number of NTG Tablets taken since last visit" differed from the subject's self-kept diary. [See Trans. at 108-9; CX 7 at 5, 9-11, and 13.] In reviewing the CRF and the diary documents, it appears that Dr. Boyles had completed the CFR form by combining the number of NTG **patches** and **tablets**

recorded in the subject diary in the space provided for the reporting of NTG **tablets**, i.e., sublingual doses (The form did not provide a space for reporting NTG patch use.). [See supra; CX 7 at 5 and 11; CX 24 at 6; see also **Subcharges III.B.4. and IV.G.**, infra.] For this reason, I find that the Center demonstrated that for study subject 12009, Dr. Boyles failed to report accurately the **concomitant** drug use to the sponsor on the CRF.

The Center also charged that study subject 801 had taken **prior** or **concurrent** medication, which Dr. Boyles did not report on the CRF. The Center stated that 801 had participated in the study from July 8, 1985 until November 1, 1985. For this study subject and for subsequent charges concerning study subjects, the records which documented the study periods did not clearly state that was the investigational product used. [See, e.g., CX 10 at 2-3.] Instead, the Center contended that the study was identified in the subjects' records as Study." [Trans. at 64.] When questioned as to whether the records submitted as exhibits by the Center identified the actual study drug by name, the Ms. Segal testified: "No, it just says, here for study. Then it goes into, here for new study, which was our study. is an ACE inhibitor . . . ." [Id. at 64 and 69.] The

Center argued that the accuracy of Ms. Segal's statement could be corroborated by comparing the study subject record notation to the CRFs and the protocol for for each of the study subjects, as identified by either a study number or the subjects' initials. [Id. at 69.] For each study subject where the notation for the investigational product was unclear, I, therefore, performed such corroborative analysis.

For example, the progress notes for study subject 801 showed that the Study" started on July 8, 1985 and ended on November 1, 1985. [CX 10 at 2-3.] The protocol had been submitted as "' Protocol 250" for the investigational agent ' a code name for the drug [See CX 25 at 1; Trans. at 62.] The Center exhibit for this study subject included a number of CRF forms, which referred to and protocol 250. [See forms, CX 10 at 5-8.] All of the CRF forms included the same study subject identifiers (i.e., the initials of the study subject and subject number 801). [Id.; see also id. at 2-3.]

801 apparently participated in the study from July 8, 1985 until November 1, 1985. [CX 10 at 2-3.] The FDA Form 483 listed the same dates for the study period and was used to corroborate the dates of participation. [CX 26 at 4-5.] Therefore, I find that study subject F 801 did participate

in the study from July 8, 1985 until November 1, 1985, based on all of the corroborative evidence, as described above.

801 was prescribed on June 19, 1985, and on September 25, 1985, [See CX 10 at 2-3; CX 26 at 4-5.] Since no "stop" date was recorded for either drug, and since 801 was already enrolled in the study on the date that was prescribed, [see, supra], 801 would have had to have taken the prior to and concomitantly with, and concomitantly with, the investigational drug,

Moreover, an instruction sheet from the sponsor provided guidance regarding the reporting of current/concomitant medication:

> For each prescribed or over-the-counter medication taken by subject at any time during study, enter the required information. If dosage remains unchanged during study, only one entry is required. If medication is stopped or a change in dosage occurs, enter stop date; for a medication that continues at a different dosage, enter new information as a separate entry.

[CX 10 at 4.] For 801, neither were listed on the study forms for "Previous Antihypertensive Medications" [Id. at 7.], or for "Current or Concomitant Medications" [Id. at 8.].

Although neither the Center nor Dr. Boyles provided additional information, e.g., a study subject diary of medication taken, to

indicate whether these concomitant medications were actually taken by this study subject, the prescriptions noted in the hospital notes were sufficient to establish the usage of these medications by study subject 801. Therefore, I conclude that for this subject, Dr. Boyles failed to report both **prior** and **concomitant** medication on the CRF, as required by the sponsor.

The Center alleged that for study subject 804, Dr. Boyles failed to note in the CRF that the subject had received during the study. The Center presented an information sheet for this study subject that lacked any subject identifiers, e.g., initials or study number. Instead, the sheet had only dates, body weight, and status of the study. As in the previous example, the Center presented an exhibit that referred to the There was no actual identification of the investigational product or the protocol used. [CX 12 at 1.] The same document noted that this study began on August 5, 1985 and ended on December 5, 1985, which was corroborated by FDA Form 483 [CX 26 at 4.] and two other study forms [CX 12 at 1-2.].

Information on two of the "Vital Signs & Physical Examination" forms in the CRF linked the unidentified study subject's weight to 804. [See CX 12 at 4-5.] Based on the interconnection of these documents, I find that the Center

established that 804 did participate in the study during the above dates.

Next, the Center demonstrated that the records showed that the study subject was prescribed on July 15, 1985, based on a prescription notation on the clinic record. As described above, the Center showed that the subject's records documented the use of on July 15, 1985, prior to the study, which the subject entered on August 5, 1985. [See CX 12 at 1.] Since no "stop" date was recorded, I conclude that the subject received prior to and concomitantly with the study. [See supra.] On the subject's "Current/Concomitant Medication" form, however, the only medication entered was with a "start" date of October 30, 1985. [Id. at 7.] Therefore, I find that the Center proved that Dr. Boyles failed to report the **concomitant** use of for 804 on the appropriate study form.

For study subject 805, the Center alleged that the subject had taken the drugs and during the study, and that these medications were not duly recorded as **concomitant** medications on the CRF. As above, the Center's exhibit failed to provide the proper identifiers, and the FDA Form 483 was needed to corroborate the dates of the subject's study participation (August 5, 1985 to December 2, 1985). [CX 13

at 2; CX 26 at 5.] Since the clinic record noted that and were prescribed on August 5, 1985, and since no "stop" date was indicated for either of these medications [supra; CX 10 at 4.], I conclude that the subject continued to take the two drugs while on the trial. [Id.] The subject's "Current/Concomitant Medication" form reported "None" for medications taken during the study. [CX 13 at 4.] Moreover, Dr. Boyles did not deny the information presented by the Center prior to, during, or following the hearing. [See CX 26.] For these reasons, I find that for 805 Dr. Boyles failed to enter the appropriate information regarding **concomitant** medications on the CRF.

For study subjects 807 and 808, the Center presented clinical records to show that each subject had been involved in a **prior** investigational blood pressure study, and that Dr. Boyles had failed to report this information accurately, as required on the respective CRFs.

For 807, the clinic records, in conjunction with the FDA FORM 483, documented that the subject had participated in an unidentified Study" from March 18, 1985 to July 9, 1985. [CX 15 at 1-2; CX 26 at 5.] However, the NOOH referred to the stopping date of this study as "July 16, 1985." In her testimony, Ms. Segal noted the discrepancy in the date recorded

in the NOOH and the date in the Center's exhibit. [Trans. at 127; see also CX 26 at 5.]

The Center presented 807's "Previous Antihypertensive Medication" form, which required the investigator to "List all previous antihypertensive medications taken within the last 3 months . . . . " [CX 15 at 4.] This form failed to list the dates of 807's first blood pressure study. [Id.] Although the ending date was incorrect in the NOOH, the "start" date established that the first blood pressure study took place **prior** to the trial, and either ending date occurred within the 3-month period required for reporting of the study drug in the CRF.

Since the CRF failed to disclose the previous trial with an antihypertensive agent, I find that for 807, Dr. Boyles failed to report accurately **prior** therapy, as required on the CRF.

The clinic records for 808 showed that, like 807, this subject had participated in an unidentified blood pressure study, which ran from March 26, 1985 to July 16, 1985. [CX 16 at 4-5.] From August 20, 1985 to December 10, 1985, the same record stated that the subject started on a Study" or

Study," i.e., the study. [Id.;

see also supra.] Since the form for "Previous Antihypertensive Medication" did not reflect the subject's participation in the previous study [Id. at 6.], I find that Dr. Boyles failed to document **prior** therapy, as required on the CRF.

Therefore, I find that the Center proved **Subcharge III.B.2.**, because the Center demonstrated that Dr. Boyles failed to report prior or concomitant therapy on the CRFs for study subjects 12009 and study subjects 801, 804, 805, 807, and 808.

Regarding **Subcharge III.B.1.**, which charged that Dr. Boyles failed to keep records of hypertensive histories for study subjects in the study, the Center failed to address this subcharge specifically. Nevertheless, the evidence presented in **Subcharge III.B.2.** for 801, 804, 805, 807 and 808 -- establishes Dr. Boyles' failure to keep hypertensive histories. The specific relevant examples are as follows: 801 took and which was not reported on the CRF; 804 took which was not reported on the CRF; 805 took which was not reported on the CRF; 807 and 808 had participated in unidentified blood pressure studies, which were not reported on the CRF. Since the above examples demonstrate that Dr. Boyles did not keep records of hypertensive histories for study subjects in the RAMIPRIL study, I find that the Center demonstrated **Subcharge**

III.B.1.

Subcharge III.B.3. **Dr. Boyles failed to report intercurrent illnesses or reactions to the sponsors for study subjects 801 [Subcharge III.B.3.a], 804 [b] and 812 [c], and 12006 [d].**

In **Subcharge III.B.3.**, the Center alleged that Dr. Boyles failed to report intercurrent illnesses or reactions for the above referenced study subjects. The regulations require that the investigator record and submit information to the sponsor regarding "any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug . . . . " [See 21 C.F.R. § 312.64(b).]

The instructions provided to Dr. Boyles by the drug sponsor for completing the "Intercurrent Illness or Injury" form stated:

> Use this form to report incidence or occurrence of any CLEARLY DEFINED infection or injury, totally independent of drug therapy and resulting in symptoms CLEARLY ATTRIBUTABLE to the insult.
>
> This form should NOT be used to report exacerbations of previous or chronic conditions (unless unmistakably related to an injury or infection), or symptoms of unknown, questionable, or even suspicious etiology. Such symptoms should be reported as SIDE EFFECTS.

[CX 10 at 6.]

As discussed under **Subcharge III.B.2.**, the Center demonstrated that study subject 301 participated in the trial from September 15, 1985 to November 1, 1985. [See supra.] The subject's "Progress Notes" for September 25, 1985 noted the subject as "[f]eeling tense — dizzy — & nervous — hands are wet — Having episode of not feeling well most of day until has 2-3 beers . . . ." [CX 10 at 3.] The Center then presented the study subject's "Intercurrent Illness or Injury" form which stated "None." [See id. at 6.] Therefore, I find that Dr. Boyles failed to record study subject 801's intercurrent complaint on the CRF.

As established in **Subcharge III.B.2.**, supra, study subject 804 participated in the trial from August 5, 1985 to December 5, 1985. The "Current/Concomitant Medication" form stated that 804 had taken "Tuss-Ornade" for "Sinus & Cold" with a "start" date of October 30, 1985. [CX 12 at 7.] This event was not reported on the "Intercurrent Illness or Injury" form in the CRF. [Id. at 15.] Therefore, I find that Dr. Boyles also failed to record the intercurrent illness for study subject 804.

Although the NOOH stated that study subject 812 had participated in the study from July 30, 1985 to November 25, 1985, the clinic records established that the subject did not

enter the study until August 6, 1985. [CX 20 at 7.] The Center presented the subject's progress notes which reported that 812 had experienced what appeared to be an oral temperature of "100" following a week of not "feeling well" on October 8, 1985. This intercurrent event was not recorded on the "Noteworthy Comments" form, which listed the study subject as "Cl. [Clinical] Normal" on October 8, 1985 [CX 20 at 1.], or on the "Intercurrent Illness or Injury" form, which stated "None" (although no dates were referenced on this particular form). [CX 20 at 5.] Since the Center demonstrated that 812 experienced the above event during the study, and the event was not reported in the CRF, I find that the Center established its charge that Dr. Boyles failed to report an intercurrent illness or reaction for 812 on the CRF.

Finally, for study subject 12006, the Center charged that Dr. Boyles had not properly reported seizure activity experienced by this subject during the study on the CRF. The subject started the study on April 27, 1987. [CX 4 at 1-2.] The study "History & Physical" form, dated May 18, 1987, reported the subject as: "Feeling good except for headache this AM - No chest pain - Having **more seizures** 4x ["times"] this past week." [CX 4 at 2; emphasis added.] The concomitant medication form for this subject listed the drug "PHENYTOIN" for "seizures," which had been started in 1984, and no "stop" date

was recorded. [Id. at 4.] For this reason, I conclude that for 12006, seizures were a "previous" or "chronic" event. Also, the CRF form "Adverse Event Record" for May 18, 1987, listed only "headache," for which no therapy was required. [Id. at 4.] Since the Center did not address the subject's baseline seizure activity prior to the study, and since the only reference to seizure activity was the clinic note stating that the subject had experienced "more" seizures while on [supra], I conclude that the effect of on the subject's seizure activity could not be ruled out. For this reason, Dr. Boyles should have recorded this event on the "Adverse Event Record" form and reported it to the sponsor, as required in section 312.64(b).

Therefore, I find that Dr. Boyles failed to record "seizures" properly on the CRF.

Subcharge III.B.4. **Dr. Boyles failed to report use of NTG tablets consistently with the diaries of study subjects 12002 [Subcharge III.B.4.a], 12004 [b], 12006 [c], and 12009 [d].**

To support **Subcharge III.B.4.** for the above study subjects, the Center presented discrepancies between the recorded numbers of NTG tablets on the CRFs of the above subjects and the

numbers recorded in the subject-kept diaries.[17] [Supra.] Since NTG tablet use would represent a **concomitant** medication administered during the investigational study, and since NTG might affect the results from the investigational agent, such information would be data pertinent to the investigation. [See 21 C.F.R. § 312.62(b).] Therefore, Dr. Boyles should have recorded the use of **concomitant** medication accurately on the CRFs.

For study subject 12002, the Center charged that Dr. Boyles erroneously reported NTG tablet usage on the CRF for Study Visits 3 and 7. Ms. Segal testified that the NOOH should have stated that Dr. Boyles erroneously reported NTG tablet usage for Study Visits 2 and 7. [Trans. at 140.]. Therefore, Dr. Boyles was not provided with sufficient notice regarding deficiencies reporting Study Visit 2.

According to the CRF, Study Visit 7 should have reported events which transpired between Study Visit 6 (May 17, 1987) and Study Visit 7 (June 10, 1987). The Center failed to demonstrate an inconsistency between 12002's CRF and diary report:

[17] The CRF recording of the subject's use of NTG tablets was based on the subject's diary completed during the study. Any discrepancies between the diary and the CRF reporting of the diary entries should have been noted either on the CRF or the diary.

The diary report indicated that seven NTG tablets had been taken during this time interval; the CRF reported on Study Visit 7 that seven NTG tablets had been taken. [See CX 1 at 1 and 4-5.] Therefore, the Center failed to establish a reporting error in the CRF of NTG tablet usage for 12002 on Study Visits 3 or 7.

For study subject 12004, the Center charged that Dr. Boyles had incorrectly reported the number of NTG tablets taken by the study subject on Study Visit 3. Since the dates for Study Visit 2 and Study Visit 3 were illegible, and since neither the FDA Form 483 [CX 26 at 7.] nor the NOOH specified the dates between Study Visits 2 and 3, I was unable to assess the validity of the Center's charge. [See CX 3 at 1.] Therefore, I find that the Center failed to prove an NTG tablet discrepancy between the study subject diary and the CRF for study subject 12004.

For study subject 12006, the Center charged that Dr. Boyles failed to report an angina attack and the proper number of NTG tablets taken on the CRF for Study Visit 2. According to the CRF, Study Visit 2 should have reported events that transpired between Study Visit 1 (April 27, 1987) and Study Visit 2 (May 4, 1987). [CX 4.] The Center presented the subject diary which reported that for the above referenced time interval, 12006 had

used 3 NTG tablets and had experienced one anginal attack: On April 28, 1987, the study subject experienced one angina attack and took one NTG tablet; and on May 1, 1987, the study subject took two NTG tablets. [Id. at 12-3.] However, Dr. Boyles reported for Study Visit 2 that "zero" NTG tablets had been taken and "zero" anginal episodes had been experienced since Study Visit 1. [Id. at 11.] Therefore, the Center demonstrated that Dr. Boyles failed to report accurately the number of NTG tablets taken and anginal episodes experienced in the CRF for Study Visit 2 for 12006.

For study subject 12009, the Center presented discrepancies between the NTG tablets taken for Study Visits 2 and 4. [See CX 7 at 5.] First, the Center charged that the subject diary showed that the subject had used an NTG patch on December 16, 1987. However, NTG patch use was not reported under Study Visit 2 in the CRF. [Id. at 5.] This allegation was corroborated by the Center's exhibits. [See id. at 5 and 9.] The subject diary, however, noted that the patch was used on the "test day," i.e., Study Visit 1, which was recorded in the CRFs as December 16, 1987. Thus, this patch usage did not have to be recorded as an entry for Study Visit 2 in the CRF, which represented the time interval **between** December 16 and 22, 1987.

Secondly, the Center charged that Dr. Boyles incorrectly reported

the NTG **tablet** usage for Study Visit 4, representing the time interval between December 29, 1987 and January 5, 1988. The Center presented the subject diary. [CX 7 at 11.] In the columns labeled "Number of NTG taken," 5 doses of NTG were recorded in the diary during the above time interval: one "NTG" on January 2, 1988; two NTG and one 10 mg NTG **patch**, on January 3, 1988; and one 10 mg **patch** on January 4, 1988. [Id.] In the CRF Dr. Boyles reported in the NTG **tablet** space for Study Visit 4 that 5 **tablets** had been taken; he did not differentiate between NTG **tablet** and NTG **patch** doses. As discussed in **Charge III.B.2.**, the CRF form only permitted the reporting of NTG **tablets**. [Id. at 5; see also supra.] Therefore, I find that the Center demonstrated that Dr. Boyles failed to report accurately the NTG **tablet** usage for study subject 12009 for Study Visit 4.

In summary, for **Subcharge III.B.4.**, I find that Dr. Boyles failed to report the use of NTG tablets consistently with the diaries for study subjects 12006 and 12009.

For the above reasons, I find that Dr. Boyles violated 21 C.F.R. § 312.62(b) by failing to maintain adequate case histories as alleged in the following subcharges: **III.A., III.B.1., III.B.2., III.B.3., and III.B.4.**

Charge IV. **Dr. Boyles violated 21 C.F.R. § 312.60 by failing to follow investigational plans delineated in the and protocols.**

The definition of "General responsibilities of investigators" in 21 C.F.R. § 312.60, states: "An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations . . . ."

Charge IV. alleged that Dr. Boyles failed to insure that the and studies were conducted according to their respective investigational plans, as delineated by their respective study protocols [CX 24 and 25].

Subcharge IV.A. **Dr. Boyles violated the protocol proteinuria exclusion for study subject 804.**

The Center charged that Dr. Boyles admitted study subject 804 to the trial in violation of the protocol. Specifically, the study protocol excluded subjects with "significant hepatic or renal disease as evidenced by . . . [p]roteinuria 1+ or greater." [CX 25 at 9.] The Center presented two data sheets for study subject 804, which contained laboratory values consistent with proteinuria [protein in the urine]. [CX 12 at 9 and 12.] However, the key dates on

the data sheets were illegible. Although Ms. Segal testified as to the dates which she had seen on the sheets [Trans. at 63-4.], the dates on the respective copies of the laboratory data sheets were so faint as to be completely illegible, whereas the remaining information on the sheets was legible. It was evident from the data sheets that study subject 804 did indeed have "+1 proteinuria" on two occasions. However, it was impossible to establish whether these occurrences fell within the study time period. [CX 12 at 9 and 12; Trans. at 62-4.] Therefore, in the absence of additional documentation, I do not consider Ms. Segal's testimony sufficient to establish the dates on these particular data sheets. [Id.] In addition, the Center had previously testified to the poor condition of Dr. Boyles' records. [See, e.g., Trans. at 29, 64, and 120; see also supra.] Therefore, in the absence of other substantiating evidence, the dates of the data sheets could not be confirmed, and I find that the Center failed to prove the allegation in **Subcharge IV.A.**

Subcharge IV.B. **Dr. Boyles violated the protocol experimental drug use exclusion for study subjects 809 [Charge IV.B.1] and 810 [2].**

The Center alleged that Dr. Boyles admitted study subjects 809 and 810 to the study, in violation of protocol criteria which excluded subjects who had received prior investigational drugs. Specifically, the protocol excluded

"Patients receiving any investigational new drug for any therapeutic reason within one month of study initiation." [CX 25 at 8.] The study protocol did not further define the term "month."

The Center presented the clinic record of study subject 809, which recorded an office visit (noted as "Here for Study") on August 26, 1985. [CX 17 at 6; Trans. 64-8.] However, the clinic record also indicated that on September 3, 1985, eight days later, the study subject was "Here for New Study/See Case Report." [Id.; see also supra.] Since a minimum interval of a month was required between the completion of a prior study and entry onto the study, the entry of this subject onto the study eight days after the prior investigation constitutes a protocol violation.

For study subject 810, from the progress notes, this subject apparently also participated in a blood pressure study before entering the study. [See CX 18 at 2.] An entry, dated August 28, 1985, stated "Here for study withdrawal," which was taken by the Center as signalling the conclusion of the subject's participation. [See id.] An entry dated September 6, 1985 stated "To start Study" (aka study). [Id.; see also supra.] These dates

clearly indicate a time period of less than one month between the two entries. Since a minimum interval of a month was required between the completion of a prior study and entry onto the study, the entry of this subject onto the study constitutes a protocol violation. [See Trans. at 68-75.]

In the absence of any information indicating that these study subjects had not taken investigational drugs before entering onto the study, I find that the Center proved the allegations of **Subcharge IV.B.**

Subcharge IV.C. **Dr. Boyles violated the protocol weight exclusion for study subject 810.**

The Center alleged that Dr. Boyles failed to follow the investigational plan by entering study subject 810 into the study in violation of the protocol's morbid obesity exclusion. The Center testified that the protocol excluded "Subjects with morbid obesity (100 lbs. overweight, based on desirable weight from the Metropolitan Life Insurance Co. table)."[18] [Trans at 78; see CX 25 at 9.] During the

[18] In the protocol submitted as an exhibit by the Center, the section "Exclusions", item "1." appeared blackened out, rendering it illegible. [See CX 25 at 9.] The Center testified that this section was the exclusion criteria referring to morbid obesity which had been "highlighted" by agency staff creating the appearance that it was deleted in the photocopied

hearing, the Center presented testimony that it had erroneously charged Dr. Boyles with violating this protocol exclusion criteria for study subject 810. The Center stated that it had intended to refer to study subject 815. [Trans. at 78.]

Since the Center failed to establish that study subject 810 violated the exclusion criteria, I find that the Center failed to provide sufficient evidence to document **Subcharge IV.C.**, as specified in the NOOH.

Subcharge IV.D. **Dr. Boyles violated the protocol EKG exclusion for study subject 12008.**

The Center alleged that Dr. Boyles violated the protocol by admitting study subject 12008. The protocol excluded study subjects with a resting EKG showing ST depression of greater than 0.5mm. [CX 24 at 5.] In support of **Subcharge IV.D.**, the Center presented an unlabeled EKG tracing on which no leads or subject identifiers were marked, and on which a written note stated "slight angina" pointing to a region of the tracing that was so faint as to be uninterpretable. [CX 6 at 12.] For this reason, it was impossible to determine

exhibit. The Center confirmed that the section [which could not be read] had not been deleted from the protocol. [Trans. at 76.]

from the tracing what constituted a "resting EKG," or which portion had been identified as representative of "an ST depression of greater than 0.5mm," as alleged by the Center. [Id.] Therefore, I find that the Center failed to demonstrate that Dr. Boyles violated the protocol by admitting study subject 12008 to the study.

Subcharge IV.E. **Dr. Boyles violated the protocol ST segment exclusion for the following study subjects: 12002, 12005, 12007, and 12011.**

The Center alleged that Dr. Boyles violated the protocol by admitting study subjects 12002, 12005, 12007, and 12011, who did not meet the EKG entry requirements. The protocol provided in its inclusion criteria: "Patients must have classically positive exercise treadmill tests, with ST segment depression of a horizontal or downsloping type, lasting at least 0.08 seconds after the J-point, of at least 1 mm below the PR segment, over and above any ST segment depression present on resting ECGs [= "EKG"]." [CX 24 at 3.]

First, the Center charged that study subjects 12002, 12005, and 12007 had not exhibited a 1 mm ST depression during treadmill tests. The Center submitted correspondence between Dr. Boyles and the sponsor, to prove this

charge. [See CX 32.]

On June 24, 1987, , M.D., Associate Medical Director, Medical Research, representing the sponsor, , wrote Dr. Boyles:

> As we discussed I believe that 3 patients who have enrolled in the study at your site are invalid. As you know, for technical reasons, Patient V.D.[19] did not have 12-lead electrocardiograms taken during the exercise tests. . . . Patient T.S.[20] as well as subject L.D.[21] do not demonstrate a classical ST segment depression which is horizontal or downsloping. Both of these patients have upsloping ST segment changes with exercise and therefore, do not comply

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[19] aka subject 12002. [See CX 1 at 2.]

[20] The Center exhibits did not clearly identify "Patient " CX 5, to which the Center's exhibit list referred as " Patient 12007," only included records from " " but no documents in that exhibit included a subject number for " " Center testimony identified "Patient ." as " Patient 12002" [Trans. at 90 and 102.]. However, the Center exhibit clearly identified subject 12002 as "Patient " [See CX 1 at 2.] Also, Center testimony identified " Patient 12007," as " " [Trans. at 90 and 102.]

[21] Again, the Center's exhibits failed to identify clearly " " None of the Center's exhibits included a subject with these initials. As noted in the previous footnote, Center testimony identified " " as " Patient 12007" [Trans. at 90 and 102.]. However, the Center listed "12007" as " ." in its list of exhibits.

One of the sponsor's monitors, , identified " as 12007 on a "Periodic Monitoring Report," but this same report also incorrectly identified " " as 12002 (aka "Patient V.D."). [CX 32 at 2.]

with the protocol requirements.

[CX 32 at 3.]

Since I was unable to determine who study subjects " " and " ." were in terms of study subject numbers used by the Center [See supra FN 20 and 21 at 50.], I find that the Center failed to demonstrate that Dr. Boyles committed any violations of the protocol related to these study subjects referenced in the above letter.

Regarding study subject 12002 ( ), Dr. Boyles responded by letter on July 2, 1987, stating that this subject was unable to demonstrate 1 mm ST depression during exercise when tested on July 1, 1987, and would, therefore, be dropped from the double-blind study. [CX 32 at 4.] The last entry in the CRF for study subject 12002 ( ) was in June of 1987, so it appeared that Dr. Boyles also dropped this study subject once he discovered that the subject did not meet the entry requirements. [See CX 1 at 1.] Nevertheless, the protocol required Dr. Boyles to perform the ST depression tests prior to entering the subject into the study to determine the subject's eligibility for the study, which he failed to do. As discussed, Dr. Boyles only dropped 12002 upon the conclusion of the study at the sponsor's request for such a test. Therefore, I find that Dr. Boyles violated the protocol by entering study subject

12002 onto the study.

In terms of this subcharge, the Center provided no ST depression information during treadmill tests in the exhibits for study subjects 12002 [CX 1.], 12005[22] or 12007 [CX 5.]. The Center presented ST depression information (EKG tracings) for study subject 12011 that was uninterpretable. [See CX 9 at 4-5, 8-9; Trans. at 93.] Therefore, based on the information presented, I am unable to determine whether Dr. Boyles violated the protocol entry requirements for study subjects 12005, 12007, or 12011.

Based on the foregoing, I find that Dr. Boyles violated **Subcharge IV.E.**, because the Center demonstrated that Dr. Boyles violated the protocol entry requirements for study subject 12002.

Subcharge IV.F. **Dr. Boyles violated the protocol "time to angina" exclusion for study subjects 12008 and 12010.**

The Center alleged that Dr. Boyles violated the protocol by including study subjects 12008 and 12010 in the study.

[22] The Center did not submit an exhibit for subject 12005.

The double-blind part of the protocol limited permissible variation between treadmill tests. [CX 24 at 9.] Specifically, on the last test before entering the double-blind portion of the study, the "time to angina" and "time to termination" could vary no more than two minutes or 25 percent from the values on the previous treadmill tests. [Id.; see also Trans. at 117.] Subjects who met the study criteria would begin the double-blind portion of the study following the evaluation of their treadmill tests at Study Visit 3. [CX 24 at 9.] The entry criteria would, therefore, depend on the differences between the treadmill tests at Study Visits 2 and 3 (or 3 and 3a, if the optional Study Visit 3a is used). [Id. at 7-8, 25-8.]

For study subject 12008, two CRF's were filed for Study Visit 2. [CX 6 at 4-5; Trans. at 39.] The first CRF recorded the "time to angina" as "7:00" ("seven") minutes. [CX 6 at 4.] However, in the second CRF for the same Study Visit 2 an "8" had been written over the original "7" and appeared to be initialed by Dr. Boyles. [See id. at 5.] For Study Visit 3, the last study visit before entering the double-blind portion of the trial, the CRF recorded a "time to angina" of "9:31" minutes. [Id. at 6.] The change in time reflected in the second CRF reduced the difference between treadmill tests for Visits 2 and 3 from 2:31 to 1:31 minutes, thereby qualifying this subject for the double-blind portion of the study. A difference in time of

2:31 minutes between Study Visits 2 and 3 would clearly have exceeded the two minute or 25 percent variation permitted by the double-blind protocol. Nonetheless, the subject continued on the study through Study Visit 7, as recorded by the CRF clinical record form. [Id. at 2.]

The sponsor also addressed this discrepancy in a letter from Ms. a medical research associate for the sponsor, to Dr. Boyles, dated September 18, 1987: "With regard to Subject [study subject 12008], Study Visit 2, first awareness of angina, Dr. would rather you left the time as it was originally (7:00) unless the tracing actually shows the 8:00 time." [CX 32 at 11.]

Based on this letter, it appeared that the CRF page with the altered time (i.e., "8:00") was the form to which Ms. referred, and that she was requesting that Dr. Boyles confirm this change from "7:00" minutes with the subject's actual EKG tracing. [See CX 6 at 4 and 5.] Since there existed another Page 10 with the "7:00" number, I conclude that Dr. Boyles must have prepared a new page 10 with the "7:00" time as it was originally. [See id.] Therefore, the Center proved that this study subject, 12008, should have been excluded from the study, because the correct time of "7:00" would have eliminated this subject from the study, as discussed, supra.

In a similar manner, the CRF for study subject 12010 at Study Visit 2 [CX 8 at 4.] recorded the "time to angina" as "6:00" minutes, and the CRF for Study Visit 3 [Id. at 6.], which appeared to be this subject's last visit prior to the double-blind portion of the study, recorded the "time to angina" as "12:00" minutes. The difference of six minutes between the two measurements clearly exceeded the two minute or 25 percent variation allowed by the protocol, and this subject should not have been entered into the study. Therefore, I find that Dr. Boyles violated the investigational plan, as alleged in **Subcharge IV.F.**

Subcharge IV.G. **Dr. Boyles violated the protocol cardioactive concomitant medication reporting requirement for study subject 12009.**

The Center alleged that Dr. Boyles violated the protocol by permitting study subject 12009 to use NTG **patches.** [See supra (**Subcharge III.B.2.**)] The protocol stated: "Subjects may not be given digitalis, or other cardioactive medication other than **sublingual** NTG." [CX 24 at 6 (emphasis supplied).] The subject diary presented by the Center clearly showed the use of NTG patches on January 3, 1988. [CX 7 at 11.] In addition, the Center showed that this subject's CRF failed to document the patches as prior or concomitant medication. [Trans. at 108; see also supra.] While the

subject's CRF documented the correct number of doses of NTG which were administered, it did not differentiate between the **patch** doses and the **tablets** of NTG. [Id.]

The protocol stated: "The protocol must be read thoroughly and the instructions must be followed exactly. Any deviations should be agreed to by both the sponsor and the investigator with appropriate written protocol amendments made to reflect the changes agreed upon." [CX 24 at 17.] Neither the Center nor Dr. Boyles submitted any exhibits that included or suggested that a protocol deviation amendment had been agreed upon to permit NTG patch usage. Therefore, I find that Dr. Boyles violated the investigational plan, as alleged in **Subcharge IV.G.**

Subcharge IV.H. **Dr. Boyles violated the protocol concomitant drug reporting requirement for the study subjects 801 and 804.**

The Center alleged that Dr. Boyles violated the protocol by allowing study subjects 801 and 804 to continue in the study despite concomitant antihypertensive drug use. The protocol stated:

> The subjects must not take any concomitant therapy without the physician's knowledge and permission. Documentation of concomitant drugs, dosage taken, dates, and reason will be entered on the case record forms. **Treatment with any other antihypertensive**

agent will disqualify the subject from the study except during the follow-up period.

[CX 25 at 8 (emphasis supplied); see also Trans. at 81.]

The Center alleged that was a **concomitant** medication for study subjects 801 and 804. [Supra.] Evidence presented by the Center and discussed in **Subcharge III.B.2.b. and c.** provide the basis for finding that the Center proved this charge. Specifically, study subject 801 participated in the study from July 8, 1985 to November 1, 1985, and was prescribed on June 19, 1985, and no "stop" date was recorded. As stated earlier, I conclude that the drug was continued during the study period. [Supra.] However, this drug was not mentioned in the study subject's CRF as a **prior** or **concomitant** medication. Study subject 804 participated in the study from August 5, 1985 to December 5, 1985, and was prescribed on July 15, 1985. Again, this drug was not mentioned in the subject's CRF as a **prior** or **concomitant** medication.

Therefore, I find that Dr. Boyles violated the investigational plan by not reporting as a **prior** or **concomitant** medication for 801 and 804, as alleged in **Subcharge IV.H.**

For the above reasons, I find that Dr. Boyles violated

21 C.F.R. § 312.60 by failing to follow the investigational plans as alleged in **Charge IV., Subcharges IV.B., IV.E., IV.F., IV.G., and IV.H.**

6. CONCLUSION

After considering the four charges in the NOOH, I find that Dr. Paul W. Boyles violated a number of the regulations cited one or more times. Specifically, I find that Dr. Boyles violated 21 C.F.R. § 312.70(a), as detailed in **Subcharge I.F.**; 21 C.F.R., § 312.62(a), as detailed in **Subcharge III.A**; 21 C.F.R. § 312.62(b), as detailed in **Subcharges III.B.1., III.B.2., III.B.3., III.B.4.**; and 21 C.F.R. § 312.60, as detailed in **Subcharges IV.B., IV.E., IV.F, IV.G.**, and **IV.H.**

7. RECOMMENDATION

Based on my findings as set forth above, I recommend that the Commissioner disqualify Paul W. Boyles, M.D., from receiving investigational new drugs.

Freddie Ann Hoffman, M.D.
Presiding Officer

FEB 16 1993