DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

REGULATORY HEARING ON THE PROPOSAL TO

DISQUALIFY MARTIN S. MOK, M.D., FROM

RECEIVING INVESTIGATIONAL NEW DRUGS

REPORT OF THE PRESIDING OFFICER

APPEARANCES: Donald E. Segal, Esq., for the Bureau of Drugs

Robert A. Dormer, Esq., for Martin S. Mok, M.D.

INTRODUCTION

This hearing was held under 21 CFR Part 16 on the Bureau of Drugs' proposal to disqualify Dr. Martin S. Mok from receiving investigational new drugs. The Bureau alleged that Dr. Mok had repeatedly and/or deliberately failed to comply with the conditions of exempting regulations in clinical investigations in which he was principal investigator. With respect to two clinical drug studies, one concerning and the other concerning , the Bureau alleges that he (1) submitted false information to sponsors in violation of 21 CFR 312.1(c)(2) and (2) failed to prepare and maintain adequate case histories in violation of 21 CFR 312.1(a)(12)(6c) and, with respect to the study only, failed to maintain adequate records of drug accountability in violation of 21 CFR 312.1(a)(12)(6b). 312.1(a)(12)(6b). Consequently, the Bureau argues, Dr. Mok

should no longer be entitled to receive investigational-use drugs, citing 21 U.S.C. 355(i) and 21 CFR 312.1(c)(2).

During the hearing, which took place on December 9 and 10, 1981, the Bureau presented the testimony of Dr. Michael Hensley, who testified concerning his investigation of Dr. Mok; Raymond Dionne, D.D.S., who testified as to how pain studies are conducted and to the irregularities he observed in the records of Dr. Mok's study; and Dr. David Lees, an anesthesiologist, who testified concerning deficiencies which he saw in the records of Dr. Mok's study.

In addition to the testimony of Dr. Mok himself, the respondent presented the testimony of Dr. , a clinical investigator at Institute , who testified that, although mistakes were made, in his judgment they did not warrant the disqualification of Dr. Mok.

What follows are my findings and conclusions based on the full administrative record of the hearing including post-hearing briefs by both sides, copies of which, along with copies of exhibits and the hearing transcript, are attached.

I. The Study

A. Alterations in Case Report Forms

The most serious allegation against Dr. Mok was that, with his concurrence, his study nurse altered the case report forms of 22 subjects on study prior to their submission to

the sponsor. The Bureau alleges that the patient responses were initially recorded by Dr. Mok's study nurse, . Later, certain of the patients' responses were altered and new case report forms were completed incorporating the changes but not revealing the alterations. Subsequently, the case report forms, incorporating the changed data but not the original entries, were submitted to , the sponsor. It is alleged that , the contract monitor, requested the changes be made for the sake of consistency. G-7, p. 40, TR. I. 111. Ms stated that the case report forms were rewritten over her objection, that Dr. Mok was present and approved the changes, and that he, along with a employee, directed her to sign the case report forms. G-42, TR. I. 110-11.

It is alleged that the data were altered not to make the drug's performance look better but to make the data look more consistent. In other words, the changes were designed not to make the drug look better but to make the study look better. The aim was to make comparative responses gibe with absolute responses.

There is no factual dispute as to what happened. Dr. Mok raises two defenses, however. First, he contends that, because is an agent of the sponsor, , any action by representatives must be attributed to because of principles of agency law. Therefore, goes the argument, could not have been misled because

the changes in patient responses were ordered by the sponsor's own representative. Thus, there is no violation.

The applicable regulation reads as follows:

> 21 CFR 312.1
>
> ...
>
> (c)(1) Whenever the Food and Drug Administration has information indicating that an investigator has repeatedly or deliberately failed to comply with the conditions of these exempting regulations outlined in Form FD-1572 or FD-1573, set forth in paragraph (a)(12) and (13) of this section, or has submitted to the sponsor of the investigation false information in his Form FD-1572 or FD-1573 or in any required report [the investigator shall be offered an opportunity for a hearing] pursuant to Part 16 of this chapter, on the question of whether the investigator is entitled to receive investigational new drugs.

I find that no "agency"[1/] relationship existed between sponsor and monitor in this situation but that , as a contract monitor, was an independent contractor.[2/] I. 28. Therefore, the fact that personnel actively solicited these changes does not, for purposes of 21 CFR 312.1, relieve Dr. Mok of responsibility for failure to have reported them.

1/ I refer to "agency" in the legal sense, namely, that body of law relating to principal and servant. See Black's Law Dictionary, 4th ed.

2/ Dr. Hensley stated that, "I think you have to ... impute what the contract monitor knew to the sponsor." II. 64. His statement was not, however, a correct exposition of the law on this point.

In any event, it does not matter whether or not an agency relationship existed. The violation in question was submission of false information in a report to the sponsor and to the FDA. The falsity of information under 21 CFR 312.1 does not depend on whether the recipient knows it is false. Reporting the changed scores without reporting the initial scores and the fact of the changes is a submission of false information within the meaning of section 312.1 regardless of what or the sponsor knew.

The Bureau argues that, not only is this a violation of FDA's regulations, it is a deliberate violation within the meaning of 21 CFR 312.1(c)(1). I agree. I accept the Bureau's definition of the term, "deliberately," namely, wilfully, intentionally, but not necessarily with intention to commit an act known to be unlawful. Dr. Mok must have had some idea that he was doing something wrong because he initially objected to changing any data but eventually was convinced to do so by the monitor in order to make the secondary comparative data consistent with primary ratings. TR. II. 200; Mok brief at 6.

In the context of 21 CFR 312, a deliberate action is a willful action that need not entail knowledge that it is a violation of law as long as there is some perception of wrongdoing or of reckless disregard for obvious or known risks. See Monday v. United States, 421 F.2d 1210 (7th Cir. 1970), cert. denied 400 U.S. 821, cited in the Bureau's brief. In light of Dr. Mok's hesitation, as noted above, I find that his action in having case report form pain results recopied as changed constituted a deliberate action within the meaning of 21 CFR Part 312. However, the fact that this violation was urged upon him by the monitor, whose representative gave the appearance of knowing what was right, mitigates the seriousness of the violation in respect to Dr. Mok's actions.

B. Reporting Of Degree Of Injury And Level Of Pain

The Bureau alleges that in five instances Dr. Mok failed adequately or accurately to report the injuries suffered by patients on test. The alleged discrepancies are reflected in G-9, G-17, G-18, G-32, and G-35. In each instance the case report form Dr. Mok submitted reported the subject to have had a fracture instead of something less severe. Hospital records, on the other hand, reflect sprains, contusions, "arm trauma," and the like. G-39.

Further, the Bureau argues that in four instances Dr. Mok failed accurately to report the level of pain or discomfort experienced by the patients as reflected in the hopital records. G-26, G-35, G-36, and G-37.

With respect to the fracture versus lesser injury issue, Dr. Mok explained how the study nurse might have been mistaken in taking information from hospital records. In addition, Dr. Mok explained that he had often not requested the patients' hospital records (which would have given later, more confirmatory or revised information on diagnoses) in order to save them the $47 it would have cost for a visit to the pain clinic for treatment, an unwarranted expense in light of the fact that the patient would not receive treatment. However, Dr. Mok does not contest the fact that the description of a fracture in these five instances was erroneous.

Therefore, I find that, with respect to the five patients in question (1201, G-9; 1210, G-17; 1212, G-18; 1231, G-32; and 1265, G-35). Dr. Mok failed to keep adequate and accurate case histories in that the diagnoses presented thereon were incorrect. For the same reason, I find that Dr. Mok here submitted false and misleading data to the sponsor.

With respect to allegations concerning inaccurate reports of pain and discomfort levels, the evidence is less clear. For example, for patient No. 1221 (G-26), the

allegation of a discrepancy in pain rating arises from the statement in the outpatient clinical record that the patient had "no complaints" during a cast check. G-26, p. 7. Other entries in the hospital records indicate that the patient was in pain, however. See, e.g., statement that patient was in moderate pain at 9:10 a.m. upon entry into surgery. G-26, pp. 1-2; prescription for Talwin on April 15 as recorded at G-26, p. 7; and G-26, pp. 34, where the records show that the patient obtained no relief from the study medication and was prescribed additional Talwin.

Therefore, I find that, with regard to patient 1221 (G-26), the Bureau has not satisfied its burden of proof.

Likewise, with respect to patient 1265 (G-35), a statement by a doctor performing a cast check that the patient had "no complaints of pressure points" does not necessarily mean that the patient was not in pain but, rather, may mean that the cast was not too tight (e.g., no discoloration of skin, edema, etc.) Therefore, I find that the Bureau has not satisfied its burden of proof with respect to that patient.

As to patient 1266 (G-36), the Bureau's allegation is based upon a statement in the hospital records to the effect that the patient had "no acute distress." As Dr. Mok testified, and as Dr. Hensley apparently agreed (Tr. II. 217), this does not necessarily mean that the patient had no pain. Other entries in the patient's medical record

either show or strongly imply that the patient did have pain. I find that the Bureau has not satisfied its burden of proof with respect to that patient.

Finally, concerning patient 1292A (G-37), there is an apparent discrepancy between an observation made on October 5 in the patient's record that the patient had "minimal pain" (G-37, p. 11), whereas when he entered the study on October 6 he allegedly had moderate pain. I find that the Bureau has not satisfied its burden of proof with respect to that patient. Clearly, as Dr. Hensley admitted, patients can suffer different degrees of pain on successive days. TR-I. 236.

The Bureau responds with the argument that there is a pattern to these discrepancies in that, in each instance, the hospital records indicate that the patient was suffering less discomfort than that alleged in Dr. Mok's case report form. Thus, the Bureau argues that, even if each discrepancy does not rise to a separate violation, there is a disturbing pattern of overestimating pain in order to qualify potential subjects for a study.

While this is worrisome, I find that a definite pattern cannot be deduced from only four patients and the Bureau's burden of proof was not met.

C. Concomitant Medication

There is some dispute between the parties as to what "concomitant" means. I will accept the language of the protocol, which required exclusion from the study of "patients taking concomitant, interfering or potentially

interacting medications such as other analgesics, psychoactive medications, or anticoagulants," and of patients having taken any such medication "within 3 hours of entry into the study." The protocol also prohibited the use of "other analgesics, 'skeletal-muscle relaxants' or interfering or interacting medications, physiotherapy, or adjunctive measures ... during any portion of the study. Notation of any other concomitant medication for pre-existing ailments" was to "be made in the appropriate section of the case report form." G-5, pp. 2-3. Dr. Hensley testified that the case report forms failed to reflect the administration of concomitant medication in that the specific entry in the case report form where concomitant medication should have been entered was filled in as "none." See, e.g., TR-I. 96-7.

The Bureau alleges that concomitant medication in the form of Ancef, penicillin, and Keflex (G-33), Tylenol and Valium (G-36), and Tylenol alone (G-38) were administered without notations in the proper space having been made in the case report forms. (Subjects 1235, 1266, and 1300A.)

Patient 1235 (G-33) received the antibiotics, Ancef, penicillin, and Keflex. Dr. Mok argues that these antibiotics were given concomitantly but did not need to be listed because they would not have interfered with the study medication. In this he is correct only if the patients were suffering pain due to causes other than infection or if some drug-drug interaction existed and interfered (the latter was not raised as an issue).

It is well known that infections can cause symptoms to which pain is related. I conclude that these medications are concomitant in the sense that they were given during the prescribed timespan, even if they have not been shown to be interfering concomitant medications. Regardless, the medication should have been noted on the Patient Entry Form (i.e., page 3 of G-33). The seriousness of this omission is not clear from the evidence presented.

As to patients 1266 and 1300A (G-36 and G-38), their medications would have been interfering concomitant medications because Tylenol and Valium do affect pain or the perception of it. Dr. Mok did not dispute this but contends that there is no proof (1) that the order that the patient received the prescription was followed; (2) that the prescription was filled; (3) that the patient took the medication as prescribed; and (4) that the patient either forgot that he had taken these medications or lied to the study nurse about having taken them.

By failing to introduce evidence on these matters, Dr. Mok argues, the Bureau has failed to satisfy its burden of proof by a preponderance of the evidence. In my opinion, Dr. Mok is confusing the burden of proof which the Bureau must satisfy in this hearing (i.e., proof by a preponderance of evidence) with the burden of proof that the prosecution shoulders in a criminal case (proof beyond a reasonable

doubt). I believe that evidence that the medication was ordered is sufficient to satisfy the Bureau's burden of proof.

In any case, if Dr. Mok believed that these patients did not receive the medication or take it, he nevertheless would have had an obligation to explain the discrepancy between the hospital records and the case report forms to eliminate any possible confusion. The allegation is ultimately failure to keep adequate and accurate case histories. In the study, Dr. Mok was required to note any concomitant medication which might have confounded evaluation of the study. By proving that the hospital records show concomitant medication with respect to the two patients involved, the Bureau 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. I believe that Dr. Mok, in order to make his case histories adequate and accurate, would have had to note and explain this apparent discrepancy, even if the discrepancy were apparent and not real. Therefore, with respect to the allegation that Dr. Mok failed to report concomitant medication, I find that, as to three patients (1235, G-33; 1266, G-36; and 1300A, G-38), he failed to keep accurate and adequate case histories.

D. Adequate Records of Drug Disposition

Lastly, 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 has conceded that he did not maintain "separate" drug accountability records. TR-II. 183. He does contend that he kept sufficient records which do prove that he did administer the test medication to subjects in the study. However, the Bureau argues that this is not enough--that he is required to keep some record not only of the quantities of the investigational drug he received from the sponsor but also of what he dispensed and what he returned unused. Bureau brief at 19. The Bureau would accept, it says, the maintenance of a notebook or ledger containing entries of receipt, dispensation, and unused returned quantities. Id.

Dr. Mok stated that FDA's regulations do not require separate drug accountability records. The language of the regulation in question reads as follows:

> (b) The investigator is required to maintain adequate records of the disposition of all receipts of the drug, including dates, quantity, and use by subjects and if the clinical pharmacology is suspended, terminated, discontinued, or completed, to return to the sponsor any unused supply of the drug ....

To me this clearly justifies the Bureau's interpretation of the requirement. Whether it is "separate" or not does not

matter as long as it is there and can be checked. Dr. Mok does not contend that he kept records of the amount of the drug received, dispensed, and returned unused. That being the case, he is clearly in violation of the regulation insofar as his study is concerned.

E. Conclusion: Study

To recapitulate, 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, 21 CFR 312.1(a)(12)(6c); (2) reported false information to the sponsor, 21 CFR 312.1(c)(2); and (3) failed to maintain adequate records of drug accountability, 21 CFR 312.1(a)(12)(6b). The first two violations were deliberate within the sense of the regulations where they involved unreported changes in response ratings.

II. The Study

The Bureau also alleges that Dr. Mok violated FDA regulations in his conduct and reporting of the study for This double-blind, parallel-group comparison of to morphine was a study of pain in postoperative patients. The Bureau alleges significant discrepancies between Dr. Mok's case report forms and hospital records in that Dr. Mok failed to prepare and maintain adequate case histories and submitted false information to the sponsor. At pages 21-22 of its brief, the Bureau charts its allegations against Dr. Mok concerning

the study. There, the Bureau cited for three categories of allegedly inadequate reporting: inadequate reporting of time and duration of operation; inadequate reporting of time and duration of prior anesthesia and analgesics; and inadequate reporting of prior or additional medication or extent of pain relief. I will consider these in order.

A. Time and Duration of Operation

The Bureau contends that in nine instances (Bureau investigators examined only nine case reports in toto) Dr. Mok, in reporting only the time of commencement of the surgery, omitted important information--namely, the duration of the surgery and the time of its termination. Dr. Mok admits that he did not record this information but states that the sponsor did not ask for it and the case report form did not call for it. He received some support from Dr. , a clinical investigator who has performed many analgesia studies, who agreed with Dr. Mok that he (Dr.) would have completed the case report form the same way that Dr. Mok did. He criticized the form, but not Dr. Mok's completion of it. TR-II. 127-128.

acknowledged: "It was understood that the stated 'time of operation' represented the time at which the operating procedure began." R-5.

In light of this, I can understand why Dr. Mok proceeded as he did. However, 's understanding and intention are not the issues being considered. I am required to determine whether Dr. Mok followed FDA's regulations, which require the

maintenance of adequate and accurate case histories. The duration and time of completion of an operation are important in a clinical investigation such as Dr. Mok's study in order to determine the expected amount of pain, the impact of concomitant medication, and other crucial elements in analysis of the study from the point of view of drug efficacy in the post-anesthetic period. Dr. Mok should have known this and recorded this information somewhere on his case report forms, even if the form as developed by the sponsor did not specifically provide for it. For this reason, I find that Dr. Mok failed to keep adequate case histories in all nine instances. I agree, however, that this form was inadequate. This fact mitigates to a degree the culpability of the investigator but does not mitigate the seriousness of the omission.

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

Specifically, the Bureau alleged that Dr. Mok failed adequately to report prior or additional medication or the extent of pain relief regarding eight patients (402S, G-43; 408S, G-44; 414S, G-45; 421S, G-46; 424S, G-47; 442S, G-48; 500M, G-49; and 512M, G-51). The Bureau contends that the case reports for these patients either failed to record prior or additional medication at all or else did not accurately report how close in time to the administration of the study drug that the additional medications were administered.

Dr. David Lees, testifying for the Bureau, stated that, aside from failure to report anesthetics, Dr. Mok failed to report other potent sedatives and analgesics. Tr. II. 78-79.

Dr. Mok acknowledges that "some slight discrepancies in reporting of prior or additional medication in the study did exist." He goes on to argue, however, that the discrepancies did not affect the validity of the study data. Some other alleged discrepancies, he argues, were the result of FDA's failure to understand pertinent records. For example, Dr. Mok points to patient 402S, whose record Dr. Mok corrected and initialed. G-43, p. 3. I agree with Dr. Mok that his initialed changes on the case report form of patient 402S were perfectly proper, as Dr. Hensley apparently agreed. Tr. II. 9-10. Likewise, I find that the Bureau has not satisfied its burden of proof as to patient 500M (G-49), in respect to whose records the Bureau found a discrepancy in that the case report form said that Demerol and Benadryl were given at 8:45, whereas the patient's chart said that it was given at 9:15 a.m. The study medication was given at 12:45 p.m. Dr. Mok argues (and the Bureau does not dispute) that this would have created only a one-half-hour intrusion into the wash-out period even assuming the Bureau's 8:45 a.m. time to have been correct. Lacking evidence to the contrary (which was not introduced in this proceeding), I believe that that is too small a period of time in the context of this study to constitute a violation that would cause the case history to be considered inadequate, even if it were a

protocol violation. It is also noteworthy that the sponsor conceded that a four hour wash-out period was overrestrictive for the study (R-5).

For three subjects (424S, G-47; 442S, G-48; and 500M, G-49), additional medication was admimistered after the patient had already been rated as a treatment failure. In another case (512M), the discrepancy between the case report form and patient record regarding the time of administration of pre-study analgesia was meaningless because either time of administration was outside the four-hour wash-out period.

However, with respect to the other subjects whose case report forms were audited (414S, G-45; 421S, G-46; 504M, G-50; and 512M, G-51), Dr. Mok does not contest that the discrepancies existed or were significant. Therefore, I find that, as to four case report forms, Dr. Mok inadequately reported the time and duration of prior anesthesia and analgesics and, therefore, maintained inadequate case histories.

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

Lastly, the Bureau alleges that, with respect to eight of the nine patients whose case report forms were audited, Dr. Mok inadequately reported prior or additional medication or the extent of pain relief. The Bureau points to discrepancies between the hospital records and the case report forms as to the pain patients were suffering. Dr. Mok stated, as he did concerning the study, that the study nurse is better trained and is, therefore, a more reliable observer.

Dr. agreed. TR. II. 175. However, others point to the experience of recovery room nurses in quantifying pain and their reliability.

Clearly, discrepancies do exist. For the study, I found that many apparent inconsistencies could be satisfactorily explained. However, for the study, no convincing explanations for inconsistencies have been offered. I am not able to resolve the question of which records are correct. However, I do find that where, as here, case report forms significantly differ from hospital records, these differences should be noted and explained in the case report forms. Because this was not done with respect to patients 402S, G-43; 408S, G-44; 414S, G-45; 421S, G-46; 424S, G-47; 442S, G-48, 500M, G-49; and 512M, G-51, I find that the case report forms were inadequate. This does not mean that in all cases they had to be proven inaccurate.

Then, too, the Bureau also showed that Dr. Mok failed to report the administration of general anesthesia to patients within four hours of the study drug. This constitutes interfering concomitant medication (TR-I. 150), a conclusion that Dr. Mok does not contest in his brief.

Finally, the Bureau alleged that one subject, 504M (G-50), had EKG changes indicative of a myocardial infarction. Although Dr. Mok did not view these changes as reflecting a possible myocardial infarction, he did not contest that he failed to report these changes. All witnesses testifying on the matter agreed that this was an error and a serious deficiency. TR-II. 88, 176, 238. I deem this a very serious omission in the case report form.

D. Conclusion: Study

Concerning the study, I conclude that Dr. Mok violated 21 CFR 312 in that he failed to prepare and maintain adequate case histories (21 CFR 312.1(a)(12)(6c) and that he submitted false information to the sponsor (21 CFR 312.1(c)(2)). The basis for my conclusion is proof by the Bureau of Drugs by a preponderance of the evidence that Dr. Mok inadequately reported time and duration of surgery in more than one instance; that he inadequately reported the time and duration of prior anesthesia and analgesics in four separate instances; that he inadequately reported prior or additional medication and failed to note and explain differences between reported pain relief in case report forms and hospital records in nine instances; and that he failed to report important EKG irregularities of one patient.

III. Ultimate Finding

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

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

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

Therefore, Dr. Mok's violations were all repeated and some were deliberate.

IV. Assurances

Dr. Mok has provided the following assurances and taken the following actions:

1. He has promised in the future to report all discrepancies in data directly to the sponsor.

2. He has dismissed the two nurses who were involved in the studies that the Bureau has complained about. Further, the nurse who is currently doing studies for Dr. Mok has, he says, considerably more experience and has been thoroughly trained in proper conduct of an analgesic study.

3. He has determined to do no more outpatient studies so as to eliminate discrepancies between hospital records and case report forms. He states that, if he does decide to do additional outpatient studies, he will make sure that the sponsor is willing to pay to have the hospital records sent to the pain clinic.

4. He has instructed his study nurse to make sure that she enters the administration of the study drug onto the patients' hospital chart and is careful to ascertain the administration of any concomitant medication.

5. He promises to spot check not only the work of the study nurse but the work of the floor nurse to make sure that

his orders have been carried out. He himself will also check hospital records on a random basis. To eliminate the likelihood of conflicting medications, he states an intention to limit research to single-dose studies.

6. He promises to increase direct contact with the subjects in any future study and states that he will obtain informed consent from the patients himself and/or will obtain patients' medical history.

7. He has established a drug accountability file, he said, which is under the control of the study nurse.

8. He promises in the future to report all side effects such as EKG abnormalities regardless of whether he believes them to be drug-related or not.

V. Discussion

I face a difficult decision in making my recommendations. On the one hand, as I have found, the Bureau has proven by a preponderance of the evidence violations of FDA regulations which violations provide the basis for Dr. Mok's disqualification from receiving investigational drugs. On the other hand, Dr. Mok has, throughout the proceedings, demonstrated that he has learned a great deal about the performance of clinical trials and his ultimate responsibility as a clinical investigator. Further, he has provided assurances that are reasonable and credible. The Bureau's chief complaint against Dr. Mok's assurances is that, under his plan, the study nurse, not Dr. Mok, will be performing most of the significant study tasks. However, it

is unreasonable to expect the chief investigator to perform all tasks in all or many cases, depending on a range of variables. Some can be appropriately delegated. I agree with the Bureau that responsibility cannot be delegated, but, as Dr. Hensley acknowledged (TR. I. 103), duties can be delegated. Furthermore, I believe that Dr. Mok now fully understands the issues involved in delegation and recognizes his ultimate responsibility. I also believe that his assurances are genuine.

Nevertheless, I am troubled by the fact that Dr. Mok initially signed an affidavit (G-41) in which he asserted that the monitor, , had not requested any "factual" changes in the pain ratings. He contends that his later change of story resulted from a misunderstanding as to the word "factual." Frankly, I am not completely satisfied with that explanation.

Also, I am troubled by Dr. Mok's failure to report the EKG irregularity. Even Dr. (TR. II. 176) and Dr. Mok himself (TR. II. 247) admitted that this should have been done.

Arguing in Dr. Mok's favor is the fact that the study, in which most of the significant violations occurred, was his first study as a principal investigator. Then, too, Dr. Hensley admitted that the violations in the study were not of sufficient importance by themselves to justify disqualification. TR. II. 63.

VI. Recommendation

On the basis of the entire record, I recommend that Dr. Mok not be disqualified. In recommending against disqualification, I am relying heavily on:

(1) The fact that the deliberate errors that occurred in the early part of the study had no effect on the safety or rights of the subjects. The changes in the comparative ratings were made retrospectively to resolve obviously inconsistent data and were made, I believe, at the insistence of the monitor. Although these changes did affect the validity of the data in the sense that the comparative evaluations look more reliable than they actually were, the changes did not improve the efficacy rating of . In fact, the study showed that was only equal to or marginally superior to aspirin.

(2) The evidence that the most serious violations, changes made in case report forms, were committed in the early stages of Dr. Mok's first study as a principal investigator; and evidence that the nature, scope, and extent of those changes were limited to the first 30 patients in the study; and evidence that, though deliberate, the changes do not reflect an intent to defraud.

(3) The fact that I believe that Dr. Mok is now keenly aware of his obligations under FDA regulations.

(4) The assurances from Dr. Mok that the descrepancies of the type that occurred in the and studies will not happen again.

(5) The testimony and evidence presented at the hearing, which demonstrated deviations of varying severity from the requirements of the regulations. However, when considered with the assurances provided by Dr. Mok and the totality of the record, they do not, I believe, require disqualification.

However, the fact remains that violations did occur and, therefore, I hope that the Bureau of Drugs will carefully monitor Dr. Mok's subsequent performance to ascertain that he is carrying out those steps he has undertaken to implement.

Respectfully your,

Stuart L. Nightingale, M.D.
Presiding Officer