DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

REGULATORY HEARING ON THE PROPOSAL TO WITHDRAW

THE ELIGIBILITY OF

E. ALAN PAULK, JR., M.D.

TO RECEIVE INVESTIGATIONAL NEW DRUGS

COMMISSIONER'S DECISION

The purpose of this proceeding is to determine, pursuant to 21 CFR § 312.70(b) and 21 CFR Part 16, whether E. Alan Paulk, Jr., M.D., a clinical investigator, should be disqualified from receiving investigational drugs. Associate Commissioner for Health Affairs Stuart Nightingale, M.D., presided over the regulatory hearing in this matter on October 13, 14, and 15, 1988. Dr. Nightingale, in his "Report of the Presiding Officer" ("Report"), recommends that Dr. Paulk be disqualified.

Based upon my review of the administrative record in this matter, including Dr. Nightingale's Report and the parties' comments on that Report, I conclude that Dr. Paulk repeatedly submitted false information to a drug sponsor in required reports, within the meaning of 21 CFR § 312.70(b). Therefore, I am disqualifying Dr. Paulk from receiving investigational drugs. The reasons for my decision follow.

CMD 1

DNo. 01R-0023

I. PROCEDURAL BACKGROUND

From 1979 to 1981, Dr. Paulk was a clinical investigator involved in studies on the investigational drug is a powerful drug that was being tested by its sponsor, for use in treating patients with angina pectoris (Studies M78-006 and M78-012) and ischemic heart disease (Study M78-008). In May 1985, in response to concerns raised by concerning certain data submitted by Dr. Paulk to the Food and Drug Administration ("FDA") audited the data generated by Dr. Paulk's clinical investigations. That audit revealed significant problems with the data.

On May 6, 1987, the Center for Drugs and Biologics ("Center"), now the Center for Drug Evaluation and Research, informed Dr. Paulk of the specifics of the apparent regulatory violations uncovered during the audit and offered Dr. Paulk an opportunity to attend an informal conference to discuss those apparent violations. On September 28, 1987, an informal conference was held at the Division of Scientific Investigations. The Center concluded that Dr. Paulk's explanations for the deficiencies in the conduct of his investigations were not satisfactory. Consequently, on April 18, 1988, Associate Commissioner for Regulatory Affairs John Taylor issued a notice to Dr. Paulk providing him with an opportunity for an informal regulatory hearing under 21 CFR § 16.24 and 21 CFR § 312.70(a).

Dr. Nightingale presided over the informal hearing which was held on October 13, 14, and 15, 1988, and issued his Report on June 16, 1989. Dr. Nightingale found that, during the course of the studies, Dr. Paulk had repeatedly submitted false data in required reports to within the meaning of 21 CFR § 312.70(b) and recommended that Dr. Paulk be declared ineligible to receive investigational drugs. The parties then submitted their comments on Dr. Nightingale's Report.

II. DECISION

In order to conclude that a clinical investigator is no longer eligible to receive investigational drugs, I must find that the investigator repeatedly or deliberately violated FDA regulations, or repeatedly or deliberately submitted false data to the sponsor. Section 312.70(b) of Title 21 of the Code of Federal Regulations provides, in relevant part, that:

> [a]fter 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, or has deliberately or repeatedly submitted false information to the sponsor in any required report, 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.

Here, Dr. Paulk is charged with repeatedly or deliberately submitting false data to the sponsor of the studies.

A. Submission of False Data

The Center made five specific charges against Dr. Paulk at the hearing. The charges were set forth in the "Notice of Opportunity for a Hearing" letter dated April 18, 1988. I will, as Dr. Nightingale did, address each of the charges separately. The Center has the burden of establishing the alleged violations by a preponderance of the evidence.

1. Charge 1 - Two subjects were reentered under fictitious names.

The Center charged that Dr. Paulk submitted false information to in the form of fictitious names and other fictitious identifying data for two patients that were recycled by Dr. Paulk through Study M78-006. The Center also charged that one of those patients was then entered into Study M78-012, a continuation of Study M78-006, under the same fictitious name used during the recycling in Study M78-006. Dr. Nightingale found that the Center substantiated this charge.

In response to Dr. Nightingale's finding, Dr. Paulk admits that patients were recycled, and that fictitious names and birth dates were used. He argues, however, that, at least with respect to patient 209, recycled as patient 210, he cannot be charged with submitting false information to

because gave him permission to recycle the patient under a fictitious name. Dr. Nightingale was unpersuaded by this argument, and I am as well. Regardless of whether knew of the falsifications or not, the data submitted were false, and Dr. Paulk's submission of that data to as Dr. Nightingale found, constituted the submission of false data within the meaning of 21 CFR § 312.70(b). Dr. Paulk cannot escape the consequences of his actions merely by arguing that he acted in concert with the sponsor. The simple fact is that false names and birth dates were used.[1]

Moreover, I am impressed by the seriousness of Dr. Paulk's conduct. Dr. Robert E. Keenan, the Center's expert witness, testified that "entering the same patient twice in the same clinical trial, by any scientific standard, is totally unacceptable." Trans. Vol. II, p. 407-08. Dr. Keenan is correct. A basic tenet of clinical investigations is that data must be derived from a minimum number of <u>different</u> patients in order to ensure that a statistically significant sampling of the patient population is represented

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1/ With respect to both recycled patients, pertinent data, such as birth dates, were changed. If Dr. Paulk's explanation for permitting the recycling of patient 209 as patient 210 were to be accepted -- that permitted the recycling but insisted that the name be changed to prevent any confusion regarding the data generated from the two episodes -- there appears to have been no need to change the birth date. All data, except the name, should have been the same.

in the study. Only in this way can we be assured that the potential adverse effects of the drug will be uncovered, and its effectiveness appropriately tested, during the investigational stage. Different people react differently to the same drug. A study that does not represent an appropriate patient population is inherently unreliable. By reusing patients in a study, an investigator jeopardizes the statistical appropriateness of the patient population being studied. Therefore, regardless of whether Dr. Paulk received authorization from the sponsor, his reentering of the patient in the study makes his submission of false data particularly pernicious.

2. Charges 2 - Eye examinations, required under Study M78-006, were not performed as reported

The Center charged that Dr. Paulk falsified data with respect to the eye examinations required to be performed under Study M78-006. Specifically, the Center charged that examinations, reported by Dr. Paulk to have been performed on case report forms submitted to were not performed or were not performed on the dates reported. Dr. Nightingale found that the Center had substantiated this charge. I agree.

The evidence offered by the Center, and relied upon by Dr. Nightingale, to support this charge is compelling. First, FDA investigators exhaustively reviewed Dr. Paulk's study records and found no data to support that at least 15

of the reported examinations had been done. Second, the records that FDA investigators did find confirmed that the dates reported for the examinations were incorrect. In fact, many of the examinations appeared to have been done either before patients began the study or after the study had ended. Third, the Center provided affidavits from two patients who confirmed that at least three reported examinations had not been done. Exhibits 31 and 32. Fourth, the Center contacted physicians whom Dr. Paulk identified as physicians who would have performed the examinations. Those physicians had no records to support that the examinations had been done. Finally, Dr. Paulk's study nurse, who was delegated the task of ensuring that patients had the required eye examinations and whose testimony Dr. Nightingale found to be credible, testified that eye examinations were often not done, and that she often fabricated data. Trans. Vol. II, pp. 120, 198, 212, 285.

In response to the Center's charge and to Dr. Nightingale's finding, Dr. Paulk argues that the facts warrant the inference that the examinations were done, but that the supporting data were "lost, misplaced, or misfiled." Dr. Paulk's Comments on Report of the Presiding Officer (Dr. Paulk's Comments), p. 5. Dr. Paulk supports this argument by contending that it can be inferred that, because abnormalities were reported on a few eye examination case report forms, and the study nurse testified that she would

not have fabricated such abnormalities but would have relied upon actual data, all of the required examinations were done. Id., p. 4.

Dr. Paulk's explanation rebuts neither the affidavits of the two patients that demonstrate that three reported examinations were not done, nor the Center's evidence from examining physicians, whose names were given to the Center by Dr. Paulk, that they had no records supporting certain of the reported examinations. Given the lack of raw data and the patient affidavits, Dr. Paulk had the burden, and one easily fulfilled, to produce records from other physicians documenting that the examinations had been performed as reported. He did not. Therefore, I conclude that at least some examinations were not done, and consequently, that the data reported for those examinations were false. Moreover, there is no dispute that the reported dates for the examinations for which records could be found were false. It appears that the dates were falsified because many of the examinations were performed at times that did not meet the requirements of the study protocol. I find that, by the preponderance of the evidence, the Center substantiated this Charge.

3. Charge 3 - Raw data does not exist to confirm that examinations, required under Study M78-012, were performed as reported

Dr. Nightingale, for the same reasons stated in his discussion of Charge 2, found that the Center had

substantiated this Charge. Data reported by Dr. Paulk with respect to certain eye and ear examinations for Study M78-012 were false. Dr. Paulk objected to this finding for the same reasons he noted with respect to Charge 2.

There is no dispute that raw data cannot be found to support the data submitted to by Dr. Paulk regarding several of the eye and ear examinations required under Study M78-012. In addition, there is direct evidence that data contained in the case report forms were falsified. With respect to the examinations for which records could be found (eye and ear examinations for patient 1 and an eye examination for patient 2), the dates reported with respect to when the examinations were done were false. This fact raises serious questions regarding the truthfulness of the dates reported for the examinations for which raw data could not be found. Based upon this evidence, I find that Dr. Paulk submitted false data in case report forms required under Study M78-012.

4. Charge 4 - Raw data does not exist to confirm that cardiac fluoroscopies were performed on four patients as reported in the case report forms

With respect to this Charge, Dr. Nightingale found that Dr. Paulk failed to maintain adequate case histories in violation of FDA regulations. He did not find that the data alleged to be false by the Center -- four case report forms containing cardiac fluoroscopy results -- were in fact false. Dr. Nightingale went on to conclude that, because Dr. Paulk

had been charged with submitting false data by the Center, and not with violating FDA regulations, he could not rely upon that violation in making his recommendation.

In response to Dr. Nightingale's finding, the Center argues that it presented sufficient evidence, in addition to the lack of supporting data, that the data reported on the case report forms were fabricated because the fluoroscopies were not done. In particular, the Center relies upon the study nurse's testimony that, at times, cardiac fluoroscopy data were derived from examinations that had been done on patients during a previous study. Dr. Paulk argues that the examinations were done, but that the data were erased.

Based upon my review of the record in this case, I find that Charge 4 was not framed to give Dr. Paulk adequate notice of the nature of this charge; that is, that he violated FDA's requirement that he maintain adequate case histories. Therefore, I agree with Dr. Nightingale that no action can be taken against Dr. Paulk on the basis of this charge.[2]

2/ Dr. Paulk argues with respect to this charge that the regulation that underlies it, 21 CFR § 312.62, was not in existence until 1987, well after the conduct that is at issue in this proceeding occurred. Dr. Paulk's Comments, p. 2. Because of my conclusion with respect to this charge, I find that I need not reach Dr. Paulk's contention. I note, however, that under FDA's 1979 regulation, the FD 1572 and FD 1573 forms, which clinical investigators were required to sign and one of which was signed by Dr. Paulk, required the investigator to prepare and maintain adequate and

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5. Numerous laboratory determinations (Study M78-006) and other data reported to in case report forms were false

The Center presented clear evidence that numerous laboratory test results reported to were false. Dr. Paulk concedes, as he must, that these data were false. Biochemistry, urinalysis, and hematology data were often reused; that is, results from one test were used to reflect results from two, three, or even four tests. In his report, Dr. Nightingale lists the numerous instances of duplication.

In addition, the Center presented evidence that, on at least two occasions, EKG strips were reused. Specifically, EKG strips for patient 201/T.C. were reused for patient 205/S.A.M. As noted above, patient 201 was recycled as patient 205. The EKG strips, when superimposed, are identical. While one might expect EKGs for the same person performed at different times to be very similar, it is virtually impossible for them to be identical. Given the evidence presented, I agree with Dr. Nightingale that the EKG results were reused, and that the data submitted for patient 205 were false.

In light of the amount of data that was admittedly or clearly false under parts D and E of Charge 5, Dr.

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accurate case histories designed to record all observations and other data pertinent to the investigation. 21 CFR § 312.1(a), ¶ 6(c) (1979).

Nightingale did not feel the need to address all of Charge 5. I agree.

Based upon the evidence underlying Charges 1, 2, 3, and 5, I find that Dr. Paulk repeatedly submitted false data to within the meaning of 21 CFR § 312.70(b).[3]

B. Necessity of Disqualification

I have concluded that Dr. Paulk repeatedly submitted false information in required reports to the sponsor of the studies, within the meaning of 21 CFR § 312.70(b). My next inquiry is whether, having made this finding, Dr. Paulk should be disqualified. I find that Dr. Paulk should be disqualified. The circumstances presented here and the nature of the violations proved are significant, and I agree with Dr. Nightingale that they do not warrant a sanction less than disqualification.

Dr. Nightingale's recommendation of disqualification is predicated upon two factors: 1) the significance of Dr. Paulk's conduct in terms of its impact on the drug approval

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3/ In addition, with respect to Charges 2, 3, 4 and 5, the Center presented evidence that Dr. Paulk failed to maintain adequate records, and that a significant amount of raw data were missing to support the case report forms submitted to For example, Dr. Paulk failed to maintain raw data to support biochemistry, urinalysis and hematology data (Charge 5), heart rate and blood pressure data generated from stress EKG tests (Charge 5), and cardiac fluoroscopy results (Charge 4). While not directly relevant to my decision on disqualification, this evidence still provides the background against which I make that decision.

process; and 2) the nature, scope and extent of Dr. Paulk's conduct. Dr. Paulk does not dispute Dr. Nightingale's assessment of the first factor. Indeed, as Dr. Nightingale found, the degree of falsification, including the recycling of study patients, was extreme and undermined the validity of Dr. Paulk's portion of the studies. It had the potential to seriously compromise the drug approval process had the data been used in an application by for approval of Any conduct that jeopardizes or has the potential to jeopardize the integrity of the drug approval process is extremely serious.

Dr. Paulk does dispute, however, Dr. Nightingale's assessment of the second factor and argues that, despite the significance of his conduct, the circumstances here do not warrant disqualification. Dr. Paulk's Comments, p. 10. First, Dr. Paulk takes issue with Dr. Nightingale's finding that he "knew or should have known that false data were being submitted." Report, p. 21. Dr. Paulk argues that he had no knowledge that there were any problems with the studies, and that his study nurse was the source of the problems. Dr. Paulk's Comments, p. 6. He also argues that there was no reason that he should have known that problems existed. Id., p. 14-15. However, I agree with Dr. Nightingale that the evidence demonstrates that either Dr. Paulk knowingly submitted the false data or he knowingly abdicated his responsibility as a clinical investigator to

ensure that false data were not submitted. Indeed, Dr. Paulk admits that he knew of the recycling of patient 209 under a fictitious name and birth date.

Regardless of Dr. Paulk's knowledge or lack of knowledge, it was his responsibility to ensure that the data being submitted to the drug sponsor were complete and correct and reflected examinations that were actually and timely done. Dr. Paulk acknowledges that he had this responsibility. Id., p. 5. However, he tries to deflect the significance of this responsibility by arguing that the standard in 21 CFR § 312.70(b) is whether the submission of false data was deliberate or "reckless." Id., p. 6-7. In so arguing, Dr. Paulk misperceives the standard established by the regulation. Section 312.70(b) provides, and the evidence establishes, that an investigator is to be disqualified if he repeatedly submits false data to a sponsor. By failing to assure the validity of the data that he submitted to the sponsor, Dr. Paulk failed in his obligations as an investigator.

Dr. Paulk also argues that, because he has been in compliance with FDA regulations with respect to the studies that he has conducted since the studies, disqualification is unwarranted. Id., pp. 12-13. He argues that some lesser sanction is thus appropriate. Id., p. 25. However, current compliance does not ensure future compliance. This is particularly true given the record here,

where the amount of falsified data is substantial, and where the evidence shows that Dr. Paulk submitted such false data with respect to patients that had been recycled under fictitious names and for examinations that appear not to have been performed. In addition, a review of the applicable regulatory standard confirms that disqualification, as Dr. Nightingale recommends, is the appropriate sanction here.

Under the applicable regulatory standard, in order to conclude that a clinical investigator is no longer eligible to receive investigational drugs, I must determine: 1) that the investigator has repeatedly or deliberately violated FDA regulations, or has repeatedly or deliberately submitted false information to the sponsor; and 2) that the circumstances warrant disqualification. See 21 CFR § 312.70(b); 52 Fed. Reg. 8826 (March 19, 1987). With respect to this second element, however, § 312.70(b) and the preamble to the investigational drug regulations (52 Fed. Reg. 8798, et seq.) make clear that disqualification will be the primary sanction imposed against clinical investigators who violate FDA regulations or who submit false data. Only under the most exceptional circumstances will disqualification not be imposed where the threshold showing of repeated or deliberate conduct is made.

First, and most importantly, the purpose of § 312.70 is to protect, and ensure to the greatest extent possible, the integrity of the drug approval process and the safety of the

patients involved in clinical investigations. 52 Fed. Reg. 8798. To this end, the regulation is to be interpreted and applied in the manner most likely to fulfill this purpose.

Second, § 312.70 (formally § 312.1(c)) was recently revised to narrow the issues to be considered at a Part 16 clinical investigator disqualification hearing. Previously, the regulation provided that a clinical investigator would be disqualified if

> the investigator has repeatedly or deliberately failed to comply with the conditions of the exempting regulations in this section or has repeatedly or deliberately submitted false information to the sponsor of an investigation and has failed to furnish adequate assurance that the conditions of the exemption will be met....

(Emphasis added.) See 52 Fed. Reg. 8826. This portion of the regulation was revised in 1987 to delete this reference to "adequate assurances." In the past, investigators found to have committed violations sufficiently serious to warrant disqualification were not disqualified if they provided adequate assurances of future compliance. Id. The regulation now provides that adequate assurances will only be considered independent of the disqualification proceeding; that is, an investigator may no longer escape disqualification by providing adequate assurances. 21 CFR § 312.70(f). The preamble provides:

> ... the disqualification procedure will operate more effectively and efficiently if it is limited to objective questions about whether there have been violations of FDA's regulations.

52 Fed. Reg. 8826. Once disqualified, the investigator must now, in a separate proceeding, seek to be reinstated by providing "adequate assurances" of future compliance. 21 CFR § 312.70(f).

Finally, the preamble to the investigational drugs regulations makes clear that disqualification, with the option of subsequent reinstatement, is to be the primary sanction. In revising § 312.70, FDA expressly rejected a suggestion that it revise the investigator disqualification regulation to specifically require consideration of the "significance of the violation" or whether "lesser regulatory actions would be adequate" in the disqualification process. 52 Fed. Reg. 8826. The agency said that "these criteria are so subjective as to make them extremely difficult to apply fairly in disqualification proceedings." Id. Contrary to assertions made by Dr. Paulk, see Dr. Paulk's Comments, pp. 10-11, FDA therefore rejected consideration of lesser sanctions in deciding whether disqualification is appropriate. Rejection of these criteria and deletion of the "adequate assurances" language from § 312.70(b) were intended to streamline the disqualification process. 52 Fed. Reg. 8826. Therefore, where a finding is made that an investigator "repeatedly or deliberately" violated FDA regulations or submitted falsified data, the normal course will be that that investigator will be disqualified. The burden then shifts to the investigator to come forward in a

separate proceeding and provide adequate assurances of future compliance.

As noted in the 1987 preamble and Dr. Nightingale's Report, the Commissioner always retains the discretion not to disqualify an investigator. However, given the above considerations, it will be an unusual circumstance, if ever, where I exercise that discretion when the investigator has been, as here, shown to meet the threshold requirement for disqualification.[4] The agency's responsibility to ensure the integrity of the drug approval process and to ensure that the American public is exposed only to drugs whose demonstrated safety and effectiveness is based upon reliable data demands nothing less. Dr. Paulk failed to carry his burden.

III. CONCLUSION

I find that Dr. Paulk repeatedly submitted false data in required reports to within the meaning of 21 CFR § 312.70(b), in connection with the clinical

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4/ Here, Dr. Paulk asserts that, as a result of changes he has made in how he conducts studies, he has had no problems with his studies since the studies. Therefore, he could argue that this is a case in which disqualification "would accomplish nothing." I disagree. A lack of discovered problems does not always evidence an adequate correction. By disqualifying Dr. Paulk and thus requiring that he apply for reinstatement, pursuant to 21 CFR § 312.70(f), FDA will have an opportunity to evaluate the changes that he has made and to determine whether they, in fact, adequately address the problems that he has had, or whether additional steps are necessary.

studies of the investigational drug I also find that the violations are sufficiently serious so as to require disqualification. Therefore, I conclude that Dr. Paulk is no longer entitled to receive investigational drugs. Dr. Paulk may seek to have his eligibility to receive investigational drugs reinstated pursuant to 21 CFR § 312.70(f).

James S. Benson
Acting Commissioner
of Food and Drugs

Dated: 1/4/90