

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
REGULATORY HEARING ON THE PROPOSAL TO WITHDRAW
THE ELIGIBILITY OF
PAUL W. BOYLES, M.D.
TO RECEIVE INVESTIGATIONAL NEW DRUGS

COMMISSIONER'S DECISION

The purpose of this proceeding is to determine, pursuant to 21 C.F.R. § 312.70 and 21 C.F.R. Part 16, whether Paul W. Boyles, M.D., a clinical investigator, will be disqualified from receiving investigational new drugs. Freddie Ann Hoffman, M.D., Deputy Director, Medicine Staff, Office of Health Affairs, Food and Drug Administration (FDA), presided over the regulatory hearing held on December 18, 1991. Her recommendation is that Dr. Boyles be disqualified.

I conclude that Dr. Boyles repeatedly failed to comply with regulations governing the conditions for exemption of new drugs for investigational use. Therefore, Dr. Boyles is disqualified from receiving investigational new drugs. The reasons for my decision follow.

I. PROCEDURAL BACKGROUND

Between 1983 and 1989, Dr. Boyles conducted a study of the drug _____ for _____, a study of the drug _____ for _____ and a study of the drug _____

for In 1987, FDA audited the study conducted by Dr. Boyles. During that audit, FDA learned that the Institutional Review Board (IRB) for some of Dr. Boyles' studies was the Boyles Foundation, Inc. In July 1989, FDA inspected the Boyles Foundation. That inspection revealed several discrepancies with the operation of the IRB and that the IRB had not reviewed the study. By letter dated September 13, 1989, to Dr. Boyles, Frances O. Kelsey, Ph.D., M.D., Director, Division of Scientific Investigations, Office of Compliance, Center for Drug Evaluation and Research (Center), requested that the IRB terminate all studies subject to 21 C.F.R. Parts 50 and 56, until the Center received assurances that the IRB had corrected its procedures to comply with applicable regulations. Dr. Boyles changed the IRB requirements and provided assurances that the IRB would improve its recordkeeping.

In February and March 1990, FDA conducted a follow-up inspection of the Boyles Foundation. As a result of that inspection, FDA found several problems involving the and studies conducted by Dr. Boyles. Consequently, on July 10, 1990 and October 5, 1990, Dr. Kelsey sent letters to Dr. Boyles specifying various violations of the regulations and offering Dr. Boyles an opportunity to respond to the violations in writing or at an informal conference.

By letter dated April 26, 1991, Ronald G. Chesemore, the Associate Commissioner for Regulatory Affairs, issued to

Dr. Boyles a notice of opportunity for a hearing (NOOH) under 21 C.F.R. §§ 312.70 and 16.22. Because FDA did not receive a response from Dr. Boyles, the NOOH was sent again by letter dated June 4, 1991. On June 21, 1991, Dr. Boyles requested a hearing. On December 18, 1991, the hearing was held.

On March 2, 1993, the Presiding Officer issued her report regarding the 21 C.F.R. Part 16 hearing to Dr. Boyles and the Center for comments. The report concluded that Dr. Boyles had violated the regulations governing investigational new drugs and recommended that Dr. Boyles be disqualified from receiving investigational new drugs. Both Dr. Boyles and the Center submitted comments on the Presiding Officer's report.

My decision is based on the administrative record. Under 21 C.F.R. § 16.80, the record includes the transcript of the hearing ("Tr."), the Report of the Presiding Officer ("Report"), the comments of the parties on that Report ("Comments"), the pre- and post-hearing submissions by the parties, the exhibits submitted by the parties, and the other materials specified in the regulation.

II. DECISION

I turn now to the merits of this proceeding. I must determine whether the investigator has repeatedly or deliberately violated FDA regulations, or has repeatedly or deliberately submitted false information to the sponsor. 21 C.F.R. § 312.70.

The Center has brought four Charges against Dr. Boyles. Several of the Charges contain Subcharges. I will address each

Charge in the order in which the Presiding Officer considered it. The Center has the burden of establishing the alleged violations by the preponderance of the evidence.

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

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

SUBCHARGE 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.

SUBCHARGE 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.

SUBCHARGE 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.

The Presiding Officer found that the evidence presented by the Center, which consisted of photocopied records of alleged earlier IRB actions, did not show that the IRB had not considered the AND studies. The Presiding Officer noted that, if the minutes of the IRB meetings at which the study was allegedly discussed were silent of any mention of the study, perhaps a persuasive circumstantial showing might have been made by the Center. Report at 13-15. Dr. Boyles did not comment specifically on these Subcharges. The Center's

comments contend that it presented uncontested evidence to support these Subcharges. The Center relies on the testimony of Investigator Frazier at the hearing that Dr. Boyles admitted to falsifying numerous documents relating to his clinical studies before submitting them to their respective sponsors. Center Comments at 9. The Center refers to Ms. Frazier's testimony that Dr. Boyles admitted that the IRB letters were not authentic, and that he fabricated the letters from photocopies of old IRB letters. Center Comments at 10-12. The Center further argues that Dr. Boyles' failure to dispute the Center's allegations or to offer any evidence to the contrary establishes that he submitted the alleged false information. Center Comments at 13-15.

The Center comments seem to infer that once the Center has presented any evidence, the burden shifts to the investigator to rebut that evidence, and that if the investigator fails to do so, the Center has met its burden of proof. The Presiding Officer apparently took a somewhat different view. It is not necessary that I resolve this issue in this case since the investigator clearly is disqualified based on charges discussed later in this decision.

SUBCHARGE I.E.: The signature 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.

The Presiding Officer also found that the Center failed to substantiate this Subcharge. Report at 16-17. Dr. Boyles did not comment on this Subcharge. The Center's comments argue that the testimony of Ms. Frazier and Ms. Segal that Dr. Boyles admitted that he falsified IRB correspondence, Dr. Boyles' failure to offer any evidence to the contrary or to deny that the signatures were not authentic, and the fact that the signatures of the study subjects bear no resemblance to each other establish that Dr. Boyles fabricated the signatures. As indicated above, I find that it is unnecessary to reach the issue of the evidentiary burden in the case of un rebutted evidence.

The Center further contends that the Presiding Officer's contention that a handwriting expert was necessary to establish this Subcharge is misplaced because Ms. Segal's experience in assisting the FBI in reviewing signatures for a criminal case was sufficient to establish that the signatures were different. The Center also states that its failure to provide a handwriting expert was due to budgetary constraints, and that if evidence from such an expert is required, then the Presiding Officer should obtain it. Center Comments at 15-16.

On this issue, I do not agree with the Presiding Officer that a handwriting expert was necessary. Nevertheless, while Ms. Segal's experience in reviewing handwriting may very well establish that there were differences in the signatures, the evidence that the signatures are different does not establish that the signatures were not from the same study subjects, or

that Dr. Boyles falsified the subjects' signatures on any documents. While in appropriate circumstances, an FDA investigator's testimony alone may be enough to establish such a charge, I am unwilling to make such a finding in this case in the face of the Presiding Officer's contrary recommendation.

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.

The Presiding Officer concluded that Dr. Boyles did change the time of first awareness of angina on the CRF for study subject 12008. Accordingly, the Presiding Officer found that Dr. Boyles violated 21 C.F.R. § 312.70(a) as alleged in this Subcharge. Report at 17-19. Neither Dr. Boyles nor the Center commented specifically on the Presiding Officer's findings on this Subcharge.

I agree with the Presiding Officer. The Center presented two versions of the CRF with the same page number and the same date. One CRF specified "7:00" minutes as the time of first awareness of angina. Center Ex. 6 at 4. The other CRF had an "8" written over the "7" and appeared to be initialed by Dr. Boyles. Center Ex. 6 at 5. The Center also presented a letter from [redacted] to Dr. Boyles which indicated that the time to first awareness should be left as it was originally unless the EKG tracing showed 8:00 minutes. The letter further stated that Dr. Boyles could send a new page. Center Ex. 32 at 11. The CRF page which specified 7:00 appears to be the new page

Dr. Boyles created after he received the letter from the sponsor. This evidence presented by the Center establishes that the CRF for study subject 12008, on which Dr. Boyles would indicate the time of first awareness of angina, had been changed. Therefore, I find that Dr. Boyles violated 21 C.F.R. § 312.70(a) by submitting the CRF with the incorrect time to the sponsor as alleged in Subcharge I.F. I also find that Dr. Boyles did not violate 21 C.F.R. § 312.70(a) as alleged in Subcharges I.A. through I.E.

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

The Presiding Officer concluded that the Center failed to prove that Dr. Boyles did not obtain initial and continuing IRB approval. The Presiding Officer, therefore, found that Dr. Boyles did not violate 21 C.F.R. § 312.66 as alleged. Report at 19-21. Dr. Boyles' comments do not address these findings of the Presiding Officer. The Center's comments restate the evidence that it presented at the hearing and argue that the IRB was invalid and, therefore, it could not review or approve any studies. Center Comments at 16-19.

The Center seeks to rely on the same evidence that it presented to establish the violations alleged in Subcharges I.A. through I.E. As I indicated for Subcharges I.A. through I.D., I need not resolve the evidentiary issue, and with regard to Subcharge I.E., I was unable to find in the Center's favor. With regard to the Center's contention that the IRB was invalid under

21 C.F.R. Part 56 and, therefore, could not review and approve studies, the Center did not make this allegation in the NOOH sent to Dr. Boyles. While the Center could have notified Dr. Boyles of this additional charge prior to the hearing, the Center cannot at the hearing present a new charge to which Dr. Boyles has had no notice and opportunity to respond. Therefore, I find that Dr. Boyles did not violate 21 C.F.R. 312.66 by failing to obtain initial and continuing IRB review and approval.

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

The Presiding Officer found that Dr. Boyles failed to maintain adequate records of the disposition of investigational drugs. Report at 21-24. Dr. Boyles' comments do not specifically address this Subcharge. The Center's comments merely reiterate the evidence it presented to establish this violation. Center Comments at 20-21.

I agree with the Presiding Officer. As the Presiding Officer held, this charge focused on the absence of records kept by Dr. Boyles. The FDA investigators were unable to locate any drug accountability records during the inspections of Dr. Boyles. Report at 22. Dr. Boyles had the responsibility to make those records available for inspection and failed to do so. Dr. Boyles has not addressed this lack of records. Therefore, I find that Dr. Boyles violated 21 C.F.R. § 312.62(a) by failing to maintain adequate records of the disposition of the investigational drugs.

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.

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

The Presiding Officer found that Dr. Boyles failed to keep hypertensive histories for the study subjects. Report at 24-36. Dr. Boyles' comments do not specifically address the findings of the Presiding Officer on this Subcharge. The Center's comments also do not address the findings of the Presiding Officer but merely reiterate the evidence submitted in support of Charge III. Center Comments at 21.

I agree with the Presiding Officer. It is the responsibility of the clinical investigator to keep adequate records. The evidence presented by the Center, the patient's diaries and other records as compared to the case reporting forms completed by Dr. Boyles, clearly establishes that Dr. Boyles failed to record prior or concomitant antihypertensive drug use for study subjects in the study. For example, Dr. Boyles failed to report use by study subject 801. Center Ex. 10 at 2-3. For study subject 804, Dr. Boyles failed to report HCTZ use. Center Ex. 12 at 1. Therefore, I find that Dr. Boyles violated 21 C.F.R. 312.62(b) as alleged in Subcharge III.B.1.

SUBCHARGE III.B.2.: Dr. Boyles failed to report prior or concomitant therapy, as required on case report forms (CRFs) for study subjects 12009 and 801, 804, 805, 807, and 808.

The Presiding Officer found that Dr. Boyles failed to report prior or concomitant therapy on the CRFs for study subject 12009 and study subjects 801, 804, 805, 807, and 808. Report at 25-35. Dr. Boyles' comments do not address this Subcharge. The Center's comments restate its evidence but do not address the Presiding Officer's findings. Center Comments at 21-23.

I agree with the Presiding Officer. The evidence presented by the Center establishes that Dr. Boyles did not report prior or concomitant therapy for the study subjects specified in this Subcharge. As indicated above for Subcharge III.B.1., Dr. Boyles did not list as concomitant medications on the Current/Concomitant Medication form for study subject 801. Center Ex. 12 at 7. For study subject 805, Dr. Boyles failed to list on the Current/ Concomitant Medication form. Center Ex. 13 at 4. The Center provided similar evidence for the other study subjects specified in this Subcharge. Therefore, I find that Dr. Boyles violated 21 C.F.R. § 312.62(b) as alleged in Subcharge III.B.2.

SUBCHARGE III.B.3.: Dr. Boyles failed to report intercurrent illnesses or reactions to the sponsors for study subjects 801, 804, and 812 and 12006.

The Presiding Officer found that Dr. Boyles failed to report intercurrent illnesses or reactions for study subjects

801, 804, and 812 and study subject 12006. Report at 36-39. Again, the Center's comments do not address the Presiding Officer's findings but merely restate the Center's evidence. Center Comments at 23-24. Dr. Boyles' comments do not address this Subcharge.

I agree with the Presiding Officer. The Center's evidence demonstrates that Dr. Boyles did not report intercurrent illnesses or reactions for the study subjects 801, 804, and 812 and 12006. For example, for study subject 801, Dr. Boyles failed to report on the Intercurrent Illness or Injury form an episode of not feeling well included in the subject's progress notes. Center Ex. 10 at 3. For study subject 804, Dr. Boyles did not report on the Intercurrent Illness or Injury form an episode of sinus and cold listed on the Current/Concomitant medication form for the subject. The Center provided similar evidence for the study subject 812 and study subject 12006. Therefore, I find that Dr. Boyles violated 21 C.F.R. 312.62(b) as alleged in Subcharge III.B.3.

SUBCHARGE III.B.4.: Dr. Boyles failed to report use of NTG tablets consistently with the diaries of study subjects 12002, 12004, 12006, and 12009.

The Presiding Officer found that Dr. Boyles failed to report use of NTG tablets consistently with the diaries for study subjects 12006 and 12009. Report 41-43. The Presiding Officer, however, found that for study subject 12002, the Center charged that Dr. Boyles erroneously

reported NTG tablet use for Study Visits 3 and 7, and the Center's witness testified that the Center intended to cite Study Visits 2 and 7. As such, the Presiding Officer held that Dr. Boyles was not provided sufficient notice as to Study Visit 2. Report at 40. With regard to Study Visit 7, the Presiding Officer found that the patient diary and the CRF presented by the Center both indicated that seven NTG tablets had been taken. Accordingly, the Presiding Officer found that the Center failed to establish that Dr. Boyles erroneously reported NTG tablet usage for study subject 12002. Report at 41.

With regard to study subject 12004, the Presiding Officer found that the evidence presented by the Center was insufficient to assess the validity of Subcharge as to this study subject. The Presiding Officer, therefore, held that the Center failed to prove a NTG tablet discrepancy between the diary and the CRF for this subject. Report at 41.

The Center's comments restate the evidence presented but do not address the Presiding Officer's findings. Center Comments at 24-25. Dr. Boyles' comments do not address this Subcharge.

I agree with the Presiding Officer. The evidence presented by the Center for study subjects 12006 and 12009 establishes that Dr. Boyles failed to report NTG tablet usage on the CRF consistent with the patient diary. Center Ex. 4 at 11-12; Center Ex. 7 at 5,9, 11.

With regard to study subject 12002, I agree with the Presiding Officer that there is no discrepancy between the

NTG tablet usage reported in the CRF and patient diary for Study Visit 7. Center Ex. 1 at 1, 4-5. For study subject 12004, I agree with the Presiding Officer that the evidence presented by the Center is not sufficient to assess the validity of the charge. The Center alleged that Dr. Boyles reported NTG tablet usage incorrectly for Study Visit 3. The evidence presented by the Center, however, was illegible or silent as to the dates of Study Visit 2 and Study Visit 3. Therefore, the dates of the patient diary presented by the Center cannot be correlated with the Study Visit date.

Based on the discussion above, I find that Dr. Boyles violated 21 C.F.R. § 312.62(b) by failing to report NTG tablet usage accurately for study subjects 12006 and 12009 as alleged in this Subcharge and that Dr. Boyles did not violate 21 C.F.R. § 312.62(b) for study subjects 12002 and 12004.

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

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

The Presiding Officer held that the Center failed to prove this Subcharge. Report at 44-45. The Center's comments restate its evidence but do not address the Presiding Officer's findings. Center Comments at 26-27. Dr. Boyles' comments do not specifically address this Subcharge.

I agree with the Presiding Officer that the evidence presented by the Center was not sufficient to establish that study subject 804 had proteinuria during the study time period. While the laboratory data sheets presented by the Center show a value of +1 for protein, the dates on the sheets are illegible. Center Ex. 12 at 9, 12. Therefore, the Center was unable to corroborate the testimony of Ms. Segal as to the dates. Trans. at 63-64. Accordingly, I cannot find that Dr. Boyles violated 21 C.F.R. § 312.60 as alleged in Subcharge IV.A.

SUBCHARGE IV.B.: Dr. Boyles violated the protocol experimental drug use exclusion for study subjects 809 and 810.

The Presiding Officer found that the evidence presented by the Center established that Dr. Boyles did violate the protocol experimental drug use exclusion for study subjects 809 and 810 because both subjects had taken investigational drugs before entering the study. Report at 45-47. The Center's comments do not address the findings of the Presiding Officer but merely reiterate the evidence it presented in support of Charge IV. Center Comments at 27. Dr. Boyles' comments do not address this Subcharge.

I agree with the Presiding Officer. The evidence presented by Center establishes that the study subjects took an investigational drug before entering the study, and that Dr. Boyles still allowed the subjects to participate in the study. Center Ex. 17 at 6; Center Ex. 18 at 2. Therefore, I find that Dr. Boyles violated 21 C.F.R. § 312.60 by failing to

follow the investigational plan in the protocols as alleged in Subcharge IV.B.

SUBCHARGE IV.C.: Dr. Boyles violated the protocol weight exclusion for study subject 810.

The Presiding Officer found that the Center did not establish this violation because the Center did not present any evidence as to study subject 810 but indicated that it had intended to refer to study subject 815 in the NOOH. Report at 47-48. The Center's comments do not address the Presiding Officer's findings but rather summarize the evidence it presented regarding study subject 815. Center Comments at 28. Dr. Boyles' comments do not specifically address this Subcharge.

I agree with the Presiding Officer. The Center did not present evidence to establish the violation with regard to study subject 810 as alleged in this Subcharge. Therefore, I find that Dr. Boyles did not violated 21 C.F.R. § 312.60 with regard to the protocol weight exclusion for study subject 810.

SUBCHARGE IV.D.: Dr. Boyles violated the protocol EKG exclusion for study subject 12008.

The Presiding Officer held that the evidence presented by the Center did not establish the allegations in this Subcharge. The Presiding Officer found that she was unable to determine the "resting EKG" or "an ST depression of greater than 0.5mm" based the Center evidence consisting of 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 on the

tracing that was so faint as to be uninterpretable. Report at 48-49. Neither the Center's nor Dr. Boyles' comments address the Presiding Officer's findings. The Center comments again restate the evidence it presented in support of the Subcharge. Center Comments at 28-29.

I agree with the findings of the Presiding Officer. The evidence presented by the Center is not sufficient to establish this Subcharge. The Center's evidence, the unlabeled EKG tracing, is unreadable. Center Ex. 6 at 12. Therefore, I find that Dr. Boyles did not violate 21 C.F.R. § 312.60 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 Presiding Officer found that Dr. Boyles violated the protocol by admitting study subject 12002 because the Center evidence established that this subject had not demonstrated 1mm ST depression during exercise as required by the protocol. Report at 51-52. The Presiding Officer also found that, because the Center did not present any ST depression information for study subjects 12005 and 12007, and the EKG tracings presented for study subject 12011 were uninterpretable, she was unable to determine whether Dr. Boyles had violated the protocol by admitting these subjects to the study. Report at 52. The Center's comments do not address these findings by the Presiding Officer. Dr. Boyles' comments also do not address the Presiding Officer's findings.

I agree with the Presiding Officer. The evidence presented by the Center only establishes that Dr. Boyles violated the protocol with regard to ST depression during exercise by admitting subject 12002 to the study. The Center presented a letter dated July 2, 1987 from Dr. Boyles to the sponsor indicating he would drop this subject from the study. Center Ex. 32 at 4. Therefore, I find that Dr. Boyles violated 21 C.F.R. § 312.60 as alleged in this Subcharge for study subject 12002.

With regard to study subjects 12005, 12007, and 12011, the Center did not present any relevant evidence regarding the first two subjects. The EKG tracings presented for study subject 12011 are illegible and cannot be interpreted. Center Ex. 9 at 4,5,8,9. Therefore, I find that Dr. Boyles did not violate 21 C.F.R. § 312.60 with regard to study subjects 12005, 12007, and 12011.

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

The Presiding Officer held that Dr. Boyles violated the protocol for study subject 12008 as alleged in this Subcharge. The Presiding Officer found that the following evidence presented by the Center established that Dr. Boyles admitted subject 12008 with a difference in "time to angina" of greater than two minutes in violation of the study protocol: 1) a CRF for Study Visit 2 with "time to angina" recorded as 7:00

(seven) minutes; 2) another CRF for Study Visit 2 with an "8" written over the "7" and apparently initialled by Dr. Boyles; 3) correspondence from the study sponsor requesting that Dr. Boyles leave the time on the CRF at the original 7:00; and 4) a CRF for Study Visit 3 with "time to angina" of "9:31" minutes. Report at 53-54.

The Presiding Officer also held that Dr. Boyles violated the protocol for study subject 12010 since the CRFs for Study Visits 2 and 3 presented by the Center established a difference in "time to angina" of six minutes. Report at 55.

Neither the Center's comments nor Dr. Boyles' comments address the Presiding Officer's findings. The Center's comments again summarize the evidence it presented at the hearing in support of this Subcharge. Center Comments at 29.

I agree with the Presiding Officer. The Center's evidence establishes that Dr. Boyles failed to follow the protocol by admitting subjects 12008 and 12010 to the study with time to angina of greater than 2 minutes. Center Ex. 6 at 2, 4, 5, 6; Center Ex. 32 at 11; Center Ex. 8 at 4, 6. Therefore, I find that Dr. Boyles violated 21 C.F.R. § 312.60 as alleged in this Subcharge.

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

The Presiding Officer held that Dr. Boyles violated the protocol by permitting study subject 12009 to use NTG patches. The Presiding Officer found that the evidence presented

by the Center, the study subject's diary showing use of NTG patches and the absence of any deviation from the protocol agreed to by both the study sponsor and Dr. Boyles, established that Dr. Boyles violated the protocol with regard to cardioactive concomitant medication. Report at 55-56.

The Center's comments do not address the Presiding Officer's findings but rather restate the evidence it presented. Center Comments at 29. Dr. Boyles' comments once again do not address the findings of the Presiding Officer.

I agree with the Presiding Officer that the evidence presented by the Center establishes that Dr. Boyles allowed study subject 12009 to use NTG patches in violation of the protocol. Center Ex. 7 at 5, 11. Therefore, I find that Dr. Boyles violated 21 C.F.R. § 312.60 as alleged in this Subcharge.

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

The Presiding Officer held that Dr. Boyles violated the protocol by not reporting HCTZ as a prior or concomitant medication for study subjects 801 and 804. The Presiding Officer's findings were based on Center evidence which established that both subjects were prescribed HCTZ prior to the start date of the study with no stop date for the medication recorded, and that the drug was not reported as prior or concomitant medication on the study subjects' CRFs. Report at

56-58. Neither the Center's nor Dr. Boyles' comments address these findings.

I agree with the Presiding Officer that the evidence presented by the Center establishes that Dr. Boyles violated the protocol requirement for reporting concomitant drug with respect to study subjects 801 and 804. Center Ex. 10 at 2-3, 8; Center Ex. 12 at 1, 7. Therefore, I find that Dr. Boyles violated 21 C.F.R. § 312.60 as alleged in this Subcharge.

III. DR. BOYLES' COMMENTS

As I indicated, Dr. Boyles' comments do not address the specific allegations against him or the Presiding Officer's findings. Rather, Dr. Boyles' comments discuss his conduct of a study and a lawsuit resulting from that study.

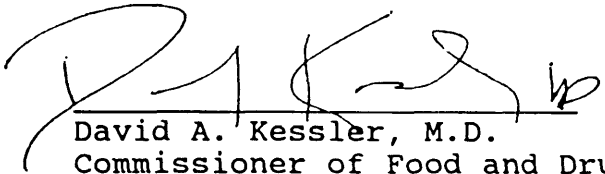
Dr. Boyles comments that during the lawsuit against him by the monitor of the study, he heard Dr. testify that he was a former employee of FDA and had been in contact with Dr. Kelsey, and that they agreed that Dr. Boyles violated the protocol. Dr. Boyles' comments also discuss a lawsuit against him by and a resultant fine of \$10,000. Dr. Boyles further comments that, on October 21, 1986, he sent a certified letter to Dr. Robert Temple that was never acknowledged. Dr. Boyles states that, because of the time required to respond to lawsuit, he lost his patients, had large legal expenses, and was forced to file personal bankruptcy. He further states that one year after the trial on the suit, FDA arrived to audit the study

but he never received a written report. He also states that, since July 1989, FDA has had an ongoing vendetta against him, and that there have been a four investigations against him and the Boyles Foundation. Dr. Boyles contends that the IRB has operated within the FDA regulations, and that two studies were carried out carefully with intensive monitoring by the sponsors. He states that "so called breach" in the protocol was discovered by the company monitors and clarified. Dr. Boyles asserts that careful drug assignment lists and return of medication, together with all case reports and data were accepted by the companies, and that no false data has been generated. He further states that he performed two ethical and scientifically valid double blind studies and that he highly resents and is offended by the falseness and pragmatism by Dr. Kelsey, Ms. Frazier, Ms. Segal, and Ms. Workman, who say "You are guilty until you prove your innocence." He concludes by commenting that "[i]n this country one is considered innocent until proven guilty which they have not done." Boyles Comments at 1-2.

Based on my review of Dr. Boyles' comments, I conclude that they do not present any evidence that warrants reversing any of the Presiding Officer's findings against him. His comments do not address any of the specific evidence against him. Therefore, they do not justify any different conclusions.

IV. CONCLUSION

As discussed in this decision, Dr. Boyles has repeatedly violated FDA regulations governing clinical investigations. Accordingly, under 21 C.F.R. § 312.70, I conclude that Dr. Boyles is no longer eligible to receive investigational new drugs.



David A. Kessler, M.D.
Commissioner of Food and Drugs

Dated: April 13, 1995