DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

29 JAN 1988

REGISTERED MAIL
RETURN RECEIPT REQUESTED

Ronald R. Fuller, D.V.M.
Animal Hospital
Street

Dear Dr. Fuller:

Notice of Disqualification to Receive
Investigational-Use New Animal Drugs

I have reviewed the record of the regulatory hearing conducted by Stuart L. Nightingale, M.D. on March 31, 1987 concerning your eligibility to receive investigational-use new animal drugs. The record does not contain any satisfactory explanation for the discrepancies observed in your clinical reports as set forth in the March 11, 1986 Notice of Opportunity for Hearing.

The report of the Presiding Officer was sent to you for comment on August 20, 1987. I find, based on DHL Airbill No. 49715702, that the report was received by your office by on August 21, 1987. Thus, you had a full opportunity to comment on that report but chose not to do so.

Therefore, I am affirming and adopting the October 1987 Report of the Presiding Officer and have determined that you have repeatedly and deliberately submitted false information on case report forms thereby violating the regulations on investigational new animal drug use. Specifically:

1. The affidavits from the owners of the dogs supposedly enrolled in the study fail to support the case report entries. The owners either denied or could not remember any injury suffered by or any treatment given to their pets. In contrast, the case report forms frequently noted the cause of the injury.

CMD1

DNo. - 01R0021

2. The medical records for the animals supposedly enrolled in the study also fail to support the case report forms. The entries in the medical records are inconsistent with the dates during which the animals were supposedly participating in the study.

3. The medical records were altered during the course of an FDA inspection.

In accordance with 21 CFR 511.1(c), you are hereby advised that you are no longer eligible to receive investigational-use new animal drugs. All such drugs in your possession should be promptly returned to their supplier.

For your information, I have enclosed copies of letters which have been sent to all sponsors of investigations in which you have been named as a participant. These letters inform the sponsors that you are not entitled to receive investigational new animal drugs.

Sincerely,

Frank E. Young, M.D., Ph.D.
Commissioner
Food and Drug Administration

Enclosures

cc: HF-1
HF-2
HFA-1
HFY-1
GCF-1
HFV-1
HFA-225

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : The Commissioner
Through: The Acting Deputy Commissioner

DATE: NOV 26 1980

FROM : Acting Associate Commissioner for Health Affairs, HFY-1

SUBJECT: Michael C. Gelfand, M.D., and His Entitlement to Receive New Drugs for Investigational Use--ACTION

ISSUE

To propose a course of action with respect to the entitlement of Dr. Michael C. Gelfand to receive new drugs for investigational use.

BACKGROUND

Prior to 1977, Dr. Michael C. Gelfand had been participating in a study of the drug as a co-investigator. In January 1977 he decided to become a principal investigator, and he signed a Form FD-1572 and submitted it to the sponsor, In November 1978 FDA investigators began an inspection of Dr. Gelfand's study. They found what they believed to be several significant violations of the FDA regulations governing such studies. Dr. Gelfand was informed of the results of the investigation by letter several months later and was offered an opportunity for an informal conference. He declined to attend such a conference and chose instead to reply in writing. His written explanation was rejected by the Bureau of Drugs, and he was given a notice of an opportunity for a formal Part 16 regulatory hearing. After several unsuccessful attempts by Dr. Gelfand's counsel to settle the dispute without a regulatory hearing, the actual hearing took place on April 9 and 10, 1980.

The Bureau of Drugs presented eight basic charges supported by the testimony of one of the FDA investigators who conducted the inspection of Dr. Gelfand's data, and by Dr. Robert Temple, Director of the Division of Cardio-Renal Drugs (FDA). The Bureau offered 21 exhibits to support those charges.

After the Bureau of Drugs had concluded its presentation and before Dr. Gelfand began his response to specific charges, Dr. Gelfand's attorney presented respondent's exhibit R-1, a copy of the August 8, 1978, Federal Register, pages 35210-36. This document is a proposed

FDA regulation to clarify existing regulations concerning persons who conduct clinical investigations. The preamble to the proposal states that FDA inspections have disclosed numerous deviations by investigators from current standards, and that these discrepancies may be related, at least in part, to misunderstandings over the precise meaning of FDA regulations relating to clinical investigations, as presently written. Dr. Gelfand asserted that by publishing this proposed regulation, FDA has admitted that current regulations in 21 CFR 312 are vague or ambiguous. This position was amplified in the post-hearing brief submitted by Dr. Gelfand's attorney. The brief stated:

> The notice afforded to Dr. Gelfand has been severely criticized by the Food and Drug Administration in its proposal which would amend existing regulations concerning the obligations of clinical investigators of regulated articles. See Obligations of Clinical Investigators of Regulated Articles, Proposed Establishment of Regulations, 43 Fed. Reg. No. 153 (August 8, 1978), pp. 35210-35229. In particular, in that proposal, the FDA categorizes existing Form FD-1573 as follows:
>
> > Many portions of the forms describe obligations in general terms such as 'adequate' and refer to other requirements in terms commonly understood but subject to misrepresentation in specific cases. 43 Fed. Reg. at 35210.
> >
> > In addition, the "supplementary information" section describing the circumstances creating a need for the proposed new rule indicated that "the Commissioner is of the opinion that the way these requirements are stated may have contributed to misunderstandings concerning the conduct FDA expects of a clinical investigator --misunderstandings manifested by FDA findings of noncompliance or inadequate performance by a number of clinical investigators." This section indicated that in 1972, the Bureau of Drugs undertook a special survey of IND studies involving 155 investigators. According to the notice, "the results of this survey showed varying degrees of deficiencies by 115 investigators in one or more of six areas." 43 Fed. Reg. at 35210. Further, it is indicated that "these surveys. . .indicate that a serious problem of communication exists between FDA and at least some clinical investigators. . . .The first step to compliance with these policies is to restate them with precision (emphasis added) and reaffirm the goals being sought." 43 Fed. Reg. at 35211.

Dr. Gelfand's attorney sought from the Presiding Officer, but did not receive, a dismissal of the charges based upon the foregoing alleged admissions by the Commissioner.

The hearing closed with summary statements from both attorneys. The Presiding Officer offered both parties the opportunity of making post-hearing submissions. Both sides submitted post-hearing proposed findings of fact and conclusions of law. Both sides were provided with copies of the two volumes which constitute the transcribed record of the hearing, and both submitted lists of corrections (mostly typographic) to the transcript. These corrections were made.

A full chronology of events leading to the hearing, is given in the Appendix.

CHARGES BROUGHT BY THE BUREAU OF DRUGS

The charges as set forth in Dr. Kelsey's letter of March 30, 1979, and in the letter of September 25, 1979, from the counsel for the Bureau of Drugs to Dr. Gelfand, were modified at the outset of the hearing (see below). The reason for modification was that correspondence between the Bureau's attorney and Dr. Gelfand's attorney had satisfied some of the Bureau's questions about Dr. Gelfand's record-keeping. The modifications consisted of changes in the names and the number of patients whose records, or absence of records, were used to support the charges. Furthermore, the September 25, 1979, letter from the counsel for the Bureau of Drugs had introduced one charge not contained in the March 30, 1979, letter from Dr. Kelsey. That charge was dropped by counsel for the Bureau at the time of the hearing.

In the following section, the charges contained in Dr. Kelsey's letter appear in quotation marks. Modifications to the charges, as noted, were made at the time of the hearing.

Charge 1: "Dates for some EKGs (electrocardiograms) in the case reports differ from dates on EKGs found in medical histories" (patients M.C. and H.R.). This charge was modified by dropping patient M.C. and adding patient S.B.

Charge 2: "Identical (superimposable) EKGs were submitted with two different dates for L.B. and H.R."

BUREAU PRESENTATION OF CHARGES 1 AND 2

In support of the charge that dates for some EKGs in the case reports differ from dates on EKGs found in medical histories, and in support

of the charge that identical (superimposable) EKGs were submitted with two different dates, the Bureau offered the testimony of Gurston Turner, Ph.D., one of the investigators who conducted the inspection of Dr. Gelfand's practices as a clinical investigator, and Robert Temple, M.D.

Through Dr. Turner's testimony and the presentation of government exhibits G4, G5, G6, and G16, the Bureau established that EKGs for were submitted by Dr. Gelfand to the sponsor of th investigation bearing dates that differed from those of identical EKGs in the medical histories of the subjects. (The charge relating to was added during the hearing.) Furthermore, identical (superimposable) EKGs were submitted for these patients on different dates. That is, the same EKG was submitted more than once for each of the four patients. Only the date was changed on these subsequent submissions of the same EKG. The Bureau then presented Dr. Temple who testified to the special character of the drug and the seriousness of the conditions for which it is used. He also testified to the significance of EKGs in the study of

DR. GELFAND'S RESPONSE TO CHARGES 1 and 2

In response to charges 1 and 2 (regarding EKGs) Dr. Gelfand asserted that he had given the responsibility of performing electrocardiograms on patients in the study and of submitting the EKGs to to an experienced "renal nurse," Ms. Dr. Gelfand testified to the experience, reliability, and generally superior performance of Ms. He stated that when he discussed with Ms. the discrepancies noted by the FDA investigators, she told him that she misunderstood the requirements of the protocol and intended the date on the EKGs to represent the date of submission, and in addition, she thought that the most recent EKG was to be submitted, so she saw nothing wrong in submitting the same EKG twice. Dr. Gelfand explained that another physician read the EKGs and that all he (Gelfand) did was review them and have them sent to the sponsor. Dr. Gelfand claimed that he was not aware of Ms. practice with respect to EKGs and had no reason to reconcile each EKG with previous tests on the same patient. He stated that superimposability would not otherwise be evident.

Dr. Gelfand referred to Appendix B-6 of the protocol which states:

> "Patients on Chronic Maintenance Hemodialysis
>
> Clinical observations, x-ray and ECG (sic) requirements are as listed for other patients', the difference is in blood analyses. We believe it would be a disservice to demand extensive laboratory testing in a group of patients whose hemoglobins average 7 g/100 (range 3-11 g/100) and who have a substantial number of laboratory tests performed periodically as part of their medical care. We will be content if these are reported on the appropriate forms and if at 3 month intervals, those tests listed in Appendix that have not been done as part of the customary patient management, be done and reported. Obviously, if urine is not produced, urinalysis cannot be conducted."

Ms. interpretation of Appendix B-6 was said to be responsible for the superimposable EKGs having been submitted, since she was accustomed to submitting results from the most recent test that was run (which could theorectically result in submitting the same test result twice, although the frequency of laboratory testing vis a vis the frequency of clinic visits would usually preclude this from happening). Dr. Gelfand further testified that as soon as he was informed by FDA investigators of the discrepanices in dates and the superimposability of the EKGs, he discussed the problem with Ms. and took steps to assure that it would not happen again. Thus Dr. Gelfand agreed that charges 1 and 2 were correct as set forth.

FINDINGS RELATED TO CHARGES 1 AND 2

The Bureau of Drugs established, and Dr. Gelfand freely acknowledged, that cover-sheets for EKGs contained the date of submission rather than the date the EKG was performed. Further, Dr. Gelfand admitted that superimposable EKGs had been submitted for the patients named in the bureau's charge.

CONCLUSIONS RELATED TO CHARGES 1 AND 2

Charges #1 and #2, were substantiated by the evidence. These discrepancies were brought to Dr. Gelfand's attention during the inspection, and he discussed them with his assistant Ms. and corrected the procedure that had allowed the errors. There does not appear to have been any suggestion of a deliberate attempt to deceive the sponsor, nor of any changes in the EKG itself. Once Dr. Gelfand became aware of the mistake, he informed the sponsor.

CHARGE 3: "Clinical laboratory tests could not be confirmed as actually having been performed on any subject at the time reported." The Bureau of Drugs applied this charge specifically to the records of patient

BUREAU PRESENTATION OF CHARGE 3

In support of the charge that the clinical laboratory tests which Dr. Gelfand reported to the sponsor could not be confirmed as actually having been performed on any subject at the time reported, the bureau referred to records of patient, .. Through Dr. Turner's testimony and government exhibits G-17,G-18, and G-19, the bureau established that a laboratory report submitted to the sponsor included incorrect dates for laboratory work performed on samples taken from For example, results of tests performed on April 28, 1978, were placed in the laboratory report submitted to the sponsor in a column dated June 5, 1978, and results of tests performed on May 11, 1978, were placed in a column of the form dated April 28, 1978.

DR. GELFAND'S RESPONSE TO CHARGE 3

In response to the charge that clinical laboratory tests reported could not be confirmed as actually having been performed on any subject at the time reported, Dr. Gelfand acknowledged that the laboratory report submitted to for patient included incorrect dates for laboratory work performed. Dr. Gelfand ascribed this deficiency to an error in transcribing the data from 's. patient records to a report form used to submit data to the sponsor. The error was attributed to Dr. Gelfand's assistant Ms. Exhibits R-22 and R-23 were used to illustrate data-recording procedures.

Dr. Gelfand admitted that on the second day of the hearing he learned for the first time that the protocol instructions for the Laboratory Report Form dictated that the "date" be the day on which the specimen being tested was collected. Dr. Gelfand stated that the incorrect procedure of applying the date of analysis rather than the date of specimen collection, would seldom result in differences of more than a few days in the date being reported to the sponsor. The case of patient was compounded by the fact that there were also errors in transcription, in that the results of laboratory work performed on May 11, 1978, were placed in a column of the form dated April 28, 1978.

FINDINGS RELATED TO CHARGE 3

The charge that clinical laboratory tests reported could not be confirmed as actually having been performed on any subject at the time reported, was supported by demonstrating that laboratory test results for patient were submitted to the sponsor with incorrect dates. The presence of erroneous dates was clearly estabished in this instance.

There was no contention or evidence that actual test values were ever changed or that values were reported incorrectly.

CONCLUSIONS RELATED TO CHARGE 3

Charge 3 alleged that clinical laboratory tests could not be confirme d as actually having been performed on any subject at the time reported. The Bureau established that for one patient, ., Dr. Gelfand had submitted reports that were dated incorrectly, and thus, for one patient, this charge was substantiated. No evidence was produced to suggest that clinical laboratory test results were ever modified incorrectly.

CHARGE 4: "Some subjects medical records could not be located ( )." This charge was modified to delete patient and to add patients . and The patient, , previously incorrectly identified as female, was correctly identified as a male.

BUREAU PRESENTATION OF CHARGE 4

In support of the charge that the medical records of some subjects of Dr. Gelfand's study could not be found, the Bureau offered the testimony of Dr. Turner and presented government exhibit G-15. Dr. Turner identified five subjects whose medical records could not be located, and he named the hospital locations where he had sought the records. Dr. Turner testified that he had informed Dr. Gelfand that he (Dr. Turner) was unable to locate these records and that Dr. Gelfand had told Dr. Turner that he (Dr. Gelfand) would try to locate some of the records and would notify the FDA investigators when they were located. Dr. Turner said that Dr. Gelfand never contacted him subsequently about the records.

DR. GELFAND'S RESPONSE TO CHARGE 4

In responding to the allegation that some subject's medical records could not be located, Dr. Gelfand's attorney asserted that the Bureau of Drugs had produced no evidence that Dr. Gelfand had refused to produce patient records which were located at the facility. Dr. Gelfand testified that some of the records in question were located in various hospitals throughout the metropolitan area. The hospitals are affilated in the sense that the group of nephrologists to which Dr. Gelfand belongs are on the attending staff. Dr. Gelfand asserted that he had explained this situtation to the FDA investigators. Dr. Gelfand and his attorney then presented specific rebuttal testimony for the following patients:

____: On the day of the hearing, Dr. Gelfand submitted medical records for .. Dr. Gelfand testified that he personally located the records at ' Hospital. Laboratory data in the patient records coincided with copies of records available to the FDA, which had been submitted to the sponsor. (Exhibits R-9 and R-10 were submitted in support of this).

____: Included with a letter of January 31, 1980, from Dr. Gelfand's attorney to the attorney for the Bureau of Drugs, were thirteen pages of patient records for , obtained from the by Dr. Gelfand. Laboratory reports relating to were submitted by Dr. Gelfand on the day of the hearing. These reports coincided with reports submitted to the sponsor. (Exhibit R-11 was submitted in support).

____.: During the time that . was on therapy, he was an outpatient of the On the day of the hearing, Dr. Gelfand submitted a copy of a letter to him from M.D., of indicating that .'s medical records were maintained at the facility. Enclosed with the letter to Dr. Gelfand (and submitted by Dr. Gelfand on the day of the hearing) were electrocardiograms, records of metabolic bone series, chest x-rays, and laboratory chemistries performed with respect to .. (Exhibit R-13 was submitted in support).

____.: On the day of the hearing, Dr. Gelfand produced a letter to him from Dr. which indicated that was a patient at the outpatient facility of the in its outpatient facility. Enclosed with the letter from Dr. (and submitted by Dr. Gelfand on the day of the hearing) were medical records of obtained from that facility. These records included reports of tests performed at the out-patient department of (Exhibit R-14 was offered in support).

___: On the day of the hearing, Dr. Gelfand submitted a letter from the medical librarian at the attesting to the fact that . had been a patient of Dr. Gelfand's at the time Dr. Gelfand reported him to be a patient, and that 's records had been lost, apparently at the time the hospital had them microfilmed. (Exhibit R-12 was the letter from the librarian).

In Dr. Gelfand's direct testimony, he said that he maintained a "black book" with copies of protocol forms for each new patient, followed by copies of each Clinic Visit Form for that patient, laboratory reports, and drug disposition records. At the sponsor's suggestion, a "flow sheet" was added showing the date of each visit and the pulse rate and blood pressure determinations made at the time of the visit.

Under cross examination by Dr. Gelfand's attorney, Dr. Turner acknowledged that Dr. Gelfand had assisted FDA investigators in getting some of the records at and also admitted that Dr. Gelfand was never given a list of patients whose records could not be found.

FINDINGS RELATED TO CHARGE 4

Some subject's medical records could not be located prior to the time of the hearing, and a large amount of new information was presented by Dr. Gelfand at the time of the hearing. However, none of the records produced at the hearing by Dr. Gelfand anteceded the start of FDA's November 1978 inspection.

CONCLUSIONS RELATED TO CHARGE 4

This charge was substantiated as far as material that should have been available prior to the hearing is concerned. Dr. Gelfand brought back-up records that had not been obtained earlier. However, there appears to have been a misunderstanding on the part of the investigators as to the location of some of the records. Also, Dr. Turner testified that Dr. Gelfand had said he would try to locate certain of the records and then notify the investigators. However, Dr. Gelfand never called them.

CHARGE 5: "One subject was reported to have died in 1975 when in fact the recrods indicate that the subject received test substances in 1976 ( )."

BUREAU PRESENTATION OF CHARGE 5

To support the charge that patient . was reported to have died in 1975 when in fact he was still being treated in 1976, the Bureau relied on the testimony of Dr. Turner and the presentation of government exhibits G-7, G-8, and G-9. The Bureau established that died April 10, 1976, but that a Patient History Form and Final Report Form listing the date of death as "11/75" were obtained by the Bureau from the sponsor.

The Bureau contended that Dr. Gelfand did not report .'s death promptly and that the incorrect date of death noted in the sponsor's copy of a Patient History Form probably resulted from an August 11, 1977 conversation between Mr. the sponsor's representative, and Ms. Dr. Gelfand's assistant.

DR. GELFAND'S RESPONSE TO CHARGE 5

In response to the charge that one subject was reported to have died in 1975, when in fact he received in 1976, Dr. Gelfand submitted the original of what the Bureau had presented as Exhibit G-7. Exhibit G-7 had the date of a 2/23/76 examination crossed out. Dr. Gelfand's "original" version did not have the date of the 2/23/76 examination crossed out. Dr. Gelfand also submitted an original of the "Final Report" Form which he had submitted to the sponsor. In this copy, the space for indicating the date when was discontinued is blank. Dr. Gelfand testified that had died at home and that since instructions under the protocol were to report a death immediately, the form was sent to the sponsor without waiting to determine and record the time of death. In addition, Dr. Gelfand submitted a copy of a "Clinical Research Association Contact Report" prepared, according to Dr. Gelfand, by a representative of the sponsor. This report indicates that J.M. died in November 1975. Dr. Gelfand's position was that the 11/25 date was introduced because of an error by the sponsor and did not originate with Dr. Gelfand. (Exhibits R-3, R-4 and R-5 were submitted in support).

FINDINGS RELATED TO CHARGE 5

Evidence presented by the Bureau established that patient was reported to FDA by the sponsor to have died in 1975, when the actual year of death was 1976.

CONCLUSIONS RELATED TO CHARGE 5

This charge was substantiated, but Dr. Gelfand's responsibility for the error was never established.

It appears that had Dr. Gelfand supplied the correct date of death instead of leaving the date blank, the error would probably not have occurred. The only records with an incorrect date of termination, belonged to the sponsor.

CHARGE 6: "Consent forms were dated well after the subjects were entered at the study (." This charge was modified to delete the names of , and

BUREAU PRESENTATION OF CHARGE 6

In support of the charge that consent forms for two patients were dated well after the subjects entered the study, the Bureau presented testimony by Dr. Turner and government exhibits G-13 and G-14. The

Bureau established that entered the study on September 28, 1977, while his consent form was dated January 20, 1978, and that entered the study on November 9, 1977, while her consent form was dated April 5, 1978.

DR. GELFAND'S RESPONSE TO CHARGE 6

The Bureau's assertion that the consent forms were dated well after the subjects were entered into the study was based on the date of the forms relating to and . Dr. Gelfand testified that informed consent had been obtained from these patients by their attending physicians, who were Renal Fellows under Dr. Gelfand's supervision. Exhibits R-20 and R-21 were submitted from the two Renal Fellows indicating in the case of that Dr. had obtained oral informed consent from the patient before she received and in the case of , that Dr. had discussed the side effects of with him prior to treatment with the drug. Dr. Gelfand maintained that this was tantamount to "informed consent."

FINDINGS RELATED TO CHARGE 6

Evidence presented by the Bureau demonstrated that two patient consent forms were signed after the patients entered the study. Written consent forms were signed by two patients after they began receiving Renal Fellows of Dr. Gelfand, provided statements attesting that oral informed consent was obtained from both patients before was administered, even though signed informed consent was obtained months later.

CONCLUSIONS RELATED TO CHARGE 6

This charge was substantiated in the narrow scope in which it was framed.

CHARGE 7: "Blood pressure and pulse rates were not recorded in any regular fashion in the case reports or patient medical histories."

BUREAU PRESENTATION OF CHARGE 7

In support of the charge that blood pressures and pulse rates were not recorded in any regular fashion, the Bureau relied upon the testimony of Dr. Turner, and the submission of government exhibits G-11 and G-12. This was characterized by the bureau's counsel as the presentation of negative evidence, i.e., exhibit G-11, a Clinic Visit Form, requires the taking and recording of blood pressures in

different postures. Exhibit G-12 was a copy of an April 2, 1979 letter from Dr. Gelfand to Dr. Kelsey in which Dr. Gelfand stated "it is impossible for anyone to go back and resurrect the precise moment when blood pressure and pulse determinations were obtained to enter into the case record." Dr. Turner was not able to trace these recorded values for any patients to the medical records from which they should have come.

DR. GELFAND'S RESPONSE TO CHARGE 7

In response to the charge that blood pressure and pulse rates were not recorded in any regular fashion in the case reports or patient medical histories, Dr. Gelfand submitted "flow sheets" for five patients. Those flow sheets were serial records of blood pressure and pulse readings. They were reconciled with "Clinic Visit Forms" for the same five patients. Dr. Gelfand showed that the values recorded on the "Clinic Visit Forms" were the same as those on the flow sheet from the patient's medical records. (Exhibits R-15, R-16, R-17, R-18 and R-19 consisted of flow sheets and "Clinic Visit Forms").

FINDINGS RELATED TO CHARGE 7

Dr. Turner testified that he was unable to find records which contained proper notations. Dr. Gelfand submitted flow sheets and corresponding Clinic Visit Forms for each of five patients. In each case, the data from the flow sheets which were taken from the patients' medical records agreed with the data contained on the Clinic Visit Forms which had been submitted to the sponsor, and which Dr. Gelfand entered in evidence. However, as noted by the Bureau, all five of the records were dated after the inspection began in November 1978, and, therefore, did not refute Dr. Turner's statement that he found no such charts at the time of the inspection in early November 1978.

CONCLUSIONS RELATING TO CHARGE 7

The charge that blood pressure and pulse rates were not recorded in any regular fashion in the case reports or patient medical histories was supported by Dr. Turner's testimony. At the time of the hearing, Dr. Gelfand submitted Flow Sheets and corresponding Clinic Visit Forms for five patients. Since the records submitted in evidence by Dr. Gelfand were all dated after the start of FDA's inspection, he was only able to demonstrate that the systematic recording of blood pressure and pulse rates was practiced since the time of the inspection.

The total evidence offered to refute Charge 7 was insufficient to prove that blood pressure and pulse rates were recorded in a regular fashion prior to the FDA inspection in November 1978.

CHARGE 8: "Drug accountability was inadequately maintained for most subjects."

BUREAU PRESENTATION OF CHARGE 8

The charge that drug accountability was inadequately maintained for most patients was supported with government exhibit G-10 (a Final Report Form for patient .) and by testimony from Dr. Turner that patient had been taken off treatment and later restarted on it, but that reinstitution of therapy had not been adequately noted in the patient's records.

DR. GELFAND'S RESPONSE TO CHARGE 8

Dr. Gelfand testified that patient was taken off because she underwent a nephrectomy, which was expected to relieve her hypertension. When the nephrectomy did not produce the desired result, she was restarted on Dr. Gelfand testified that the study protocol did not have a readmission form per se. He produced a copy of a Clinic Visit Form which he had submitted to the sponsor, stating that the patient was off for one month and then restarted due to readmission in hypertensive crisis (exhibit R-7). Dr. Gelfand also submittted an Intercurrent Medical Events Form which reported that patient . was "unstable" following a unilateral nephrectomy, and was placed on and two other drugs (Exhibit R-8). Exhibit R-6 a "flow sheet" covering 16 clinic visits by . was submitted by Dr. Gelfand, and contained the notations "off 11/24 hold; back on 1/4/78; Nephrectomy 5/26/78."

FINDINGS RELATED TO CHARGE 8

The general charge that drug accountability was inadequately maintained for most subjects, was applied by the Bureau to one patient, . She was discontinued from the study and reentered without an admission or readmission form and procedure being used.

CONCLUSIONS RELATED TO CHARGE 8

The charge that drug accountability was inadequately maintained for most subjects was not substantiated. With respect to the one patient on which the Bureau based its general charge, Dr. Gelfand made no attempt to disguise 's resumption of therapy. He submitted to the sponsor both a Clinic Visit Form stating that patient was restarted on the drug and an Intercurrent Medical Events Form showing why she was restarted on on June 9, 1978. While neither the sponsor's protocol nor the FDA regulations dictate or suggest use of a special "reentry" form whenever treatment with an

investigational drug is discontinued for a time, and later reinstituted, it is reasonable to expect that such a significant occurrence should be highlighted by the investigator through use of an admission form, if no readmission form exists.

DISCUSSION

The Bureau maintained that the evidence presented in support of the preceeding eight charges also established the general charge that Dr. Gelfand failed to fulfill the committment required of him by paragraph 6(c) of Form FD-1572, in that he failed "to prepare and maintain adequate case histories designed to record all observations and other data pertinent to the clinical pharmacology." The Bureau also felt that the principal investigator should keep full patient records centrally at his principle location. I find that the "flow sheets", Clinic Visit Forms, Laboratory Report Forms, and other reports and hospital records now stated to be used routinely by Dr. Gelfand and his associates constitute adequate case histories. However, either a readmission form should be developed or an admission form should be modified. I find nothing in paragraph 6(c) of Form FD-1572 that requires the principle investigator to maintain in a central location, the records of hospitalized patients or patients seen at various outpatient clinics. However, I do find that the investigator is required by Form FD-1572, paragraph 6(e) to make copies of records available for inspection and copying. These should be reasonably available.

Some of the charges introduced by the bureau were disproved during the hearing, by the presentation of information that had not heretofore been provided. If Dr. Gelfand had availed himself of the opportunity for an informal hearing, or if the FDA investigators had asked Dr. Gelfand for assistance in locating specific records and discussed the findings of the inspection with Dr. Gelfand at the conclusion of the inspection, these charges might have been obviated. We note that under the heading "Inspection Procedures" of Part III of the FDA Compliance Program 7348.811A, which was the applicable guidance document in this inspection, the statement appears: that "even though a form FD-483 will not be issued, the discrepancies noted during a directed inspection should be discussed with the clinical investigator at the conclusion of the inspection." Dr. Gelfand testified that no such discussion took place. The Bureau did not contradict Dr. Gelfand, nor offer testimony that the discrepancies, other than those relating to electrocardiograms, were brought to Dr. Gelfand's attention. This is in spite of the fact that Dr. Kelsey's letter of March 30, 1979, states in part: "Several items were brought to your attention at the conclusion of our field investigation." Perhaps, this was due to an assumption on Dr. Kelsey's part based upon the known requirement in the Compliance Program.

Several of the charges and corresponding responses tended to point up a failure to construct the charges in such a way that they relate precisely to the regulations. For example, the charge that consent forms for two patients were dated well after they entered the study is unclear as to the specific violation of the regulations. The Bureau's position is that informed consent as defined in 21 CFR 310.102(h), and as required by paragraph 6.g. of Form FD-1572, was not obtained for two patients, because consent forms were not signed prior to the patients' entry into the study. However, paragraph 6.g. of Form FD-1572 says only that "the investigator certifies that he will inform any patients or any persons used as controls, or their representatives, that drugs are being used for investigational purposes, and will obtain the consent of the subjects, or their representatives, except where this is not feasible or, in the investigator's professional judgement, is contrary to the best interests of the subjects." It does not require that the investigator obtain written consent prior to the administration of an investigational drug. Although paragraph III(F) of the protocol for the study of requires written consent, oral consent is allowed under the FDA regulations, providing certain conditions are met, including the documentation on the patients' chart that informed consent was obtained prior to initiation of the research.

RESOLUTION OF THE CHARGES

Charges 1 and 2, were established.

With respect to charge 3, Dr. Gelfand did submit reports concerning patient which were dated incorrectly. The Bureau did not submit any evidence of incorrect dates other than for patient

With respect to charge 4, Dr. Gelfand provided records which technically refuted the allegation (records were produced at the hearing).

The accuracy of charge 5 was established by the Bureau, although it was not shown that Dr. Gelfand was responsible for the error.

Charge 6 was also true, but not shown to be related to a specific FDA regulation.

Charge 7 was established in that all of the records produced by Dr. Gelfand in response to this charge were dated after the start of FDA's November 1978 inspection. Dr. Gelfand did not produce evidence that he recorded blood pressure values and pulse rates in a regular fashion prior to the time of the inspection.

Charge 8 was not substantiated. There was no requirement in either the protocol or FDA regulations that the readmission of a patient to the study be announced in a distinctive way. Since Dr. Gelfand did provide the sponsor with repeated, albeit routine, notifications that patient was again receiving the charge was not supported, in general or in the specific case cited.

In summary, I find that Dr. Gelfand is guilty of charges 1 and 2 and in a single instance of charge 3. With respect to the remaining charges, either Dr. Gelfand was not guilty as charged, (charge 8) or the charge was substantiated but a specific violation of the relevant FDA regulations was not demonstrated (charges 4, 5, 6, and 7).

ASSURANCES BY DR. GELFAND THAT IN THE FUTURE, THE CONDITIONS OF IND EXEMPTIONS WILL BE MET

21 CFR 312.1(c)(2) states: "After evaluating all available information, including any explanation and assurance 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."

At the hearing, Dr. Gelfand submitted a document titled, "Policy Statement and Operating Procedures For All Personnel" (Tab D). This statement, according to Dr. Gelfand, constitutes the new written policy of the and each of its physicians, with respect to the conduct of clinical investigations on new drug products. The procedure draws the attention of each investigator to the details of FDA regulations, and obligates the investigator to review each record for accuracy. Complete drug accountability is mandated; records are to be maintained in a central location, and oversight by the Medical Director is to be provided.

If the policy statement is followed exactly, this 15 point program should greatly facilitate compliance with FDA regulations. The statement was signed by Dr. Gelfand and the other two Co-directors of the Center. At no time did Dr. Gelfand question the necessity of the requirements in CFR 21 312.1, nor did he question the significance or utility of FDA's IND regulations. In fact, in his 4/2/79 letter to Dr. Kelsey, Dr. Gelfand stated "I reemphasize to you that there were no deliberate attempts to mislead and we feel very strongly about the importance of careful evaluation of investigational drugs."

Dr. Gelfand changed his procedures immediately after the inspection in order to remedy deficiencies that became evident during the inspection. Dr. Gelfand testified to having taken corrective action when he learned of Ms. practice of submitting duplicate EKGs. Such actions

lend further creditibility to Dr. Gelfand's assurances, that in the future, he will meet the requirements of FDA's IND regulations.

I believe that strict adherence to the above procedures and the good faith efforts of Dr. Gelfand and the other physicians, should be adequate to assure that "the conditions of the exemption will be met" in any future clinical investigations conducted by Dr. Gelfand and other members of the Center.

CONCLUSIONS REGARDING DR. GELFAND'S ELIGIBILITY TO RECEIVE INVESTIGATIONAL DRUGS.

I conclude that Dr. Gelfand repeatedly submitted what is technically false information with regard to EKGs and he did err in the dating of the submitted data relating to patient .. I do not believe that Dr. Gelfand deliberately submitted false information to the sponsor of an investigation. Dr. Gelfand did, however, furnish what I consider to be adequate assurance that the conditions of the Forms FD-1572 and FD-1573 will be met in any future investigational drug studies undertaken at the Therefore, I conclude that Dr. Gelfand should remain eligible to receive investigational drugs.

RECOMMENDATION

I recommend that the Commissioner sign the attached letter to Dr. Gelfand informing him of his continuing eligibility to receive investigational drugs contingent on the implementation of and continued adherence to the assurances which he presented.

Stuart L. Nightingale

Stuart L. Nightingale, M.D.

Attachments

APPENDIX

CHRONOLOGY

In January 1977 Dr. Gelfand submitted a signed Form FD-1572 naming himself as a principal investigator under IND-4528 to participate in a study of the clinical pharmacology of the drug, The sponsor of the study was Three other physicians were identified on the form as co-investigators, responsible to Dr. Gelfand. Prior to this time, Dr. Gelfand had been a co-investigator in the study of the drug, responsible to Drs. and of the Dept. of Physiology at Medical School.

In November and December of 1978 FDA conducted an audit (inspection) under the Bioresearch Monitoring program of the data being generated by Dr. Gelfand's clinical investigation. At the conclusion of the audit the Bureau of Drugs, Division of Scientific Investigations (DSI) concluded that Dr. Gelfand had repeatedly failed to comply with the conditions of the regulations relating to the investigational use of new drugs as set forth in the Form FD-1572. Consequently, on March 30, 1979, Dr. Frances Kelsey of the Bureau of Drugs wrote to Dr. Gelfand and offered him an opportunity to attend an informal conference in Dr. Kelsey's office to discuss the alleged violations of FDA regulations. Dr. Kelsey enumerated eight specific deficiencies in Dr. Gelfand's performance as a clinical investigator (See Tab A). Dr. Gelfand was given the option of responding to Dr. Kelsey in writing, if he did not wish to attend an informal conference.

On April 2, 1979, Dr. Gelfand responded in writing to Dr. Kelsey's letter of March 30, 1979, and presented an explanation of the alleged deficiencies noted in Dr. Kelsey's letter. He closed by saying that "if you still feel that an informal meeting will be of help, please let me know." (See Tab B).

The Division of Scientific Investigations concluded that Dr. Gelfand's letter of April 2, 1979, did not refute the accusations contained in Dr. Kelsey's letter of March 30, 1979. Consequently, on August 9, 1979, the Associate Commissioner for Compliance issued a notice to Dr. Gelfand providing him with an opportunity for a regulatory hearing under 21 CFR 16.24 and 312.1(c)(1).

Dr. Gelfand was told that the matters to be considered at the hearing were those set forth in Dr. Kelsey's letter of March 30, 1979. Dr. Gelfand was given 3 "working days" from the time of receipt of the letter to request a hearing.

On August 15, 1979, Dr. Gelfand replied to the Associate Commissioner for Compliance, stating in part:

"I am disappointed and dismayed that you find my responses of April 2, 1979, to your questions 'unresponsive and unacceptable.' I am further very concerned that your letter of August 9, 1979, fails to point out why the responses were unacceptable. Surely, some explanation of your review would be in order. I have decided to avail myself of a hearing. However, before I make a final decision, I request full and complete copies of all records, memos, memorandums, files, correspondences related to your decision that you 'have reason to believe that' I violated any Federal law or regulations."

On September 18, 1979, the Associate Commissioner for Health Affairs, who had been designated to serve as Presiding Officer at the hearing, wrote to Dr. Gelfand acknowledging receipt of Dr. Gelfand's request for a regulatory hearing, and setting a tentative date of October 18, 1979.

On September 25, 1979, FDA's Associate Commissioner for Public Affairs wrote to Dr. Gelfand and informed him that documents to be presented at Dr. Gelfand's hearing would be provided to him by the attorney serving as Council to the Bureau of Drugs. This practice is dictated by 21 CFR 16.24.

Also on September 25, 1979, a letter was sent from the Bureau of Drugs Counsel to Dr. Gelfand. This letter amplified the charges stated in Dr. Kelsey's letter of March 30, 1979, and introduced one additional charge (see Tab C). The letter notified Dr. Gelfand that approximately two weeks before the hearing he would receive copies of documents which the Bureau of Drugs would rely upon during the hearing.

On October 2, 1979, the Counsel to the Bureau of Drugs provided Dr. Gelfand with copies of 19 documents which the Bureau intended to use during the impending hearing to support its position that Dr. Gelfand should be disqualified as a physician eligible to receive investigational drugs.

The hearing originally set for October 18 was postponed and rescheduled for December 19, 1979. However, on November 16, 1979, Dr. Gelfand's attorney petitioned the designated Presiding Officer to effect an informal conference between representatives of the Bureau of Drugs, and Dr. Gelfand and his attorney. The request was based upon the fact that Dr. Gelfand did not have the benefit of legal counsel at the time of his correspondence with Dr. Kelsey. While this matter was pending, Dr. Gelfand's attorney asked for and received a postponment of the hearing until January 22, 1980.

On January 15, 1980, the Acting Associate Commissioner for Health Affairs, who recently had been designated as Presiding Officer, wrote to the counsel for the Bureau of Drugs urging that efforts be continued towards reaching an acceptable settlement between Dr. Gelfand and the Bureau thereby eliminating the need for a regulatory hearing. It was felt that since no informal conference between Dr. Gelfand and Bureau officials had taken place, an opportunity to resolve the dispute might have been missed. The Acting Associate Commissioner also noted that Dr. Gelfand had requested, in his August 15, 1979 letter (see Tab D) but had not been given, an explanation why his April 2, 1979, reply to Dr. Kelsey's letter of March 30, 1979, was ajudged unresponsive and unacceptable. The counsel for the Bureau of Drugs was instructed to provide the desired explanation to Dr. Gelfand and his attorney by January 30, 1980. The date on which a hearing would take place, if necessary, was postponed until sometime after February 15, 1980.

On January 28, 1980, Dr. Gelfand's attorney wrote to the counsel for the Bureau of Drugs and proffered a settlement intended to dispose of the Bureau's allegations against Dr. Gelfand without a regulatory hearing. The essence of the proposed settlement was an acknowledgement by Dr. Gelfand of certain inaccuracies in the data he submitted to the sponsor of the clinical investigation, a promise of more individual attention on his part to the details of record keeping, and a willingness to refrain from participating in an investigational drug study for a period of one year (See Tab E).

On January 30, 1980, in response to the instruction contained in the January 15, 1980, letter from the Acting Associate Commissioner for Health Affairs, the Counsel to the Bureau of Drugs provided Dr. Gelfand and his attorney with an explanation of why Dr. Gelfand's response to Dr. Kelsey's letter was found "unresponsive and unacceptable" (See Tab F).

On January 31, 1980, Dr. Gelfand's attorney wrote to the counsel for the Bureau of Drugs and enclosed a series of documents which he said were relevant patient records that had not been obtained by FDA investigators during the inspection. This communication was an outgrowth of a meeting that had taken place between bureau officials and Dr. Gelfand's attorney on January 18, 1980. On February 7, 1980, Dr. Gelfand's attorney again wrote to the counsel for the Bureau of Drugs stating that certain patient records were delivered to the bureau's counsel the previous day and enclosing additional records.

On February 11, 1980, the counsel for the Bureau of Drugs wrote to Dr. Gelfand's attorney informing him that the bureau had rejected the settlement proposed in his letter of January 28, 1980. The Counsel for the bureau noted that the bureau had given full consideration to the proposal and to her own recommendation to the Bureau before rejecting the proffered settlement. She stated further that she was notifying the Presiding Officer that the parties were at an impass and was requesting that he establish a date for the regulatory hearing sometime after March 1, 1980.

On February 14, 1980, the attorney for Dr. Gelfand wrote to the counsel for the Bureau of Drugs requesting a meeting at which he and Dr. Gelfand could discuss with the Deputy Associate Director for New Drug Evaluation and the Director of the Division of Scientific Investigations, the Bureau's reasons for refusing the proffered settlement of January 28, 1980, and could further explore the possibility of settlement without a hearing. Dr. Gelfand's attorney invited participation by other members of Division of Scientific Investigations. The meeting was not granted.

Also on February 14, 1980, Dr. Gelfand's attorney requested a copy of the written recommendation of the counsel for the Bureau of Drugs to the bureau regarding Dr. Gelfand's proposal to settle without a hearing. On March 13, 1980, the Associate Commissioner for Public Affairs wrote to Dr. Gelfand's attorney denying this request. The request was denied on the grounds that the recommendation was an intra-agency memorandum containing opinions, recommendations, and policy discussions and also fell within attorney-client priviledged communication and, therefore, was exempt from disclosure under the Freedom of Information Act.

On March 17, 1980, Dr. Gelfand's attorney wrote to counsel for the Bureau of Drugs and requested "a more particularized statement of the charges against him (Dr. Gelfand) to be presented at the disqualification hearing..." On March 31, 1980, counsel for the Bureau of Drugs responded to this request. (See Tab G).

Scheduling difficulties required that the hearing date be set for April 9, 1980. The hearing began on the morning of April 9 and was concluded on the evening of April 10, 1980.

Subsequent to the hearing, counsel for Dr. Gelfand and the Bureau of Drugs submitted post-hearing briefs, including proposed findings of fact and conclusions of law. (See Tab H).