IN THE MATTER OF:

MARTIN S. HOK, M.D.
Regulatory Hearing

This regulatory hearing was held on December 9 and 10, 1981, pursuant to 21 CFR 312.1(c)(1) and 21 CFR Part 16, to determine whether Martin S. Nok, 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. His recommendation is that Dr. Kok not be disqualified.

I have carefully reviewed the transcript of the hearing, the Report of the Presiding Officer, the comments of the parties on that report, the pre- and post-hearing statements submitted by the parties, the exhibits submitted by the parties, the assurances of Dr. Kok, and all other portions of the record of this hearing. Based on my review I conclude that Dr. Mok repeatedly failed to comply with regulations governing the conditions for exemption of new drugs for investigational use. I also conclude, however, that Dr. Mok has provided adequate assurance that the conditions for exemption will be met in the future. Therefore, Dr. Mok is

not disqualified from receiving investigational new drugs. The reasons for my decision follow.

I. Procedural Background

In 1976 and 1977 Dr. Mok conducted a study involving the drug for ( ), and a study involving the drug for ( ). [I-14] In March of 1979, and later in August of that year, the Food and Drug Administration (FDA) audited the data being generated by Dr. Mok's clinical investigations as part of FDA's Bioresearch Monitoring Program [I-21]. At the conclusion of those inspections, the National Center for Drugs and Biologics (Center)1/, FDA, concluded that Dr. Mok had (1) submitted false information to sponsors in violation of 21 CFR 312.1(c)(2); (2) failed to prepare and maintain adequate case histories in violation of 21 CFR 312.1(a)(12)(6)(c); and, (3) with respect to the study only, failed to maintain adequate records of drug accountability in violation of 21 CFR 312.1(a)(12)(6)(b). Consequently, on February 27, 1980, Francis Kelsey, Ph.D., M.D., Director of the Division of Scientific Investigations, wrote to Dr. Mok and offered him an opportunity to attend an informal conference to discuss

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1/ At the times of the inspections and hearing, the Bureau of Drugs was the complaining party. That Bureau is now the Office of Drugs in the Center.

the alleged violations of FDA regulations. On July 7, 1980, the informal conference was held at the Division of Scientific Investigations. Dr. Mok and his legal counsel attended. Dr. Mok supplemented his explanations after the hearing.

By letter dated July 21, 1981, the Associate Commissioner for Compliance issued a notice to Dr. Mok providing him with an opportunity for a regulatory hearing under 21 CFR 16.24 and 312.1(c)(1).

The hearing was held December 9 and 10, 1981, Dr. Nightingale presiding. He issued his proposed report on April 30, 1982. After consideration of comments from the parties and having decided not to revise the report, he submitted his report and recommendations to me on September 27, 1982.

II. Decision

I turn now to the merits of this proceeding. As stated in the Commissioner's decision dated September 11, 1981, 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 had 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). I will separately address these elements for each of the two studies with which Dr. Mok was involved.

A. The Study.

1. Alterations in Case Report Forms

As the presiding officer's report points out [p 3], "there is no factual dispute as to what happened" in this respect. Essentially, with Dr. Mok's knowledge and agreement, the study nurse, , altered case reports forms for 22 study subjects prior to their submission to the sponsor. The alteration was done, ostensibly, in an effort to make the pain scores on two separate forms for the 22 patients internally consistent. That is, there was not the desired degree of consistency between the form for absolute pain ("severe," "moderate," etc.) as compared to the comparative reponse form ("I am better"). The changed report forms were submitted, through the contract monitor , to without any indication on the forms or in the transmission that any of the submitted case reports had been altered by Dr. Mok's group. Dr. Mok kept the original forms.

I agree with the presiding officer's rejection of Dr. Mok's defense that was an agent of the sponsor, , as well as his finding that, instead,

was a contract monitor. I also agree with the presiding officer's holding that this was the submission of false information within the meaning of 21 CFR 312.1 regardless of the knowledge which or may have had. I agree that that submission was a deliberate violation within the meaning of 21 CFR 312.1(c)(1).

I disagree with the presiding officer, however, that somehow the fact that this deliberate violation was urged upon Dr. Mok by representatives of the contract monitor exculpates or mitigates the seriousness of the violation with respect to Dr. Mok. In this connection, I must reject Dr. Mok's request that I make a finding that there "was no evidence that Dr. Mok intended to violate FDA's regulations or intended to deceive the sponsor in any respect." [Mok Post report comments, page 2; "Mok comments."] It strains credulity to argue as Dr. Mok does [Mok comments, page 3] that but for his "honesty" in keeping the original forms, after his alleged objection to the changing of the forms and subsequent act of willingly and voluntarily turning those forms over to the FDA, there would have been no violation because none would have been the wiser. That action does not establish "honesty" but that he was aware that what he was doing was in some way not the way things should be done.

I cannot find that Dr. Mok did not intend to submit false data to the sponsor within the meaning of FDA's regulations when there is nothing in the record to establish that the submission that he made to noted the fact that the forms had been changed.

2. Reporting of Degree of Injury and Level of Pain.

(a) Degree of Injury

The Center alleged, and the presiding officer found, that with respect to five patients Dr. Mok failed to keep adequate and accurate case histories in that the diagnoses presented thereon were incorrect. In doing so, the presiding officer states [report page 7] that "Dr. Mok does not contest the fact that the description of a fracture (as opposed to something less severe) in those five instances was erroneous." However, the Mok comments do dispute these charges in a number of instances.

I find that Dr. Mok presented no evidence or records respecting patients 1201 and 1265. So, in that respect Dr. Mok does not dispute the charges and I find that Dr. Mok failed to keep adequate and accurate case histories and that the diagnoses presented with respect to those two patients were incorrect, and for the same reason, that he submitted false and misleading data to the sponsor.

The records relating to the remaining three patients in this category are not as clear. I find that Dr. Mok

presented some information at the hearing (as opposed to the previous times of the inspections and the prehearing conferences with the Center) which lends credence to the conclusion that the diagnoses of fracture with respect to patients 1212 and 1231 were at least sufficiently close to the actual fact that I cannot find a deliberate violation of the regulations.

With respect to patient 1210, I am unable to discern from the records kept by Dr. Mok's group whether or not the diagnosis of fracture was correct or incorrect. This fact alone results in a technical violation of the regulations inasmuch as the records are in such poor shape that no one can discern whether or not the records submitted in conjunction with the clinical investigation are adequate and accurate or not.

(b) Level of Pain

With respect to the allegations concerning the inappropriateness of the reporting of levels of pain or discomfort experienced by four patients, I find that the presiding officer's report accurately and adequately deals with the evidence on this point. Accordingly, for the reasons set forth at page 6 through 9 of that report, I find that the Center has not satisfied its burden of proof with respect to those patients.

Further, I must decline to make the specific findings urged by the Center that Dr. Mok engaged in a pattern of over-estimating the pain or exaggerated the injury to the patients in this study [Center post comments, page 8; "Center comments"]. I do so in this case because, as pointed out above, I find that the Center did not sustain its burden of proof with respect to the patients whose degree of pain was alleged to have been reported inaccurately and, further, because I find that the Center's evidence was insufficient in some cases with respect to the alleged inaccuracies regarding the type of injury the patient suffered.

3. Concomitant Medication.

At issue here is whether concomitant medications should have been noted with respect to three patients. As the presiding officer's report points out, there has been, and indeed continues to be, some dispute between the parties as to what the phrase "concomitant medicine" means. Among the patient exclusions set forth in the study protocol [Ex. G-5, page 2] were:

* * *

> ... 8. patients taking concomitant interfering or potentially interacting medications such as other analgesics, physcoactive medications, or anticoagulants.

9. Patients having taken interfering or interacting medication, i.e., other analgesics or anticoagulents within 6 hours of entry into the study, any physcoactive medication, until effects have dissipated.

The protocol also goes on to specify under the heading of "Concomitant Medication" [Ex. G-5, pages 2-3], that: "[n]o other 'analgesics', 'skeletal-muscle relaxants', or interfering or interacting medications, physiotherapy, or ajunctive measures will be permitted during any portion of the study. Notation of any other concomitant medication for pre-existing ailments shall be made in the appropriate section of the case report form."

In this connection, I agree with the presiding officer that "by proving that the hospital records show concomitant medication with respect to the patients involved, the Center has, at the very least, demonstrated a conflict between the case report form and the hospital records which would have called into question any analysis of the results of the study." [Report page 12]. The significance of this is that, while the protocol suggests that patients should be excluded from the study entirely if they are taking concominant medication within the meaning of the protocol, there is the further protocol requirement that any other concominant

medication is to be noted in the appropriate section of the case report form. This was not done.

I cannot agree with Dr. Mok's contention [Mok comments, page 5, footnote 4] that because there is "no comma between 'concomitant' and 'interfering'" in paragraph 8 of the protocol's exclusions that this somehow excuses the failure to note concomitant medication. Nor do I agree with Dr. Mok's contention [Mok comments, page 6] that the "evidence only suggested the possibility that concominant medication may have been administered." The protocol required antibiotics, as concomitant medication, to be noted whether or not there was actual interference with the study medication [patient 1235]. Similarly, with respect to patients 1266 and 1300A, Tylenol and Valium, interfering concomitant medications, should have been noted. The allegation is not failure to exclude the patients but failure to note the fact that concominant medication was involved in these three patients' histories.

I find that Dr. Mok's failure to list these concominant medications with respect to these three patients was a violation of the protocol. The Center seeks a finding that this failure constitutes the submission of false information to the sponsor. I so find. In my opinion, the failure to follow the specific reporting requirements of the protocol with respect to concomitant medication -- whether interfering

or not -- is sufficient to constitute the filing of false information with the sponsor within the meaning of these regulations. In clinical trials of drugs, it is imperative that exclusionary and reporting requirements be meticuously followed. The taking, prescribing, etc., of concomitant medication which, in a given clinical trial, impacts upon the findings which may be made as to the study drug's effectiveness are sufficiently important that the failure to follow such protocol requirements constitutes a willful violation within the meaning of the regulations.

4. Adequate Records of Drug Disposition

Finally, with respect to the study, the Bureau alleged that Dr. Mok failed to maintain "adequate records of the disposition of all receipts of the drug including dates, quantity, and use by subjects ..." in violation of 21 CFR 312.1(a)(12)(6b). Dr. Mok conceded that he did not maintain "separate drug accountability records but contends that by the process of looking at various records one could account for the amounts of the drug received, to whom dispensed, etc." I find that insufficient. Searching and looking through six different, separate and individual types of forms and records so as to account for amounts of a test drug is not the way to determine what actually has been done with the investigational drug that is involved in a clinical study.

Further, in commenting upon the presiding officer's proposed report with respect to FDA's lack of drug accountability records, Dr. Mok points to the proposal to establish regulations covering the obligations of clinical investigators which was published in the Federal Register of August 8, 1978, 43 Fed. Reg. 35210, 35213. He contends that that proposal is an admission by the agency that clinical investigators are confused as to what sort of drug accountability records are required and that, therefore, Dr. Mok will be held to too high a standard if I find that he failed to maintain adequate drug accountability records [Mok comments, page 7]. However, I reiterate the conclusion on the Federal Register page cited that the fact that there are deficiencies in drug accountability is "not acceptable."

Dr. Mok also seeks to establish that he should not be found to have failed to maintain adequate records of drug accountability because of the so-called "standard" policy of sending a form letter to single "clinical investigators who have such a problem and 'advising them how to maintain separate drug accountability records", citing transcript testimony at page I-114. My reading of that page in the transcript leads me to the conclusion that Dr. Mok has misunderstood or misapprehended the thrust of the testimony. That is, the failure to keep adequate records of drug accountability absent other violations is usually an

insufficient reason for disqualification and that "consequently when [the Center] encounters that, we send the letter back, which advises ... of what we consider to be an adequate record of drug accountability ...". That, of course, is not the situation which pertains here when failure to maintain adequate records of drug accountability is but one charge among several.

5. Conclusion: Study

For the foregoing reasons, I find that Dr. Mok violated 21 CFR Part 312 in his study in that he: (1) failed to keep adequate and accurate case histories [312.1(a)(12)(6)(c)]; (2) reported false information to the sponsor [312.1(c)(2)]; and (3) failed to maintain adequate records of drug accountability [312.1(a)(12)(6)(b)]. The first two violations were deliberate within the meaning and intent of the clinical investigator regulations cited.

B. The Study

The Center also alleged that Dr. Mok violated FDA regulations in his conduct and reporting of the study for This was a double-blind, parallel-group comparison of the drug to morphine in a series of post-operative patients. The allegations were that Dr. Mok inadequately reported the test data in three separate ways: (1) inadequate reporting of time and duration of operation; (2) inadequate reporting of time and duration

of prior anethesia and analgesics; and (3) inadequate reporting of prior or additional medication or extent of pain relief. In order to adequately consider these allegations, a review of the protocol [Ex. G-6] is necessary.

The protocol provided for the administration of the drug "in the immediate post-operative period" [Ex. G-6, section 3.000, page 1]. Exclusions, however, were to include "patients who have had analgesics, tranquilizers, or sedatives within 4 hours preceding the administration of test medication." [Ex. G-6, section 5.201, page 2]. For purposes of this decision, I accept the testimony of Dr. Lees that "all anesthetics are analgesics, all anesthetics are sedatives, the ultimate analgesic and sedative." [II-83]. I have serious doubts that the study could have resulted in useful information respecting the drug's efficacy, therefore, because of its basic internal inconsistencies in design.

With this in mind I shall now consider the Center's allegations with respect to Dr. Mok's conduct of this study.

1. Time of Duration of Operation

The Center's allegation was that Dr. Mok, in reporting only the time of commencement of the surgery (i.e., the beginning time), omitted important information for purposes of the study -- namely the duration of the surgery and the time it ceased. Dr. Mok's "defense" is that it is true that he did not record this information but the reason is that the

form was inadequate and that there was no place to enter the time when the operation ceased and that, therefore, to expect him to report such information to the sponsor of the study when no such information was requested is asking too much. He makes much of the fact that advised by letter [Ex. R-5] that the "time of operation" referred to on the form meant the time the operation began on a 24-hour clock.

I agree with the presiding officer's report [pages 15-16] that one can understand why Dr. Mok filled in the form with the time the operation began. I also agree with the presiding officer that the regulations require that a clinical investigator maintain adequate and accurate case histories, and that Dr. Mok should have known the importance of some recordation of the duration and time of completion of the operation in each case so as to provide a base line for determining the expected amount of pain, the impact of concomitant medicines, and other critical elements which affect the analysis of the efficacy of the drug in the period in which the drug was studied. In this connection, I agree with the Center's comments on the presiding officer's report [Center comments, page 9] to the effect that a clinical investigator is not a mere "form-filler". I do not agree with Dr. Mok's comments [page 8] that expecting a clinical investigator to provide more than the form provided by the

firm places an unfair obligation on the clinical investigator. To the contrary, good science requires the reporting of all requisite and relevant data which go into an adequate and complete record, regardless of whether or not the form provided by the sponsor has a place for each of those data to be entered.

I therefore find that Dr. Mok failed to maintain adequate case histories and that by doing so he submitted false information to the sponsor.

2. Inadequate Reporting of Time and Duration of Prior Anesthesia and Analgesics.

This allegation is much more difficult to analyze than the previous one. If, as I have previously stated, anesthesia is determined to be an analgesic or a sedative, or either, then I find that all nine patients which were audited by the Food and Drug Administration with respect to this study were given the study drug within four hours from the time of previous analgesic, tranquilizer or sedative -- a violation of the protocol.

Putting the best face on this, however, and accepting the point of view of Dr. Mok to the effect that the anesthestic used in the operations should not be considered a

previous analgesic or a sedative,[2/] then I find that Dr. Mok inadequately reported time and duration of prior analgesics and sedatives.

In fact, Dr. Mok does not contest that the case report forms for four patients [G-45, G-46, G-50, and G-51] contain significant discrepancies.

Patient number 402S; G-43.

I agree with the presiding officer's finding respecting the appropriatenes of the change on the case report form initialed by Dr. Mok.

Patient 408S; Ex. G-44

The presiding officer made no findings with respect to this particular subject. I find that the records submitted by Dr. Mok on report forms I and II for this study deviated from the patient's charts. The case report forms state that the analgesics morphine, nembutol, and atrophine were given to the patient at 8:15 in the morning and that the study drug was given to the patient at 12:10. The patient's charts state that those drugs were given to the patient at 9:20 in the morning, within the four hour period excluded by the protocol. I therefore find that Dr. Mok did not accurately report this patient's data.

2/ There was conflicting testimony on this issue, Dr. testifying for Dr. Mok that anesthesia is not considered an analgesic or sedative.

Patients 424S, 442S and 500M; G47-G49

I agree with the presiding officer's report that the discrepancies respecting the time of additional medication to patients 4204S, G-47; 442S, G-48; and 500M, G-49 were insignificant with respect to the study by virtue of the fact that the patients had been rated as failures under the protocol prior to the time the additional medication was given to those patients. However, I find that, though not necessary for an evaluation of the efficacy of the study drug, the data submitted was inaccurate in the additional drug times as well.

With the exceptions noted above, I find that Dr. Mok inadequately reported the time and duration of prior anesthesia and analgesics in the study population.

3. Inadequate Reporting of Prior or Additional Medication or the Extent of Pain Relief.

For the reasons set forth in the presiding officer's report at pages 18-19, I find that the case report forms significantly differ from the hospital records and that these differences should have been noted and explained in the case report forms. I therefore find that Dr. Mok failed to submit accurate case report forms with respect to the nine patients in this study that were audited by the Food and Drug Administration.

4. Conclusion - Study

For the forgoing reasons, I find that Dr. Mok violated 21 CFR Part 312 in his study in that he: (1) failed to keep and maintain adequate and accurate case histories [312.1(a)(12)(6)(c)]; and (2) reported false information to the sponsor [312.1(c)(2)]. I further find that these violations were deliberate within the meaning and intent of the clinical investigator regulations.

III. Ultimate Findings

For the reasons set forth above, I find that with respect to the study Dr. Mok repeatedly and deliberately failed to prepare and to maintain adequate and accurate case histories in violation of 21 CFR 312.1(a)(12)(6)(c) and repeatedly and deliberately submitted false information to the sponsor of the study in violation of 21 CFR 312.1(c)(2).

With respect to the study, I also find that Dr. Mok repeatedly and deliberately failed to prepare and maintain adequate and accurate case histories in violation of 21 CFR 312.1(a)(12)(6)(c) and repeatedly and deliberately submitted false information to the sponsor in violation of 21 CFR 312.1(c)(2).

With respect to the study only, I further find that Dr. Mok failed to maintain adequate records of drug accountability in violation of 21 CFR 312.1(a)(12)(6)(b). I

find this violation, while repeated, was not deliberate within the meaning of the regulations.

IV. Assurances

Having determined that the answer to the first finding that is required is that Dr. Mok has repeatedly and/or deliberately violated FDA regulations and deliberately submitted false information to the sponsor of the drug studies, I must now consider whether he has failed to furnish adequate assurance that the conditions of exemption will be met in the future. In this connection, Dr. Mok has provided a set of assurances, which are set forth at pages 21-22 of the presiding officer's report.

The presiding officer concludes that on the basis of the entire record he believes that Dr. Mok has learned from this experience and that in the future he will make a good faith effort to comply with the regulations. The presiding officer also concludes that the assurances provided by Dr. Mok that the discrepancies of the type that occured in the studies here involved will not happen again are sufficient and that when considered with the assurances and the totality of the record, the testimony and evidence presented do not require disqualification.

I agree with the presiding officer. Dr. Mok's assurances and his credible testimony concerning his commitment to implement the policies set out in those

assurances, provide adequate assurance that future violations of the regulations will not occur.

V. CONCLUSION

Dr. Mok has repeatedly and deliberately failed to comply with the conditions of the exempting regulations and 21 CFR 312.1. He has, however, furnished adequate assurance that the conditions of the exemption will be met in the future. Therefore, I conclude that Dr. Mok remains eligible to receive investigational new drugs.

Arthur Hull Hayes, Jr., M.D.
Commissioner
Food and Drug Administration

Dated: March 23, 1983