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

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REPORT OF THE PRESIDING OFFICER

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## I. INTRODUCTION

Pursuant to 21 CFR Parts 16 and 312, on October 13-15, 1988, the Food and Drug Administration ("FDA") conducted a hearing to consider the proposal of the Center for Drug Evaluation and Research (the "Center") to disqualify Dr. E. Alan Paulk from receiving investigational new drugs. The Center charged that Dr. Paulk should be disqualified because he repeatedly or deliberately submitted false information in required reports to the sponsor of clinical studies involving the drug , in violation of 21 CFR § 312.70(b).

This report constitutes my findings and conclusions based on the full administrative record. 21 CFR § 16.80. This report, along with the parties' comments with respect thereto and the administrative record, will be referred to the Commissioner for a final determination on this matter. See 21 CFR § 16.95.

## II. BACKGROUND

From 1979 to 1981, Dr. Paulk was a clinical investigator involved in studies on the drug . Dr. Paulk signed a Form FD-1572 in February 1979 for each of three studies involving the drug and submitted them to the study's sponsor, (" "). By signing these forms, Dr. Paulk voluntarily accepted certain responsibilities in connection with his involvement in the studies. Specifically, he agreed "to prepare and maintain adequate case histories designed to record all observations and other data pertinent to the clinical pharmacology" and "to make records available for inspection and copying" without need to divulge patient names "unless there is reason to believe that the records do not represent actual studies or do not represent actual results obtained." The space on the form to designate other responsible investigators was left blank by Dr. Paulk. Center Exhibits ("CX") 6-8.

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Of the studies that was sponsoring, one short-term study (No. ) and one long-term study (No. ) were intended to determine the safety and efficacy of the drug in relieving symptoms and increasing exercise tolerance of patients with stable angina pectoris. CX 3, 5. The purpose of a third study (No. ), which was also short-

term, was to suppress ventricular ectopic beats in patients with ischemic heart disease. CX 4.

Because of 's concern regarding apparent falsifications in submissions by Dr. Paulk, FDA initiated a "for cause" inspection of Dr. Paulk in May 1985. In reviewing Dr. Paulk's studies, FDA investigators found what they believed were significant problems under FDA's regulations governing such studies. The Center informed Dr. Paulk of the results of the investigation.

In accordance with 21 CFR § 312.70(a), the Center offered Dr. Paulk an opportunity to explain the conduct of the study at an informal conference. Dr. Paulk accepted and attended a conference on September 28, 1987. CX 2. At the conference, Dr. Paulk attributed any violations that had occurred to his study nurse. The Center rejected this explanation for the alleged violations. Subsequently, Dr. Paulk received a notice of an opportunity for hearing ("NOOH") under formal Part 16 procedures by letter dated

April 18, 1988. CX 1.[1] Dr. Paulk responded by requesting the hearing that was held on October 13-15, 1988.

## III. CHARGES

In support of its position that Dr. Paulk should be disqualified as a clinical investigator because he repeatedly or deliberately submitted false information to , the Center made five separate charges:

Charge #1: Subjects were reentered in the same or a different study under a fictitious name. Specifically, in study , patient 201/ was reentered as fictitious patient 205/ , and fictitious patient 205/ . continued as patient 3/ in study

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1/ Several attempts were made to schedule the hearing at the convenience of both parties. During telephone conversations on May 23 and 24, 1988, the parties agreed to any date after August 23, 1988. On May 24, 1988, the hearing was orally scheduled for August 25 and 26, 1988. The date was confirmed by letter of June 1, 1988, and by written response of the attorneys for the parties. The parties were notified by letter of June 27, 1988, of the basis on which rescheduling requests would be considered. The Center, by letter of July 7, 1988, requested that accommodations be made for a witness who could not attend on the scheduled dates. Dr. Paulk, by letter of July 14, 1988, objected to the Center's request that, if the hearing were not postponed, the witness' deposition could be submitted in lieu of live testimony. In light of this conflict, the hearing was rescheduled for October 12 and 13, 1988. On September 23, 1988, Dr. Paulk orally requested that the hearing be rescheduled for October 13 and 14, and the Center agreed. On October 12, 1988, Dr. Paulk requested another delay because his attorney, Bobby Lee Cook, was feeling poorly from recent oral surgery. After much discussion with the parties, it was decided not to further postpone the hearing. Mark G. Burnette, instead of Mr. Cook, appeared to represent Dr. Paulk.

; and patient 209/ . was reentered as fictitious patient 210/J.O. in study . CX 1 (NOOH) pp. 1-2.

Charge #2: The majority of ophthalmologic examinations in study were not performed as reported. CX 1, p. 2.

Charge #3: In study , raw data could not be found, and no additional data was submitted, to support the signed case report forms which indicated that ophthalmologic examinations and audiograms were performed on all three patients in the study. CX 1, p. 2.

Charge #4: In study raw data to support the x-ray reports (cardiac fluoroscopy) in case report forms for four of six subjects were not found, and the additional data promised were not submitted for these patients. CX 1, p. 2.

Charge #5: Numerous laboratory test results in study and two EKG strips submitted in the case report forms were identical to others previously submitted for different subjects. CX 1, pp. 3-5.

The Center's charges against Dr. Paulk are fully described in the NOOH letter sent to Dr. Paulk, dated April 18, 1988, from John Taylor, Associate Commissioner for Regulatory Affairs. CX 1. See also CX 1A.

To support the charges against Dr. Paulk, the Center presented four witnesses. Dr. Antoine El Hage, a Compliance

Officer with FDA's Division of Scientific Investigations, and Ms. Katherine Coleman, an FDA Investigator, testified regarding the results of the findings during their inspection of Dr. Paulk's study records. Hearing Transcript (Trans.) Vol. I at 17-191 (El Hage), Vol. II at 3-60 (Coleman). Ms. , the study nurse employed by Dr. Paulk during the period of time in which the studies were performed, testified as to Dr. Paulk's conduct with respect to clinical investigations generally, and the study specifically. Trans. Vol. II at 60-294. Dr. Robert Keenan, of the Division of Cardio-Renal Drug Products (FDA), testified as an expert witness in clinical investigations. Trans. Vol. II at 362-465.[2]

Dr. Paulk presented three witnesses on his behalf: a current employee, Ms. ; ; a former employee, Ms. , who succeeded Ms. as Dr. Paulk's study nurse; and himself. Ms. and Ms. testified about Dr. Paulk's conduct during other clinical investigations as well as the state of the study after Ms. departure from Dr. Paulk's staff. Trans. Vol. II at 306-362 ( ), 465-501 ( ). Dr. Paulk testified about his involvement in the study and in

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2/ It should be noted that Dr. Keenan testified as an expert witness qualified by his training and experience in the pharmaceutical industry from 1965-1985. See CX-88, Trans. at 365-366.

clinical investigations in general. Trans. Vol. II at 501-618.

## IV. REGULATORY FRAMEWORK

FDA's regulations governing the conduct of clinical investigators are set forth in 21 CFR Part 312.[3] Specifically, 21 CFR § 312.70 governs the disqualification of investigators. That section provides, in relevant part:

> 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, 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.

21 CFR § 312.70(b).

Section 312.70(b) does not automatically require disqualification if an investigator has repeatedly or deliberately submitted false data in required reports. The Commissioner always retains the discretion to impose lesser sanctions if the facts of a certain case do not warrant

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3/ Other regulations, such as those pertaining to informed consent and institutional review boards, are also applicable to clinical investigators, but they are not material to this hearing. See 21 CFR Parts 50 and 56.

disqualification. See Preamble to Investigational New Drugs Regulations, 52 Fed. Reg. 8826 (1987).[4] Therefore, my inquiry under § 312.70(e) is two-fold. First, I must decide whether Dr. Paulk repeatedly or deliberately submitted false information to in required reports, and second, if so, whether that conduct warrants disqualification or some lesser sanction.

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4/ A significant change in the regulations should be noted. Until June 17, 1987, the regulation stated, in pertinent part:

> After evaluating all available information, including any explanation and assurances presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the conditions of the exempting regulations in the 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, the Commissioner will notify the investigator and the sponsor of any investigation in which he has been named as a participant that the investigator is not entitled to receive investigational-use drugs with a statement of the basis for such determination.

21 CFR 312.1(c)(2). On June 17, 1987, amendments to this regulation became effective so that adequate assurances were no longer considered in hearings under Part 16. 52 Fed. Reg. 8826 (1987). The amendment affects all proceedings where a NOOH letter was issued after the effective date of this rule. The NOOH letter was issued to Dr. Paulk on April 18, 1988, after the effective date of this rule.

## V. ANALYSIS

In preparing my report, I have carefully reviewed the information presented in the administrative record and regulatory hearing.[5] The threshold inquiry is whether Dr. Paulk repeatedly or deliberately submitted false information to the sponsor in a required report. Because I find that, at a minimum, Dr. Paulk did repeatedly submit false data to , I also must consider whether Dr. Paulk's submission of false data was significant, and whether a sanction other than disqualification would be adequate to ensure that he will not submit false data in the future. I will discuss these issues separately.

### A. Repeated Submission of False Data

The Center clearly demonstrated that Dr. Paulk repeatedly submitted false data to . Case report forms bore fictitious patient names, results were reported for tests and examinations that had not been performed or that were unsupported by raw data, test results already reported for one patient were often resubmitted for different patients or for the same patient but for a different visit, and other laboratory results lacked supporting data. Thus, the overwhelming weight of the evidence demonstrates that the Center proved each of its five charges. However, as

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5/ I did not consider any information submitted after the hearing except that information for which I specifically permitted additional time for submission, pursuant to 21 CFR 16.80(b).

explained below, I base my recommendation on only four of those five charges.

1. Charge 1 -- Use of Fictitious Names

The evidence establishes that Dr. Paulk, on at least three occasions, entered patients in a study under a fictitious name. Specifically, Dr. Paulk reenrolled patient 201/ , who was participating in study under his real name, back into the study as patient 205/ , using a fictitious name. That same patient was then enrolled in the continuation study as patient 3/ , again under a fictitious name. Trans. Vol. I at 30-35 (El Hage); Vol. II at 36 (Coleman). See also CX 9, 10, 70, 70A, 71B, 83, 83A. Dr. Paulk also reenrolled patient 209/J.C. back into study as patient 210/ , again using a fictitious name. Trans. Vol. I at 32, 36 (El Hage); Vol. II at 9-11, 36-38 (Coleman); CX 11, 12, 31.

Dr. Paulk did not dispute that fictitious names were used. However, he attempted to explain his conduct. With respect to patient 209/ .-210/ ., Dr. Paulk stated that he had requested, and was given, permission from to reenter the patient under a fictitious name. Trans. Vol. II at 554-60. He said that he was unaware that the study's results would be compromised by the reentry, but he accepted Dr. Keenan's explanation that the reentry created a serious flaw in the study. Trans. Vol. II at 557-58, 580. With respect to patient 201/ .-205/ .-3/ , Dr. Paulk

stated that he was unaware of the patient's subsequent reenrollment under a fictitious name. Trans. Vol. II at 552. However, he did not rebut the Center's evidence, which consisted of patient records, including identical laboratory results and EKG tracings, that revealed the use of the fictitious name.

Notwithstanding Dr. Paulk's explanations, the evidence establishes that the case report forms for patients 205/ 1., 3/ . and 210/ were submitted to the drug sponsor, , using fictitious names. These submissions, in themselves, constitute the repeated submission of false information within the meaning of 21 CFR § 312.70.

2. Charges 2-5 -- False, Duplicative, and Missing Laboratory Data

In addition to the use of fictitious names, the Center established that Dr. Paulk also repeatedly submitted false, duplicate (or previously reported), and unsupported laboratory data to Because of the number of specific instances involved, I find it unnecessary to discuss more than the most obvious or significant instances.

a. Charges 2 and 3

The Center demonstrated that numerous entries related to ophthalmologic examinations required under the protocol for study were false. The Center introduced billing records and affidavits from physicians, or physician representatives, whom Dr. Paulk had identified during the

inspection as the examining physicians, that demonstrate that either exams, reported by Dr. Paulk to have been performed, were not performed or, if performed, were not performed on the dates reported. CX 27-36; see also Trans. Vol. II at 11-17, 20, 25-26; CX 14, 26. For example, the evidence establishes that there are no raw data to support either of the two ophthalmologic examinations reported for patients 205, 206, and 208-210; that ophthalmologic examinations for patients 201, 203, and 204 were performed post-study and not on the dates reported on the case report forms; and that patients 201, 202, 207, and 211-213 did not receive at least one of the two required ophthalmologic examinations reported. CX 1 p. 2. Dr. Paulk did not dispute these discrepancies. The only explanation he offered was that his study nurse was responsible.

In addition, the billing records and affidavits also show that the ophthalmologic examinations and audiograms of patients in study were not performed as reported. For example, the evidence established that: 1) only one audiogram for patient 1 was performed although two were reported; 2) the audiogram actually performed on patient 1 was performed three months after the last reported date for an audiogram; 3) no audiograms were performed for patients 2 and 3 although two were reported; 4) the ophthalmologic examinations for patients 1 and 2 were performed two weeks to three months after the reported dates; and 5) no

ophthalmologic examinations were performed for patient 3 although, again, two were reported. CX 37-39A. Dr. Paulk did not dispute this evidence. Trans. Vol. II at 527-28.

b. Charge 4

The Center also established several instances where the medical records for patients were incomplete, in violation of 21 CFR § 312.62. For example, raw data (fluoroscopy tapes) to support x-ray reports were missing. CX 60-68, Trans. Vol. I at 92-104 (El Hage), Vol. II at 17-20, 26-27 (Coleman); see also CX 32. Dr. Paulk acknowledged that he mistakenly erased some fluoroscopy tapes that may have contained the missing data. Trans. Vol. II at 544-45. Dr. Paulk's failure to maintain these data violates the express instruction in § 312.62 that investigators "prepare and maintain adequate and accurate case histories designed to record all observations and other data."

However, Dr. Paulk was charged, in the NOOH, with submitting false data to the sponsor, not with repeatedly or deliberately failing to comply with 21 CFR § 312.62. Therefore, although I find that the Center has substantiated Charge 4, I also find that Dr. Paulk may not have been given adequate notice of its significance. As a result, I will not rely on his violation of § 312.62 in my conclusions or recommendations.

c. Charge 5

Finally, and perhaps most significantly, the Center established that numerous laboratory and other test results submitted in the case report forms were copied from, or were identical to, other submissions for the same or different subjects; that is, that the information reported on those case report forms was false. CX 44-55, 69-83. The significance of the comparable results was explained by Drs. El Hage and Keenan in their testimony.

For example, Dr. El Hage testified that the EKG strips submitted for two patients were identical (superimposable). Trans. Vol. I at 31-33; CX 83. He went on to testify that EKG strips can never be identical for different subjects, or even for the same subject, and that therefore one or both of these EKG tracings were false. Trans. Vol. I at 32-33. Similarly, the Center presented evidence that the biochemistry reports submitted for patients 201 (visits ("v") 1 and 7); 201 (v 9) and 205 (v 1); 201 (v 11) and 205 (v 2 and 5); 202 (v 7 and 11); 203 (v 9 and 11); 204 (v 1 and 7); 206 (v 1 and 7), were identical, CX 69-74, 76, and that identical urinalyses were submitted for patients 203 (v 9 and 11); 201 (v 11) and 203 (v 5); 206 (v 1, 2, 9, 11); and 207 (v 1 and 7). CX 73, 75, 78-79. Drs. El Hage and Keenan testified that it is highly unlikely that these critical values in the reports could have occurred repeatedly as reported, and that therefore these values were false. Trans.

Vol. I at 31, Vol. II at 375-85. Dr. Keenan said that the chance of the same patient having these identical numbers, as was the case in CX 73 and 74, was "about one chance in ten trillion," and the chance of different patients having identical values as reflected in CX 75 was "one chance in a million." Trans. Vol. II at 382.

Dr. Paulk does not dispute that the submitted case report forms contained results that were false, duplicative, and unsupported by raw data. For example, Dr. Paulk admitted that the superimposable EKG tracings must be duplicates because tracings can never be identical. Trans. Vol. II at 537-538, 583. Further, he did not dispute that the repetition of certain critical values in the laboratory reports indicated that the values had been copied from other laboratory reports and, therefore, were false. He also acknowledged that cardiac fluoroscopies were unsupported by raw data and could not be confirmed as having been performed, and he acknowledged that he erased some fluoroscopy tapes. Trans. Vol. II at 544-546.

In response to the Center's charges, Dr. Paulk offered evidence that shows that some laboratory tests were performed, although the results were not reported. See e.g., Trans. Vol. II at 551 (Paulk). He also argued that some lost raw data were found during an extensive search of his files, and that these raw data show that about "30 percent" of the laboratory tests that were the subject of the charges were

performed, although usually not on the date reported. Trans. Vol. II at 498 ( ). Some evidence submitted substantiates this claim. Paulk Exhibits ("PX") 5-6, 9-13. Nevertheless, Dr. Paulk did not dispute that the entries in the records were false.

The Center established that results submitted on the case report forms were false in that the exams were never performed or were not performed on the dates reported. The Center also established that laboratory test results reported in case report forms were duplicated from other reports. Furthermore, Dr. Paulk admitted that data were missing, duplicative, and inaccurately dated. These facts establish that Dr. Paulk repeatedly submitted false information to in required reports within the meaning of 21 CFR § 312.70(b).

B. The Nature and Scope of Dr. Paulk's Repeated Submissions of False Data Warrants Disqualification

As stated above, disqualification is not the only sanction available to the Commissioner under Section 312.70 if deliberate or repeated submissions of false information are found. The Commissioner still retains the discretion to "not disqualify an investigator if the violations are insignificant, or if lesser sanctions would be adequate." 42 Fed. Reg. 8826 (1987).

1. The Significance of Dr. Paulk's Conduct

Clinical investigations are designed to generate information regarding an experimental product's safety and efficacy. Despite testing an experimental product in a small number of subjects, the potential target population for a drug can be quite large as sponsors hope to apply the test results to persons affected with various diseases or conditions. Consequently, the integrity of the entire drug approval process, from initial clinical tests to final product approval, must be maintained to protect the public health and to preserve the confidence of the public and health professionals in their drug products.

In the present case, the false reports corrupted the integrity of the clinical investigation and had the potential to endanger the subjects and the public health. Dr. Keenan testified that the violations were not insignificant because laboratory tests necessary to determine a subject's response to treatment could not be confirmed as actually having been performed or performed on the dates reported. Tests must be performed and performed on the dates required in the protocols, not only to accurately assess effectiveness, but also to assess the toxic effects of the drug. As Dr. Keenan explained:

> The reason laboratory tests are done is to determine whether or not the drug is safe. And depending on the target organ of toxicity -- and there is always one, which generally we know in animal experiments -- that particular organ system you look at very closely, but you

look at all of them. And laboratory tests are very important in knowing whether or not the drug is causing bone marrow toxicity, liver toxicity, whatever.

And so they have to be looked at extremely carefully and as soon after they're done as possible. And what you need to do is, first of all, when the patient enters the trial generally -- depending on the trial -- generally the laboratory studies are normal. All the lab tests are normal.

So what you do as the study progresses is you look at every subsequent laboratory examination and determine whether there is a trend. Is there a trend in liver function studies, in renal function studies, and bone marrow studies? You know. And in order to detect the trend -- and you have to look at them close because if a trend is developing you really need to stop the drug before whatever is happening becomes serious. Like hepatitis and the patient dies.

So, laboratory studies are not casual things that people do for the sake of doing them. They're very important things to determine whether or not this drug is or is not safe. And as I mentioned, drug-induced toxicity, the serious stuff, at least, is relatively uncommon. And this is why each and every patient has to be looked at each and every time a laboratory report is done. That's why the protocol says that they have to be done. That's the purpose.

Trans. Vol. II at 375-77.

... [T]hese patients are sick. I mean, patients with angina are people who are going to have heart attacks sooner or later. And so ethically there is an obvious ethical relationship between the doctor and the patient who has that particular illness, which is very serious. And the ethics is even greater

> in my opinion when you're feeding that patient a brand new drug that you don't know very much about.
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> ... [The physician] could delegate the duty to his nurse to transcribe the lab tests from the raw data to the drug company's case report form. That would be one of her duties. But she's certainly not responsible for the -- even the accuracy, much less the validity and/or the meaning of a test if it becomes abnormal.
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> Well, the responsibility of the health and well-being of the patients cannot be delegated to anybody.
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> But monitoring the progress as far as whether or not the abnormality in the heart that was there in the beginning is getting worse, no. How would she know?

Trans. Vol. II at 386-87.

Dr. Keenan also testified with respect to the danger to public health that could occur if the falsifications were undetected, and the results served as a basis for drug approval. The falsifications would compromise the safety of future patients by exposing them to avoidable, increased risks of receiving a potentially ineffective, even toxic, drug:

> Now, we're talking about a brand new drug which is a chemical, by any definition, and it's a foreign chemical to the human body. How the human body will adapt itself, if it does, to this foreign chemical is totally unknown. And so the

> responsibilities are really quite great on investigators who are using experimental new drugs because even when a new application comes in, which has all the data that the company has, we have maybe 3,000 patients on the average -- that's the total exposure to the drug, 3,000 patients. And this a drug that will be out on the market and used in millions of patients.
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> [Physician supervision] is even more critical in a protocol because your dealing with an experimental drug that you don't know an awful lot about. And the experimental drug could do all sorts of things that are totally unexpected.
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> And not necessarily in every patient. You see, the problem with an experimental drug is that the risks with an experimental drug -- the important ones -- like hepatitis or strokes, or whatever, do not occur in every patient who takes the drug. They occur in one out of 500, one out of 1,000, one out of 2,000.
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> That's why I said earlier that every single patient is important. Because that one patient may be telling you that this drug induces hepatitis or induces redistribution of coronary blood flow and angina by itself. Or is a proarrhythmic drug and causes an arrhythmia rather than prevent[s] one.

Trans. Vol. II at 367, 369-70.

> The new drug application has, like I said earlier, maybe 3,000 patients. It might have only 1,500 or it might have 6,000. But either way, it's not very many. I mean, 3,000 patients is not very many when you're going to put it out there and treat millions.
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> So that every single one of those 3,000 patients is extremely critical. It's

> like animal trials. I mean, in rats not every rat gets cancer from carcinogenic drugs. But some do. And even if one does, you pay attention to it. And then you go further.
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> ... So every single one of those things is a warning sign.
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> Well, if somebody lies and cheats, its altogether possible that one of the patients they fudged was the one guy who was going to get hepatitis out of the 3,000. And if you don't have that, then you don't know it and you put the drug out there and it takes a million people taking the drug, of which a hundred get hepatitis to learn that, that you should have known before the drug was put on the market.

Trans. Vol. II at 405-406.

2. Whether Dr. Paulk's Submission of False Data Warrants Disqualification.

Given the pervasive nature of the falsifications involved here and various other factors that should have put Dr. Paulk on notice that problems existed or were likely to exist in the studies, Dr. Paulk's conduct, with respect to the repeated submissions of false data to must be considered deliberate or, at a minimum, reckless; that is, he knew or should have known that false data was being submitted. Regardless of whether he acted deliberately or recklessly, however, I believe that disqualification is warranted. Either Dr. Paulk knowingly submitted false data or he knowingly abdicated his responsibility as a clinical investigator to ensure that false data were not submitted.

Under the circumstances in this case, either scenario evidences a disregard for good scientific practice.

First, Dr. Paulk admits that he deliberately reentered patient 209/ as patient 210/ . in study and then continued him on into study under the fictitious name . Trans. Vol. II at 522, 554-560. In addition, with respect to patient 201/ .-205/ .-3/ ., it is difficult to conceive of a clinical investigator who is properly conducting a study being unaware that a patient was being reentered in his study.

Second, the pervasiveness of the false submissions is significant. Dr. Keenan's expert testimony is that it is "virtually impossible" for records to be falsified to the extent shown here without the physician's knowledge. Trans. Vol. II at 374. Dr. Keenan said:

> So, in this case, yes, a lot of the numbers are the same. The likelihood of that happening -- and I've talked about this with one of our statisticians ... -- the likelihood is astronomical statistically. I mean, it just does not happen and I do not believe that any investigator that I know would look at these numbers and not say that they were copied.
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> Any reasonable intelligent physician would know that this is false. And certainly every investigator who has ever done a clinical trial would know that.
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> * * * *

> This is part of [the clinical investigator's] responsibility, to look at the baseline lab tests and then the first subsequent test, the second, the third. And not individually, but side by side. That's the only way you can tell whether there is a trend [that indicates toxic effects on organ systems including the liver, kidneys, or bone marrow]. And that, again, is part of his responsibility. I don't know of any way that not doing that can have a rational explanation.

Trans. Vol. II at 377-78. Dr. Paulk responded that he was not aware of FDA's position that an investigator is responsible for comparing lab results, and that the failure to do so could mask the drug's toxic effects. He stated that he relied upon the sponsor's monitors and his study nurse to check lab results. See, e.g., Trans. Vol. II at 532. 551, 592-93.

Third, the testimony of Dr. Paulk's own witnesses established that study patient records were strewn around the office in large, unboxed piles. Trans. Vol. II at 327-28. Ms. testified that the records were so disorganized, "He couldn't help but see it. I mean, it was everywhere. It was all over -- the piles were there." Trans. Vol. II at 328. Similarly, Dr. Paulk's attention should have been raised by another sponsor's refusal to hire him to conduct a study as long as Ms. was the study nurse and the "inordinate number of pink slips" -- notices from study sponsors questioning case report forms that are issued for a variety of reasons -- he had received during

previous studies involving Ms. . Trans. Vol. II at 516-519. Moreover, Ms. described the office as "a snake pit" of gossip, including gossip about the fabrication of EKG tracings and patient reentries, which should have warranted Dr. Paulk's attention. Trans. Vol. II at 346.

Finally, the testimony of Ms. established that, under Dr. Paulk's instruction, she forged his name on numerous case report forms. The signature of the investigating physician is required on all case report forms as verification that the information contained therein is correct. Moreover, Ms. testified that Dr. Paulk had to have known that she was falsifying data with respect to the studies, and that, in fact, he had taught her how to fabricate data during previous studies. Trans. Vol. I at 72-79.[6] Dr. Paulk acknowledged that he knew that Ms. signed his name on case report forms. However, he denied that he knew of Ms. 's fabrications, or that he had instructed her to fabricate data. Trans. Vol. II at 536, 551, 547-49, 580, 588.

Dr. Paulk's response to the Center's charges does not reduce the severity of the violations. He argues that he was

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6/ Although not necessary for my resolution of this issue, I find that Ms. 's testimony was credible. Although she hesitated when answering some questions about her personal life, she otherwise was forthcoming. She frankly admitted that there were instances which she could not remember. Also, her account was an admission, and it is unlikely that she fabricated a story in which she played such a large part in the wrongdoing.

unaware of the falsifications because he had delegated "all responsibilities related to the [case report forms]," and, therefore, all responsibility related to the accuracy of the case report forms and the monitoring of patient safety, to Ms. . CX 2 at 38. However, in the context of clinical investigations, while a clinical investigator may delegate certain duties, he may not delegate his responsibilities to his study nurse. Monitoring patient safety is clearly the sole responsibility of the treating physician. Similarly, assuring that information submitted to a drug sponsor is complete and accurate is a responsibility undertaken by all clinical investigators, and they alone are responsible for any incomplete or inaccurate information. Therefore, Dr. Paulk cannot plead ignorance by blaming his study nurse. He is no less culpable simply because he chose to delegate a nondelegable responsibility.

Similarly, the testimony that Dr. Paulk did not profit from the falsifications, because many laboratory tests were actually performed, albeit late, is likewise unpersuasive. Regardless of his motive, the evidence establishes, at a minimum, that Dr. Paulk virtually abdicated his responsibilities as a clinical investigator. This abdication

resulted in pervasive falsifications.[7] Trans. Vol. II at 509-515, CX 84A. See also Trans. Vol. II at 358 ( ), 510 (Paulk), and CX 2 at 17-18, where additional absences from his practice are described. Dr. Paulk attempted to address these concerns only after he was notified of the agency's audit.[8]

Thus, I find that Dr. Paulk disregarded good scientific practice, and that the ways in which he did so contributed directly to his repeated submission of false information in required reports to the sponsor. Given these findings, I

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7/ Ms. and Ms. testified regarding Dr. Paulk's assertion that he was not motivated by profit. However, neither demonstrated any knowledge of Dr. Paulk's billing and financial records for the studies. See e.g. Trans. Vol. II at 319-21, 333, 345 ( ), 474-75 ( ). One's motives or profit margin are irrelevant to the issue of false reports; consequently, this testimony has little value.

8/ Dr. Paulk argues that, even if I find that he had repeatedly or deliberately submitted false data to , he should not be disqualified as a clinical investigator. Dr. Paulk bases this argument on his assertion that he has "substantially reformed his procedures in the conduct of drug studies" in order to, presumably, prevent any future submissions of false data. Dr. Paulk also notes that FDA has uncovered no problems with studies he has conducted since the studies were curtailed in 1981.

These assertions by Dr. Paulk, while of some relevance, do not warrant a change in my recommendation. The age of the violations and Dr. Paulk's assertion that he has changed his methods do not mitigate the seriousness of his conduct and do not, of themselves, provide any assurance that this conduct will not be repeated in the future.

conclude that no sanction other than disqualification is adequate to ensure that Dr. Paulk does not submit false data in the future.

## VI. CONCLUSION

The pervasive nature of the falsifications involved here underscore their significance. Further, that pervasiveness cannot be excused. It is the clinical investigator's nondelegable responsibility to ensure that the study protocol is adhered to and that all data submitted to the drug sponsor are complete and accurate. Given the circumstances in this case, I believe that disqualification is warranted.

I conclude that Dr. Paulk repeatedly submitted false information with regard to fictitious patients (charge 1), unsupported laboratory data (charges 2, 3, and 5), identical laboratory data (charge 5), and incorrectly dated laboratory data (charges 2 and 5). Since these submissions of false information are not insignificant and lesser sanctions are not adequate, I conclude that Dr. Paulk should not remain eligible to receive investigational drugs.

## VIII. RECOMMENDATION

I recommend that the Commissioner declare Dr. Paulk to be ineligible to receive investigational drugs.

Stuart L. Nightingale, M.D.
Associate Commissioner
for Health Affairs