DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

In the matter of:
STEPHEN N. STEEN, M.D.
Regulatory Hearing

COMMISSIONER'S DECISION

The purpose of this proceeding is to determine, pursuant to 21 CFR 312.1(c)(1) and 21 CFR Part 16, whether Stephen N. Steen, M.D., a clinical investigator, will be disqualified from receiving investigational-use drugs. Associate Commissioner for Health Affairs Stuart Nightingale, M.D., presided over the regulatory hearing on December 17 and 18, 1981. His recommendation is that Dr. Steen be disqualified.

I conclude that Dr. Steen repeatedly failed to comply with regulations governing the conditions for exemption of new drugs for investigational use and repeatedly submitted false information to the sponsor. As explained below, however, I have not made a final decision on Dr. Steen's assurances. I am giving Dr. Steen the option, under specified conditions, to submit new assurances based upon the principles I have set forth in this decision, or to be judged on the assurances he has submitted to date.

PROCEDURAL BACKGROUND

During the periods of October-December 1977, and October 1978 through October 1979, Dr. Steen conducted two studies involving the anesthetic ( ) to

evaluate the efficacy of low dose as an anesthetic and for the induction of anesthesia. In the fall of 1978, Dr. Steen conducted a study involving the analgesic drug for . The study was for the treatment of post-operative pain. In January through March, 1980, the Food and Drug Administration ("FDA") conducted investigations of Dr. Steen's investigational drug studies involving and At the conclusion of these inspections, FDA's Bureau of Drugs, Division of Scientific Investigations ("Bureau"), advised Dr. Steen by letter dated July 21, 1980, that the Bureau had concluded that he had repeatedly or deliberately violated FDA regulations by failing to maintain adequate case histories, by failing to obtain informed consent, and by failing to obtain institutional review board approval. The Bureau offered Dr. Steen an opportunity to attend an informal conference to discuss the alleged violations of FDA regulations. Dr. Steen declined this opportunity and instead submitted a series of eight brief letters in response to the allegations.

By letter dated July 21, 1981, the Associate Commissioner for Regulatory Affairs issued a notice to Dr. Steen providing him with an opportunity for a regulatory hearing under 21 CFR 16.24 and 312.1(c) ("Notice"). In addition to the allegations contained in the Bureau's July 21, 1980 letter, the Notice alleged that Dr. Steen had

repeatedly or deliberately submitted false information to the sponsors of the studies. The Notice stated that while these allegations were not expressly mentioned in the Bureau's letter, they arose from the same facts that were the basis for the concerns referenced in that letter under "Failure to maintain adequate and accurate case histories." A hearing was held on December 17-18, 1981.

After the hearing, the Presiding Officer, Dr. Nightingale, submitted his report to me on February 4, 1983.

My decision is based on the administrative record. Under 21 CFR 16.80, the record includes the transcript of the hearing ("Tr."), the report of the Presiding Officer ("Report"), the comments of parties on that Report ("Comments"), the pre- and post-hearing statements submitted by the parties ("Statement"), the exhibits submitted by the parties ("G" for FDA, "R" for Dr. Steen), the assurances of Dr. Steen, and other relevant materials.

DECISION

I turn now to the merits of this proceeding. As I stated in my September 11, 1981 decision in In the Matter of Michael C. Gelfand, M.D., I must make two findings in order to conclude that a clinical investigator is no longer eligible to receive investigational new drugs. First, I must determine that the investigator has repeatedly or deliberately violated FDA regulations, or has repeatedly or

deliberately submitted false information to the sponsor. Second, I must conclude that the clinical investigator has failed to furnish adequate assurances that the conditions of exemption will be met in the future. 21 CFR 312.1(c)(2). I will separately address these elements for each of the studies with which Dr. Steen was involved. The Bureau has the burden of establishing the alleged violations by a preponderence of the evidence.

A. The Study

1. Failure to prepare and maintain adequate and accurate case histories.

a. Failure to report concomitant medication in the case report forms.

The Bureau alleges that Dr. Steen failed to report administration of concomitant medication in the case report forms for patients 144 (G-20), 233 (G-21), 203 (G-22), 228 (G-23), 227 (G-24), 223 (G-25), 146 (G-30), 231 (G-31), 120 (G-32), and 220 (G-33). Dr. Steen does not contest the allegations regarding patients 144 (G-20), 203 (G-22),[1/] 228 (G-23), 227 (G-24), 146 (G-30), 231 (G-31), 120 (G-32), and 220 (G-33), and the Presiding Officer found that

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1/ Dr. Steen does not challenge the Bureau's evidence that concomitant medication was administered to patients 203 (G-22) and 146 (G-30) but was not recorded in their case report forms. Dr. Steen argues instead that it is not a serious violation to fail to report a concomitant medication if it did not affect the rating of the study medication.

Dr. Steen had failed to report administration of concomitant medication in the case report forms for these patients. Report at 3.

I agree with the Presiding Officer. The Bureau's uncontroverted allegations are supported by entries in Hospital ("Hospital") records. Tr. I-179-87, 196, 222-24, G-6, G-7, G-20, G-22, G-23, G-24, G-30, G-31, G-32, and G-33.

Dr. Steen contends that the Bureau did not prove its case regarding patients 233 (G-21) and 223 (G-25). For patient 233 (G-21), the Bureau introduced an affidavit from the patient stating that he had an injection of morphine to relieve pain following the operation. G-21. The affidavit does not specify the time at which the injection of morphine was allegedly given.2/ It is also unclear from the patient's Hospital medication record (G-21 at 11) and Hospital nursing notes (G-21 at 8) that the patient received an injection of morphine or any other pain medication following his operation. Indeed, the Bureau's witness testified that the patient's Hospital medical record did not indicate that morphine had been given to the patient. Tr. I-179, ll. 5-6. This witness also stated that FDA had not checked the narcotics record of the Hospital to determine

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2/ If morphine was not given to the patient within eight hours of the administration of the study medication it would not need to be reported. G-17 at 5.

whether morphine had been dispensed to the patient. Tr. II-5-6. Finally, Dr. Steen testified that demerol, rather than morphine, is ordinarily used at the Hospital. Tr. I-180.

Based upon the evidence in the record, I disagree with the Presiding Officer's finding that the Bureau made a prima facie case that morphine was administered to patient 233 (G-21). I find that the Bureau has not proven by a preponderance of the evidence that Dr. Steen failed to report administration of concomitant medication in the case report form for patient 233 (G-21).

The Bureau argues that the Hospital nursing notes reflect that patient 223 (G-25) received pain medication thirty five minutes after she was given the study medication, and that Dr. Steen did not report this concomitant medication. G-25 at 13, 31, and 33. The Bureau also presented testimony that the patient received medication for pain seven hours and five minutes after administration of the study drug. Tr. I-196. The patient's nursing notes, submitted as the FDA's exhibit G-25, at 13-16,[3/] show that the patient received medication for pain at thirty five minutes and seven hours and five minutes after the administration of the study drug. Dr. Steen's response to this charge is that the patient received a pain medication

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3/ Page 16 of the exhibit is a duplicate of page 14.

seven hours after the study drug but that this does not constitute a failure to report a concomitant medication. Tr. I-196, Statement at 26. I do not agree with Dr. Steen. The protocol specificly states that "[f]or 8 hours after administration of the study medication, the patient must not receive any other anesthetic, analgesic, sedative, or psychotropic drug ... All medication received by the patient during the 8 hours after administration of the study medication will be recorded." G-17 at 5. I find that the evidence presented by the Bureau establishes that patient 223(G-25) received concomitant medication within 8 hours of administration of the study drug, and that Dr. Steen did not report that fact in the case report form for the patient. G-25.

Based upon the above findings, I agree with the Presiding Officer that Dr. Steen has failed to prepare and maintain adequate and accurate case histories in violation of 21 CFR 312.1(a)(13)(4c), by reason of his failure to report administration of concomitant medication as required by study protocol for patients 144(G-20), 203(G-22), 228(G-23), 227(G-24), 223(G-25), 146(G-30), 231(G-31), 120(G-32), and 220(G-33).

b. Failure to report significant surgical information.

The Bureau charges that Dr. Steen failed to report accurately significant surgical information for seven

patients, 227(G-24), 223(G-25), 231(G-31), 120(G-32), 220(G-33), 202(G-34), and 119(G-37)), in that the Hospital records and Dr. Steen's case histories for these patients differ significantly on important information such as the date or type of surgery and whether or not surgery was actually performed.4/ The Bureau's evidence on patients 227(G-24), 231(G-31), 120(G-32), and 220(G-33) was not challenged by Dr. Steen. The Presiding Officer found that significant surgical information was incorrectly reported by Dr. Steen on the patients' case report forms. Accordingly, the Presiding Officer found that Dr. Steen had failed to maintain adequate case histories. Report at 7.

I agree with the Presiding Officer. The Bureau's uncontroverted evidence clearly shows that Dr. Steen's case histories contained information on date and type of surgery and whether or not surgery was actually performed which differed from the patients' Hospital records.

With regard to patients 223(G-25), 202(G-34), and 119(G-37), Dr. Steen argues that discrepancies between the Hospital records and his case histories are either slight, and thus did not affect the validity of the study data, or

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4/ The Bureau also included in this section evidence of discrepancies with respect to the date and time of administration of the study drug for patients 227(G-24) and 231(G-31). Dr. Steen did not contest these allegations, and I find that Dr. Steen failed to maintain adequate case histories for those patients in violation of 21 CFR 312.1(a)(13)(4c).

irrelevant because the patient was a proper candidate for admission to the study.[5/] Statement at 26. For patient 223(G-25), Dr. Steen does not contest the fact that the Hospital records show that surgery was performed on a different date from that reported by Dr. Steen or that the study drug was administered on a different date from that reported on the case report form. Likewise, Dr. Steen does not challenge the Bureau's allegation that the Hospital records and Dr. Steen's case report form show different dates of surgery for patient 202(G-34). Finally, the Bureau presented uncontroverted evidence that the Hospital records for patient 119(G-36) show a different surgical procedure than reported by Dr. Steen and that the study drug was administered at a time when the patient was unlikely to have had severe pain. Tr. I-237-9. Based upon the Bureau's uncontroverted evidence, the Presiding Officer found that Dr. Steen kept inadequate case histories in each of the seven instances the Bureau charged. Report at 7.

I agree with the Presiding Officer. The unrebutted evidence presented by the Bureau clearly establishes that Dr. Steen failed to report significant surgical information

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5/ The fact that a discrepancy might not affect the validity of the study data is no defense to a charge of failing to prepare and maintain adequate and accurate case histories as required by 21 CFR 312.1(a)(13)(4c). This is especially true when these "minor discrepancies" are found in studies that contain major flaws that have a debilitating impact on the validity of the study.

in the case report forms for patients 223(G-25), 202(G-34), and 119(G-37). I find that Dr. Steen has repeatedly violated FDA regulations by failing to prepare and maintain adequate and accurate case histories as required by 21 CFR 312.1(a)(13)(4c).

c. Failure to Verify Participation in the Study

The Bureau alleges that, in four instances, patients were not at the Hospital at the time that Dr. Steen reported they were participants in the study and received the drug at the Hospital. 144(G-20), 233(G-21), 231(G-31), and 202(G-34). Dr. Steen does not contest these allegations. The Presiding Officer did not make any findings regarding these charges.

I find that the Bureau has proven its charges by a preponderance of the evidence. The Hospital medical records and affidavits for patients 144(G-20) and 233(G-21) establish that they were discharged from the hospital prior to the time the study drug was reportedly administered, and that neither patient consented to participate in a new drug study. G-20, G-21. The Hospital medical records for patient 231(G-31) show that she was under anesthesia during the time she reportedly received the study drug. G-31. Patient 202(G-34) was in the Hospital during the time he reportedly participated in the study, but he did not have surgery during that hospital stay. G-34. Because the study was a post-surgical analgesic study, patient 202(G-34) could not

properly have participated in the study on the date listed by Dr. Steen in his case report form. Based upon the Bureau's uncontroverted evidence, I find that Dr. Steen failed to prepare and maintain adequate and accurate case histories for patients 144(G-20), 233(G-21), 231(G-31), and 202(G-34) in violation of 21 CFR 312.1(a)(13)(4c).

The Bureau further alleges that no Hospital records could be found that corroborate that patients 143(G-28), 234(G-29), 225(G-35), and 141(G-36) were ever patients in the hospital. Dr. Steen states that he found the Hospital record for patient 141(G-36, R-17), (Tr. II-19),[6/] but he did not present any evidence to controvert the Bureau's proof regarding patients 143(G-28), 234(G-29), and 225(G-35). Dr. Steen also argues that he should not be held accountable for records that were in the custody of a third party, namely the Hospital's records department. The Presiding Officer found that Dr. Steen failed to prepare and maintain adequate case histories by preparing case reports for subjects for whom Hospital records could not be located. Report at 11.

6/ Although Dr. Steen found the Hospital operation report (R-17) for patient 141(G-36, R-17) the uncontroverted evidence presented by the Bureau shows that the operation took place four days prior to the surgery date listed by Dr. Steen and eight days prior to the reported date the study drug was administered. Based upon this evidence, I find that Dr. Steen failed to prepare and maintain an adequate and accurate case history for patient 141(G-36, R-17). 21 CFR 312.1(a)(13)(4c).

Based upon the testimony of the FDA investigator regarding his attempts to locate the Hospital records for these patients (Tr. I-123-5, 237, 245-6), the testimony of Dr. (Tr. I-245-46), and the statement of , Assistant Director, Medical Records Service, (Hospital (G-53), I agree with the Presiding Officer. The patient chart is part of the case history, which FDA regulations required to be established and maintained. In re Gelfand, supra, at 8-9. Dr. Steen should be able to furnish some documentation to show, for example, that the patient was in the hospital at the time of the study. If the raw data (i.e. the Hospital record) cannot be located, the case report form cannot be validated, and the case history is inadequate. Tr. I-150-2, 218-21. I agree with the Presiding Officer that occasionally, a particular record may be lost; but not an entire case history. Were there only one or two missing records for patients in a study, I might give Dr. Steen the benefit of the doubt. However, where, as here, there were three patients for whom no records of any kind could be found, and where the study's case report forms are full of errors and omissions, the Bureau has, by a preponderance of the evidence, proven that it is more probable than not that at least some of these records did not exist or, more seriously, that possibly the patients themselves did not exist. I therefore find that Dr. Steen failed to maintain adequate and accurate case histories for

patients 143(G-28), 234(G-29), and 225(G-35) in violation of 21 CFR 312.1(a)(13)(4c).

d. Charting the Study Drug

The Bureau alleges that for patients 228(G-23), 227 (G-24), and 223(G-25), Dr. Steen failed to prepare and maintain adequate and accurate case histories in that he did not record in the patients' Hospital charts the administration of the study drug. Dr. Steen does not challenge the Bureau's allegations. The Presiding Officer found that without this information in the patients' medical records, their medical history is incomplete, and that it is Dr. Steen's responsibility to assure that these entries are made in the patients' medical records. Report at 12-13.7/

I agree with the Presiding Officer and find that with respect to patients 228(G-23), 227(G-24), and 223(G-25), the Bureau's uncontroverted evidence demonstrates by a preponderance of the evidence that Dr. Steen did not prepare and maintain adequate case histories. 21 CFR 312.(a)(13)(4c).

2. FAILURE TO OBTAIN INFORMED CONSENT

The Bureau charges that Dr. Steen failed to obtain the informed consent of subjects 144(G-20), 233(G-21),

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7/ This principle was established in the Gelfand Hearing (See Presiding Officer's Opinion, at 13-14) and was not contested by Dr. Steen.

and 223(G-25). The Bureau presented the testimony of an FDA investigator who testified that he interviewed patients 144(G-20) and 233(G-21). These patients stated in signed affidavits that they did not consent to participate in the drug study, and that the consent forms bearing their names were signed by someone else. G-21 at 23-25, G-26 at 28-29. Dr. Steen attempts to answer the Bureau's evidence by alleging that he was "deceived by the malfeasance of his study nurse," Ms. . Comments pp. 3-4. Dr. Steen also suggests that patients 144(G-20) and 233(G-21) did not remember giving consent or signing the consent form because they may have suffered from post-anesthesia amnesia, and that they signed the consent forms while in pain or in a prone position which caused their signatures to be unrecognizable. Statement at 20. The Presiding Officer found that the Bureau had proven by a preponderance of the evidence that the signatures purportedly witnessed by Nurse were not those of patients 144(G-20) and 233(G-21). Report at 8.

I agree with the Presiding Officer. The affidavits of patients 144(G-20) and 233(G-21) establish that neither patient gave their consent to participate in a drug study. The unqualified statements by these patients is far more reliable and believable than Dr. Steen's conjecture. The evidence in the record does support Dr. Steen's contention that he delegated responsibility for obtaining informed consent to his study nurses. Tr. I-121-22, 129, 132,

Tr. II-39, 42, 84-85, 161, 166. There is also no evidence that Dr. Steen falsified the consent forms. However, the possibility that Dr. Steen may have been deceived by his study nurse does not negate the fact that neither patient gave their consent to participate in a drug study, and Dr. Steen was responsible for ensuring that consent was obtained.

The third subject, patient 223(G-25), was deceased at the time of the FDA investigation. The Bureau alleges that she could not have given informed consent because she was a "low-functioning" individual whose last I.Q. measurement was 53. Dr. Steen argues that the patient was legally competent to give consent and in fact gave her consent to participate in the study. Dr. Steen reasons that because the patient gave her consent for medical and surgical treatment at the Hospital and because there is no evidence that the hospital environment was so coercive that the patient was deprived of her free power of choice, the patient's consent was given freely and understandingly. Statement at 25-26. The Presiding Officer found that the Bureau's sole evidence, i.e. the patient's I.Q., was not enough to satisfy its burden of proof. Report at 8.

I disagree with the Presiding Officer. The Bureau presented ample evidence to sustain its burden of proof. First, the patient, who signed her name with an "X," was a "low-functioning" individual with an I.Q. of 53. G-25 at 1,

8, 23, 28, 29. Second, a State of California Department of Developmental Services psychiatric social worker opined in a telephone conversation with an FDA investigator that it was doubtful that the patient could have understood the informed consent procedure. G-25 at 2. The psychiatric social worker also stated to FDA that the patient took psychotropic medications and had a history of psychiatric disturbances. G-25 at 2. Third, the patient's hospital medical record lists the "person to notify" as a "guardian." G-25 at 5. There is no evidence in the record that the patient's guardian consented or was even consulted about the patient's participation in a drug study. Finally, under the circumstance present here, the patient's ability to understand the need for, and to consent to, surgery does not mean she had the ability to understand and consent to participate in a new drug study. It is my opinion that patient 223(G-25) was not capable of giving informed consent and that the Bureau has proven by a preponderance of evidence that patient 223(G-25) did not give her consent to participate in the drug study. I therefore find that Dr. Steen failed to obtain the informed consent of study patients 144(G-20), 233(G-21) and 223(G-25) in violation of 21 CFR 312.1(a)(13)(4g) and 21 CFR 310.102.

Finally, for all of the reported subjects, Dr. Steen signed the consent form, under the following statement:

> I certify that I have reviewed the contents of this form with the person signing above, who, in my opinion, understood the explanation. I have explained the known side effects and benefits of the study. Any significant change in the nature of the study, from that described above, will be fully explained to the person signing it.

The Bureau urges, and the Presiding Officer adopted, the interpretation that by signing, Dr. Steen attested that he had personally participated in the consent process. During the hearing, Dr. Steen testified that he never personally participated in the consent process, never spoke to the patients, and signed the paragraph on the consent forms in batches during weekly or semi-weekly meetings with Ms. his nurse. Tr. II-31-2, 116.

Dr. Steen attacks that finding as being legally erroneous. He argues that the consent form should be interpreted in light of what he contends was accepted practice -- the study nurse obtains patient consent, while the investigator signs the form. Thus, he contends that the effect of the Presiding Officer's Report is, contrary to established agency law principles, to make him accountable for the actions of his nurse but to deny him the ability to credit these actions as his own. Statement at 19-23, Comments at 6-12.

While I believe there is some merit in Dr. Steen's argument, I need not decide whether he submitted false information to the sponsor because the certification

statements were not literally true. I do find, however, that even accepting Dr. Steen's interpretation of the consent form, he submitted false information to the sponsors, because neither he nor his nurse ever obtained consent. Therefore, I find that Dr. Steen violated 21 CFR 312.1(c)(2)(2) by repeatedly submitting false information to the sponsor.

B. THE STUDIES

1. The Applicability of FDA's Bioresearch Monitoring Regulations

The Bureau argues that Dr. Steen's studies were properly the subject of IND's and therefore that Dr. Steen was required to follow FDA's bioresearch monitoring regulations.8/ Dr. Steen offered a variety of reasons for why the regulations did not apply to these studies. Statement at 9-18. The Presiding officer found that the drugs used in the studies were new drugs, were intended solely for investigational use, and were therefore subject to FDA IND regulations, including 21 C.F.R. 312.1. Report at 17-18.

I agree that Dr. Steen's studies were subject to FDA's bioresearch monitory regulations. Dr. Steen argues that the drugs used in the studies were approved and that the type of medical treatment he performed was commonly

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8/ For both studies, Dr. Steen signed an FD-1573, by which he acknowledged the requirement of obtaining informed consent and certified that he would adhere to that requirement. G-2 at 3, G-3 at 3.

accepted medical practice. Statement at 10. Although it is true that the drugs at issue here were approved by FDA, they were not approved for the dosage, for the speed of administration, and for use in the combination in which they were administered in this investigation. G-6, G-8, G-9, G-51. There is conflicting evidence as to whether the non-approved use of these drugs was commonly accepted medical practice at the time of the investigation. Tr. I-55, II-91. I therefore make no finding on that point. Dr. Steen continues his argument by asserting that doctors may vary the dosage regimen from that recommended in the labeling, and that an IND is required only if the physician caused the drugs to be shipped in interstate commerce. Dr. Steen cites in support of this argument Dr. Hensley's testimony (Tr.I-56, 60), United States v. Evers, 643 F.2d 1043 (5th Cir. 1931), and a notice of proposed rulemaking issued by FDA in 1972 (37 Fed. Reg. 16503, August 15, 1972). Statement at 11-12. While it is true that a physician may, as part of the practice of medicine, lawfully prescribe a dosage not indicated in the drug's labeling, Dr. Steen used the drugs not merely in the practice of medicine, but as part of a new drug investigation. If an investigator limits his choices, his patients' choices, and the choices of the people working for him in the treatment of those patients, then he is conducting a drug study and that is different from the practice of medicine. Tr.I-60-62. See 48 Fed. Reg. 26733,

June 9, 1983. Therefore, Dr. Steen's reliance on FDA's Notice of proposed rulemaking and the Evers case, supra, is inapposite. Both the Notice of Proposed Rulemaking and the Evers case concern the legal responsibility of physicians who prescribe drugs for conditions not named in the labeling. Neither is relevant to Dr. Steen, who was engaged in medical research. I find, based upon 21 U.S.C. §355(i) and 21 C.F.R. §310.3 (see Report at 15-18), that the drugs used by Dr. Steen in the studies were new drugs; were intended solely for investigational use; and were subject to FDA's bioresearch monitoring regulations.9/

2. Failure to Obtain Informed Consent

The Bureau alleges that Dr. Steen did not obtain informed consent -- written or otherwise -- from any of the 71 subjects in the two studies. Dr. Steen does not contest this allegation. Instead, Dr. Steen argues that he was not required to obtain consent, and that, even if he was required to, his failure was an honest "mistake of law." Statement at 10-18. The Presiding Officer found that

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9/ Dr. Steen argues that the Bureau did not prove that the drugs at issue here were shipped in interstate commerce and therefore an IND was not required. Statement at 12-13. I disagree with this argument. FDA's exhibit G-5 at 6-7, documents that the study drugs were shipped in interstate commerce from the sponsor in to Dr. Steen in California for purposes of this investigation.

Dr. Steen was required to obtain informed consent in these trials, but that Dr. Steen's failure was not deliberate. Report at 18.

Based upon my prior finding that Dr. Steen's studies were subject to FDA's bioresearch monitoring regulations, I agree with the Presiding Officer. 21 U.S.C. 355(i) and 21 CFR 312.1(a)(13)(4g) require that Dr. Steen inform the study patients that the drugs are being used for investigational purposes, and that he obtain the consent of the patients. In addition, Dr. Steen signed a Form FD-1573 for each trial, by which he acknowledged the requirement of obtaining informed consent and certified that he would adhere to that requirement. G-2, G-3. Dr. Steen's argument that the conditions contained in the Form FD-1573 could be negated at will by either himself or the sponsor is not correct. The Form FD-1573 contains the regulatory requirements applicable to studies such as those performed here by Dr. Steen. Those requirements do not depend for their existence and continued vitality upon the execution of the Form FD-1573. The execution serves to document that the investigator is aware of those requirements. I find, therefore, that Dr. Steen failed to obtain informed consent from the patients involved in his studies in violation of 21 CFR 312.1(a)(13)(4g) and 21 CFR 310.102.

3. Failure to Obtain Institutional Review Board Approval

Dr. Steen does not contest the Bureau's allegation that he did not obtain Institutional Review Board (IRB) approval of either of his studies.[10] TR. II-89, 168. Dr. Steen contends that IRB review and approval were not required because the drugs used in the studies were marketed drugs, and that even if IRB review and approval were required, he failed to obtain them because of an honest "mistake of law." Statement at 10-18. The Presiding Officer found, for the same reasons stated regarding the requirement of obtaining informed consent, that Dr. Steen was required to seek IRB review and approval. The Presiding Officer also found that Dr. Steen's failure was not deliberate. Report p. 19.

I agree with the Presiding Officer's findings and for the reasons I stated regarding the requirement of obtaining informed consent. In this situation, 21 CFR 312.1(a)(13)(4h) requires that Dr. Steen assure the sponsor that the studies will not be initiated until the IRB has reviewed and approved the study.[11] I find that Dr. Steen was required to

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10/ There was an IRB at Hospital. Tr. I-51.

11/ Also, Dr. Steen signed the Form FD-1573, by which he acknowledged the requirement of obtaining IRB approval and certified that he would adhere to that requirement. G-2, G-3.

obtain IRB review and approval of the studies, and by not doing so violated 21 CFR 312.1(a)(13)(4h).

4. Failure to Prepare and Maintain Adequate and Accurate Case Histories

The Bureau alleges that the clinical and Hospital records of four of the nineteen subjects on Dr. Steen's studies contained discrepancies. The Presiding Officer found that for three of the four subjects, 17(G-14), 3(G-12), and 7(G-13), the Bureau had not proven by a preponderance of the evidence that a protocol violation occurred. Report at 20-22.

For the reasons stated in the Presiding Officer's Opinion (Report at 20-22), I agree with the Presiding Officer that the Bureau has not proven by a preponderance of the evidence that Dr. Steen failed to prepare and maintain adequate and accurate case histories for patients 17(G-14), 3(G-12), and 7(G-13).

The Presiding Officer also found that the Bureau had proven its case regarding patient 18(G-11), but that the discrepancy was not serious. The Bureau charges that patient 18(G-11) developed a facial rash within the 24 hour observation period for the study and that Dr. Steen did not report this on the patient's case report. The Bureau presented evidence that a rash is commonly associated with . Dr. Steen argues that the facial rash was caused by another investigational drug, , which was

administered subsequent to the and shortly before the rash appeared. Dr. Steen contends that it is more likely that the rash was caused by the , and that he reported the reaction as part of the study. Statement at 3-4. The Presiding Officer found that Dr. Steen should have included the reaction as part of the case history for patient 18(G-11). Report at 20.

I agree with the Presiding Officer. The study required the investigator to report adverse effects that occur within twenty-four hours of the administration of the study drug. Tr. I-86, G-6 at 5. Even if Dr. Steen is correct that the reaction is more common for than for the fact still remains that a rash is commonly associated with . Tr. I-36, G-8 at 2. In a situation such as the one here, where there is a possibility that a reaction is an adverse reaction to a study drug, that reaction should be included in the study patient's case history. I find, therefore, that Dr. Steen failed to prepare or to maintain an adequate and accurate case history for patient 18(G-11). 21 CFR 312.1(a)(13)(4c).

SUMMARY OF FINDINGS

Based upon the evidence presented by Dr. Steen and the Bureau, I agree with the Presiding Officer and find that Dr. Steen has repeatedly failed to comply with FDA regulations and has repeatedly submitted false information to the sponsors of the investigations in violation of 21 CFR

310.102, 312.1(a)(13)(4c), 312.1(a)(13)(4q), 312.1(a)(13)(4h), and 312.1(c)(2).

ASSURANCES

Having made this finding, I now turn to whether Dr. Steen has furnished adequate assurance that he will comply with FDA's exempting regulations in the future. To avoid disqualification, Dr. Steen has the burden of establishing that his assurances are adequate. In re Gelfand, page 18.

The Presiding Officer concluded that Dr. Steen's assurances lacked specifics and were not adequate to overcome the seriousness of the violations. The Presiding Officer also found that Dr. Steen's assurances were not believable and recommended that I disqualify Dr. Steen from receiving investigational new drugs.

I agree with the Presiding Officer regarding the adequacy of Dr. Steen's assurances. An adequate set of assurances must:12/

1. Include a general assurance of full compliance with FDA's regulations on the use of investigational articles;

12/ These guidelines are based upon 21 CFR 312.1(c), the agency's standards for reinstatement of investigators, the preamble to the agency's 1978 proposed clinical investigator regulations (43 Fed. Reg. 35210), and previous Commissioners' decisions in clinical investigator hearings.

2. Address each of the violations of FDA's regulations, or of the actions, that resulted in Dr. Steen's submitting false information to the sponsor;

3. Include a detailed description of the corrective actions that Dr. Steen has taken or intends to take to assure that the violative acts and omissions will not recur;

4. Be presented in the context of a concrete situation (i.e. Dr. Steen should submit the protocol for an investigation that he plans to conduct and should explain why his commitments will assure that his previous violative acts and omissions will not recur in the context of that investigation).

Analyzed under these principles, Dr. Steen's assurances are not adequate. First, he has not submitted a protocol for a specific investigation. In the absence of a concrete context, it is not possible to judge whether Dr. Steen's assurances will remedy his violations and omissions. Moreover, his assurances are lacking in detail and fail to address certain of the inadequacies in the way in which he conducted his investigations.

Dr. Steen repeatedly submitted false information to the sponsor of the investigation. He submitted case report forms that did not accurately reflect either the concomitant medication received by the subjects in this study or the case histories of those subjects. Dr. Steen asserts

that in the future he will spot check case report forms to assure that they are consistent with the hospital records, and that, to facilitate his checks, he will maintain duplicates of the hospital records in his files. Tr. II-94, 96, R-30. However, Dr. Steen gives no indication of what will be included in his spot checking. He does not state, for example, what percentage of the case report forms he will check. Thus, it is impossible for me to determine whether spot checking will adequately remedy this deficiency.

Another problem in Dr. Steen's studies was that informed consent was not obtained from a number of subjects. Dr. Steen states that a copy of the subject's signed informed consent form will be placed in their study files (Tr. II-99), and that subjects will be asked post-operatively whether they remember signing the informed consent form, and whether they wish to continue to participate in the study. Tr. II-92-93. Dr. Steen states that he will make sure that informed consent has been obtained by spot checking the subjects' records. Although the presence of the signed consent form in the record will facilitate Dr. Steen's checking, and the post-operative questioning of patients will help to assure that only the records of subjects who have given consent will be submitted to the agency, the only means that Dr. Steen has specified of assuring that only subjects who have given informed consent are given the test drug is his spot checking. Dr. Steen's description of his spot checking is

simply not detailed enough to allow the agency to determine whether it will occur at the appropriate time and with appropriate frequency to protect the subjects adequately.

In addition, Dr. Steen's assurances do not address how he will assure that the people admitted to his studies are actually patients at the hospital, and that they meet the requirements of the protocol. Such an assurance is clearly necessary in light of the Bureau's circumstantial evidence that some subjects in the study were never in the hospital, and that other subjects did not have surgery even though the purpose of the study was to assess the effect of the drug on post-surgical pain.

Another problem in Dr. Steen's studies was the administration of concomitant medication to subjects. Dr. Steen stated at his hearing that to minimize this problem, a copy of the protocol of a study will be given to the nursing staff. Tr. II-99. However, he did not explain how the nurses would be able to identify which patients were involved in the study and thus should not be receiving any medication other than the study drug.

Dr. Steen's assurances are also inadequate because he does not state what he will do in the future if he again confronts an investigation like the investigation about which he is uncertain as to whether it is covered by the Federal Food, Drug, and Cosmetic Act and the regulations the agency has adopted for investigational drugs. In a

letter to Dr. Nightingale dated January 29, 1982 (R-30), Dr. Steen stated that he would obtain IRB approval and informed consent following submission of a form FD-1573. However, at the hearing, Dr. Steen indicated that there might be circumstances in which, even though he signed an FD-1573, it would not be necessary for him to obtain such approval or consent. Tr. II-115-17. Thus, Dr. Steen has yet to submit an unqualified assurance outlining the steps that he will take to determine whether a study is covered by FDA's regulations and agreeing that he will comply with those regulations if the study is covered.

To correct these deficiencies, Dr. Steen must modify his assurances to include:

1. A general assurance that he will fully comply with FDA's regulations on the use of investigational new drugs.
2. A description of the steps he will take in the future to determine whether an investigation he intends to undertake is covered by FDA's regulations.
3. A protocol for a specific study.
4. A declaration that he will obtain institutional review board review of that study.
5. A detailed description of how informed consent will be obtained in the circumstances of that investigation and of the steps he will personally

take to assure that informed consent is obtained. If Dr. Steen intends to rely on post-operative checking with patients about their consent, he should specify what percentage of the patients will be asked, when, and by whom. If he intends to rely on spot checking to assure that informed consent is obtained, or for any other purpose, he will have to work with the Bureau to develop a mutually acceptable concept of spot checking. I will advise the parties as to the appropriateness of their decision.

6. A detailed description of how he will assure, including the steps that he will personally take, that only qualified patients are admitted to the study. One possible method would be for Dr. Steen to admit the patients himself. A second method would be that no subject who is admitted into the study would receive the test drug or placebo until Dr. Steen has had an opportunity to review the subject's records and is satisfied that the person is an appropriate subject.

7. A detailed description of how he will assure, including the steps that he will personally take, that no concomitant medication that would interfere with the evaluation of the study drug is given to the subjects admitted to the study, and that if such

medication is given to a subject, he is promptly notified of that fact so that he can disqualify the patient from the study.

8. A detailed description of how he will assure, including the steps that he will personally take, that the case report forms are accurately maintained with regard to such matters as concomitant medication and case history.

The Presiding Officer also recommended that I find, because of the falsifications that occurred in the study, that Dr. Steen's assurances are not believable. I do not accept this recommendation. Dr. Steen delegated the obtaining of informed consent and the conduct of the entire study to his nurses. Tr. I-121-22, 129, Tr. II-39, 84-85, 161, 166. For two of the falsifications, the forged consent forms and the absence of hospital records for several study patients, there is no basis in the record to impute that dishonesty to Dr. Steen. There is also the falsification regarding Dr. Steen's certifying that he had reviewed the consent form with the patient, when he had not personally obtained the patient's consent. This type of mistake should not affect Dr. Steen's credibility. Dr. Steen is responsible for the falsifications and all of the violations which occurred in his studies, but the record is devoid of any facts which would support an allegation that Dr. Steen is untrustworthy.

I recognize that not all of the previous Commissioners' decisions in clinical investigator hearings are consistent with the principles I have enunciated here. Therefore, I am willing to withhold a final decision on Dr. Steen's assurances until he has had an opportunity to submit a revised set of assurances that he believes are adequate under these principles. Dr. Steen must agree, however, not to participate in any new studies unless and until I have informed him that his revised assurances are adequate. Dr. Steen should inform me in writing, within 14 days from the date of this decision, whether he intends to submit a revised set of assurances and whether he agrees not to participate in any new studies pending my decision on his revised assurances. Dr. Steen should submit his revised assurances, with a copy of the protocol for a new study, to the Bureau and to me within 90 days from the date of this decision.13/ The Bureau will then have 30 days to

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13/ If Dr. Steen needs more than 90 days, he should request, in writing, an extension for a specified amount of time. I will notify Dr. Steen within 7 days on whether his extension of time has been granted.

comment on Dr. Steen's assurances.[14] I will make my decision after I have reviewed Dr. Steen's revised assurances and the Bureau's comments.

If Dr. Steen does not choose to submit new assurances, or if he does not agree to refrain from participating in any new studies unless and until I have informed him that his revised assurances are adequate, I will decide whether he should be disqualified from receiving investigational use drugs on the basis of the assurances he has submitted to date. Also, if Dr. Steen seeks to participate in any new studies before I have approved his revised assurances, I will entertain a motion by the Bureau to reconsider Dr. Steen's eligibility to receive investigational new drugs on the basis of the assurances before me at the time the agency receives his request to participate.

14/ The proposed clinical investigator regulations, 48 Fed. Reg. 35221, make clear that disqualification is not intended to be punitive but is principally a remedial action to prevent further violations and to assure that the rights and safety of subjects are appropriately protected. Therefore, it is incumbent upon the Bureau (now the Center for Drugs and Biologics) to present evidence relating not only to an investigator's violation of the regulations but also, if appropriate, to why the investigators' assurances are not adequate. In past disqualification hearings, the Bureau has often not presented the latter type of evidence.

IV. CONCLUSIONS

Dr. Steen has repeatedly failed to abide by FDA regulations and has repeatedly submitted false information to the sponsors. For the reasons previously stated, I am withholding my final decision on Dr. Steen's assurances until he has had an opportunity to submit a revised set of assurances under the principles that I have set forth in this decision. Dr. Steen may not participate in any new investigational drug studies unless and until I have informed him that his revised assurances are adequate.

Dated: May 18, 1984

Mark Novitch

MARK NOVITCH, M.D.
Acting Commissioner