Rm 11-37 Dated 9/11/81

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

file - OHA - Disqualifier

In the matter of:

MICHAEL C. GELFAND, M.D.
Regulatory Hearing

COMMISSIONER'S DECISION

The purpose of this proceeding is to determine whether clinical investigator Michael C. Gelfand, M.D., should be disqualified from receiving investigational new drugs. Pursuant to 21 CFR § 312.1(c)(1) and 21 CFR Part 16, Associate Commissioner for Health Affairs Stuart Nightingale, M.D., presided over a regulatory hearing for Dr. Gelfand in April 1980. His recommendation is that Dr. Gelfand not be disqualfied.

I conclude that Dr. Gelfand repeatedly failed to comply with regulations governing the exemption of new drugs for investigational use. I also conclude, however, that Dr. Gelfand has provided adequate assurance that the conditions for exemption will be met in the future. Therefore, Dr. Gelfand is not disqualified from receiving investigational new drugs. My decision is based upon a careful review of the hearing transcript (hereafter cited as Transcript), the Presiding Officer's Report (hereafter cited as Report), the parties' comments on that Report (hereafter cited as Comments), the parties' pre- and post-hearing statements, the exhibits submitted by the parties, and all other relevant

portions of the administrative record. As required by 21 CFR § 16.95(b)(1), my decision is based only on the administrative record in this matter. The reasons for my decision follow.

I. BACKGROUND

In January 1977, Dr. Gelfand became a principal investigator for a phase II clinical pharmacology study of the investigational new drug . is a powerful drug for the treatment of

A phase II study involves initial trials on a limited number of patients. As required by Part 312 of the regulations, 21 CFR 312.1(a)(12), Dr. Gelfand submitted a Form FD-1572 to the drug's sponsor. That form provides information about the investigator and investigation and states that the investigator understands his specific responsibilities, as outlined in the form.

In November and December 1978, the Food and Drug Administration (FDA) audited the data being generated by Dr. Gelfand's clinical investigation as part of its Bio-research Monitoring Program. At the conclusion of that audit, the Bureau of Drugs (Bureau), FDA, concluded that Dr. Gelfand had repeatedly failed to comply with the regulations relating to

the investigational use of new drugs. Consequently, on March 30, 1979, Frances Kelsey, Ph.D., M.D., Director of the Division of Scientific Investigations, Bureau of Drugs, wrote to Dr. Gelfand and offered him an opportunity to attend an informal conference to discuss the alleged violations of FDA regulations. Dr. Kelsey's letter listed eight (8) specific alleged deficiencies with Dr. Gelfand's performance as a clincal investigator. The letter further stated that Dr. Gelfand had the option of responding 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 and presented an explanation of the alleged deficiencies. The Bureau concluded that Dr. Gelfand's letter did not satisfactorily respond to the allegations of Dr. Kelsey's letter. 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. Nightingale presided over the regulatory hearing on April 9-10, 1980. He issued his Report on December 4, 1980. In brief, he finds that Dr. Gelfand has repeatedly violated FDA regulations, but that Dr. Gelfand has provided adequate assurance that in the future he will comply with the

regulations. Consequently, Dr. Nightingale recommends that Dr. Gelfand not be disqualified.

Both Dr. Gelfand and the Bureau submitted comments on the Report. On February 25, 1981, after considering those comments, the Presiding Officer decided not to revise the Report and forwarded the matter to me for decision.

II. DECISION

I turn now to the merits of this proceeding. In order to conclude that a clinical investigator is no longer eligible to receive investigational new drugs, I must first determine that the investigator has repeatedly or deliberately violated FDA regulations, or has deliberately submitted false information to the sponsor. Second, I must conclude that the clinical investigator has failed to furnish adequate assurance that the conditions of exemption will be met in the future. 21 CFR § 312.1(c)(2). These issues are addressed separately below.

A. Violation of FDA Regulations

The Bureau made eight specific charges against Dr. Gelfand at the hearing. The charges were first set forth in

Dr. Kelsey's letter dated March 30, 1979, and were subsequently modified with respect to the names of specific patients whose records were used to substantiate the charges. In my discussion of the charges below, they are set out in the language used by Dr. Kelsey.

The Presiding Officer concludes that Dr. Gelfand is guilty in whole or in part of three charges and not guilty of one charge. He further concludes that while the remaining four charges are "substantiated," Dr. Gelfand is not guilty of these charges because the Bureau failed to establish specific violations of FDA regulations. Report at page 16. As discussed below, I accept some but not all of the Presiding Officer's findings and conclusions.

CHARGES 1 & 2: 1) "Dates for some EKGs (electrocardiograms) in the case reports differ from dates on EKGs found in medical histories."

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

The Bureau introduced evidence to substantiate the charges and presented the testimony of Robert Temple, M.D.,

concerning the significance of EKGs in the study of

Dr. Gelfand did not dispute the Bureau's evidence. His response was that he had given the responsibility for performing and submitting EKGs to his nurse, Dr. Gelfand testified that as soon as FDA investigators informed him of the discrepancies, he discussed the problem with Ms. who told him that she had misunderstood the study protocol instructions. He further testified that he had taken steps to assure the problem would not occur again.

The Presiding Officer finds Dr. Gelfand guilty as charged. Without so stating, he apparently accepts Dr. Gelfand's explanation for the cause of the discrepancies. The Presiding Officer states that there is no evidence of a deliberate violation.

I agree with the Presiding Officer's resolution of these charges.

The Bureau in its Comments expresses concern that the Report suggests that a showing of deliberateness is a necessary requirement for disqualification when repeated violations are shown. I do not read the Report as in any way

suggesting that deliberateness is a necessary requirement for disqualification. I agree with the Bureau that either deliberate or repeated violations can lead to disqualification.

CHARGE 3: "Clinical laboratory tests could not be confirmed as actually having been performed on any subject at the time reported."

In support of this charge the Bureau presented the records of one patient, for whom the dates of laboratory test results submitted to differed from test dates in his patient records. Dr. Gelfand's testimony attributed the discrepancy to a combination of clerical error by his nurse and her misunderstanding of the protocol. On this basis, the Presiding Officer finds Dr. Gelfand "guilty of a single instance" of charge 3. Report at page 16.

I do not agree with the Presiding Officer's implicit finding that Dr. Gelfand was not guilty of the charge as stated. Dr. Gurston Turner, one of the Bureau's investigators, testified that Dr. Gelfand did not make records available for five patients, and that the patient records for the remaining nine patients did not contain sufficient data to verify the submissions. Transcript, Vol. I, pages 121-23. Therefore, the Bureau

could not confirm clinical test data for any of the patients. Accordingly, I find that Dr. Gelfand is guilty of charge 4 as stated.

The Bureau's only criticism in its Comments is with the Presiding Officer's finding that the violations were not deliberate. For the same reason given under charges 1 and 2, I find the Bureau's criticism to be without merit.

CHARGE 4: "Some subjects' medical records could not be located."

For four of the five patients who were the focus of this charge, Dr. Gelfand produced some records at the hearing which had not previously been made available to FDA. None of these records predated the inspection.

The Presiding Officer finds Dr. Gelfand not guilty because no "specific violation" was demonstrated. He further finds that Dr. Gelfand "technically refuted" the charge by producing records at the hearing, even though the charge is "substantiated" because records should have been made available earlier. Report at pages 9, 15, 16.

I do not accept the Presiding Officer's resolution of this charge and find Dr. Gelfand guilty. I agree with the Bureau that the Report is internally inconsistent and that the Presiding Officer applies an unduly restrictive reading of the regulations.

Form FD-1572, ¶ 6.e, requires that case histories be made available for inspection and copying. A clinical investigator has the duty to take reasonable affirmative steps at the time of inspection, or shortly thereafter, to make case histories available. Nothing requires a clinical investigator to maintain all case histories in a single location, but an investigator should take reasonable steps such as providing a list of patients and the locations of their case histories, acting as a liaison between FDA inspectors and co-investigators or health care facilties, or physically procuring the records for FDA inspectors.

The Presiding Officer notes that there was a lack of communications and some misunderstanding between FDA inspectors and Dr. Gelfand. For example, despite his promise to do so, Dr. Gelfand did not try to locate some records and then call Dr. Turner. Dr. Turner never provided Dr. Gelfand with a list of patients whose records were missing.

Viewing the evidence concerning communications problems most favorably to Dr. Gelfand, I find that he failed to take reasonable steps to make patient records available. Only under the pressure of a regulatory hearing did he produce portions of case histories 17 months after the inspection. Moreover, he never produced records that predated the inspection. Such conduct effectively thwarts FDA's Bio-Research Monitoring Program and ability to ensure that investigational new drug trials are conducted in accordance with the regulations.

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

The Bureau presented evidence to show that the error arose because Dr. Gelfand did not promptly report the patient's death and that at a much later time his assistant telephoned the wrong death date to The error, according to the Bureau, constitutes the submission of false information to the sponsor in violation of 21 CFR § 312.1(c).

The Presiding Officer finds that while this charge is factually substantiated, it was not shown to be a "specific violation of the relevant FDA regulations." Report at page

16. He finds in addition that it was not shown that Dr. Gelfand was personally responsible for the error.

I agree with the Presiding Officer that the charge is factually substantiated. For the reason stated below, however, I decline to consider this charge in determining whether Dr. Gelfand repeatedly violated the regulations. The Bureau points out that, as the principal investigator, Dr. Gelfand is ultimately responsible for the proper conduct of the study and for errors made by his assistants. It goes without saying that, as an abstract proposition, the Bureau's position is correct. Applying that proposition to the specifics of charge 5, however, I conclude that little would be gained by basing a decision whether to disqualify Dr. Gelfand on this charge. Nothing indicates, and the Bureau does not so contend, that this error affected either the validity of the data or the safety of the patients. Moreover, there is no pattern of repeated errors of this type.

<u>CHARGE 6:</u> "Consent forms were dated well after the subjects were entered at the study (H.R., B.T.)."

The Bureau introduced evidence that Dr. Gelfand had obtained signed consent forms for two patients approximately

four months after each had entered the study. Dr. Gelfand testified that the attending physicians had obtained oral informed consent from one patient and had discussed side effects with the other before either had received Dr. Gelfand further testified that the latter discussion was tantamount to informed consent.

The Presiding Officer states that the charge is "substantiated in the narrow scope in which it was framed" but was not shown to be a specific violation of FDA regulations. He notes that while Form FD-1572, ¶ 6.g, only requires "consent," 21 CFR § 310.102(h) does specifically require written consent. He apparently concludes that the § 310.102(h) written consent requirement is not controlling because it is not mentioned in Form FD-1572.

I conclude that such a restrictive reading of the regulations is not warranted, because Form FD-1572 in no way purports to be a complete recitation of applicable regulations. On the other hand, there is a possibility for confusion based on the Form FD-1572 reference to consent but not to written consent. Accordingly, I conclude that while Dr. Gelfand did violate the regulations by failing to obtain prior written consent, his culpability for the violation is minimal.

In its Comments, the Bureau asks me to reject expressly Dr. Gelfand's contention that a discussion about side effects satisfies the informed consent requirement. I agree with the Bureau. Consent as defined in § 310.102(h) can only be given after a patient has received much more information, i.e., expected duration of drug use, its purpose, method and means of administration, hazards and benefits involved, and alternatives, and must be in writing.

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

Dr. Turner, one of the FDA investigators, testified for the Bureau that he could not corroborate in the case reports or patient medical histories any of the blood pressures and pulse rates that were reported to Dr. Gelfand responded only by introducing records for five patients that contained underlying corroborative data. These records were all dated after the inspection.

The Presiding Officer states that Charge 7 is factually substantiated with respect to Dr. Gelfand's practice before and at the time of inspection. He further states, however,

that Dr. Gelfand is not guilty because no specific requirement requires the systematic recording of blood pressures and pulse rates.

Form FD-1572, ¶ 6.c, requires the maintenance of "adequate and accurate case histories designed to record all observations." The language is clear: investigators must record all observations in the case histories. Consequently, I reject the Presiding Officer's disposition of this charge and conclude that Dr. Gelfand is guilty as charged.

This shortcoming in Dr. Gelfand's recordkeeping is a most serious one, as the significance of accurate and regular blood pressure and pulse rate measurements cannot be underestimated for this particular study. is a powerful drug for the treatment

Its side effects include a potentially dangerous increase in the pulse rate. Therefore, the failure of case histories to contain blood pressure and pulse measurements goes to the very essence of the study's conduct. The complete lack of corroborative data gives rise to a possible inference that the measurements were not actually taken. At the very least verification of the data for a lack of clerical transcription errors is not possible.

In either case both the safety of study subjects and the integrity of the data are compromised.

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

The Bureau attempted to establish this general charge ("for most subjects") by introducing evidence for only one patient, who was discontinued from the study and subsequently reentered without the use of any particular documentation.

The Presiding Officer concludes the charge is not substantiated. He recommends that while the use of a special "reentry" form is not required by either FDA regulations or the study protocol, the reentry of a patient after a significant lapse should be highlighted somehow.

I agree with the Presiding Officer's conclusion and recommendation.

B. Necessity of Disqualification

I have concluded that Dr. Gelfand repeatedly violated the regulations. My next inquiry is whether his non-compliance with the regulations is so significant as to require disqualification in the absence of an adequate

assurance of future compliance.*/ I conclude that, absent adequate assurance, Dr. Gelfand should be disqualified.

My decision is based on three factors:

a) whether Dr. Gelfand's non-compliance adversely affected the validity of the data, or the safety or rights of subjects;

b) the nature, scope, and extent of Dr. Gelfand's violations;

c) whether a lesser sanction would be adequate.

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*/ The Presiding Officer did not address this issue separately and the regulations do not require it. Former Commissioner Goyan addressed this issue separately in considering whether to disqualify clinical investigator Nathan Kline, M.D., and I will do likewise here.

I do not wish to suggest that I regard any violations of applicable regulations as acceptable. FDA's regulations, like a well-designed protocol, are designed to protect not only the subjects of the investigation but also the validity of the data generated. Those data may form the basis for important, even life-and-death, decision-making. Thus, any deviation from the applicable regulations is a serious matter. Not all such deviations, on the other hand, warrant disqualification.

I concluded above that Dr. Gelfand's violations compromised both the integrity of the data and the safety of the subjects. Although Dr. Gelfand did not deliberately violate the regulations, the violations were widespread and ongoing. Some of them, such as the failure to keep adequate patient records containing crucial blood pressure and pulse rate data, are inexcusable. In view of these considerations, a lesser sanction is not adequate; disqualification is necessary absent a showing of adequate assurance.

C. Adequate Assurance Concerning Future Violations

Dr. Gelfand submitted a new written policy statement of procedures to be followed by members of his group practice with respect to investigational new drug clinical studies. Further, he testified about action he had undertaken to correct his recordkeeping deficiencies after the FDA inspection.

The Presiding Officer concludes that strict compliance with the policy statement should prevent future violations and that Dr. Gelfand will make good faith efforts to ensure compliance. He states that Dr. Gelfand's testimony concerning corrective action was credible.

I agree with the Presiding Officer. Dr. Gelfand's policy statement and his credible testimony concerning his

commitment to implement the policies set out in that statement, combined with corrective action taken after the inspection, provide adequate assurance that future violations of the regulations will not occur.

The Bureau correctly points out that the clinical investigator carries the burden of establishing that his assurance is adequate. The Bureau goes on to assert that Dr. Gelfand did not sustain his burden because his assurance is made in the abstract and not in the context of a specific investigation. (FDA approved NDA in 1979; Dr. Gelfand is not currently involved in any clinical investigations.) I need not reach any general conclusion concerning the conditions in which an assurance made in the abstract is adequate. It is sufficient that, for the reasons discussed above, Dr. Gelfand's assurance in this case is adequate. Should Dr. Gelfand decide to conduct additional clinical investigations in the future, the Bureau will have an opportunity to assess his performance as an investigator at that time.

D. Vagueness of FDA Regulations

Dr. Gelfand moved to dismiss the charges against him on the grounds that the applicable regulations are too vague. In support of his motion, he relied on the preamble of the proposed revised regulations concerning the obligations of

clinical investigators, which appeared in the Federal Register of August 8, 1978 (43 F.R. 35210). The preamble states in part that "the way [the current regulations] arestated may have contributed to misunderstandings concerning the conduct FDA expects of clinical investigators." 43 F.R. at 35210.

The Presiding Officer orally denied Dr. Gelfand's motion to dismiss.

I agree with the Presiding Officer. While there is room for improvement in the current regulations, most of the violations with which Dr. Gelfand is charged are not in the "gray area"; they are covered by the regulations' express terms. The only exception is Charge 6, concerning written consent. There, I stated that I regard Dr. Gelfand's culpability for the violation as minimal in view of the possibility for confusion caused by the difference in language between Form FD-1572 and 21 CFR § 310.102.

III. CONCLUSION

Dr. Gelfand repeatedly violated FDA regulations by virtue of his serious recordkeeping deficiencies in connection with the clinical study of the investigational new drug Although the violations are sufficiently serious so as to require disqualification absent adequate

assurance that future violations will not occur, Dr. Gelfand has provided adequate assurance that these violations will not occur again. Therefore, I conclude that Dr. Gelfand remains eligible to receive investigational new drugs.

Arthur Hull Hayes, Jr., M.D.
Commissioner of Food & Drugs

Dated: