DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

REGULATORY HEARING ON THE PROPOSAL

TO DISQUALIFY MAURICE LIPPMANN, M.D.,

FROM RECEIVING INVESTIGATIONAL

NEW DRUGS

OPINION AND RECOMMENDATIONS OF THE PRESIDING OFFICER

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

James Phelps, Jr., Esq., for Maurice Lippmann, M.D.

I. INTRODUCTION

This was a hearing pursuant to 21 CFR Part 16 in which the Bureau of Drugs sought to have Dr. Maurice Lippmann disqualified from further receiving investigational new drugs. The Bureau alleged that Dr. Lippmann, the principal investigator in two clinical trials, (a) submitted false information to the sponsors in violation of 21 CFR 312.1(c)(2); and (b) failed to comply with the conditions of the exempting regulations, also in violation of 21 CFR 312.1(c)(2), in that he (1) failed to prepare and maintain adequate and accurate case histories in violation of 21 CFR 312.1(a)(12)(6c) and 21 CFR 312.1(a)(13)(4c); and (2) failed to obtain informed consent from the subjects in violation of 21 CFR 312.1(a)(12)(6g), 21 CFR 312.1(a)(13)(4g), and 21 CFR 310.102. The Bureau based its case on an FDA audit (inspection) of two

investigational new drug studies conducted by Dr. Lippman on the analgesic drugs, and .

At the hearing, the Bureau presented testimony of Dr. Michael Hensley concerning his audit of the and studies and alleged discrepancies between Dr. Lippmann's case report forms and patient records at Hospital, where the studies were conducted. FDA investigator Mr. Kenneth Nelson testified concerning his interviews with various of Dr. Lippmann's experimental subjects, especially as to their recollection about participating in the studies and their signatures on certain consent forms. Mr. Nelson also testified concerning his search for hospital records which, he testified, he never located. Thirdly, Dr. , an anesthesiologist, testified concerning the deficiencies which he observed in the records of the two studies. He also testified as to what he considers the proper role of an investigator in supervising study personnel and obtaining informed consent.

Dr. Lippmann testified in his own behalf, and Ms. , an attorney with the firm representing Dr. Lippmann, testified to her investigational findings.

Following the hearing, the Bureau and Dr. Lippmann submitted briefs. The Bureau's brief consisted of a lengthy and detailed recounting of the allegations and the proof adduced in support of them. However, Dr. Lippmann chose, for the most part, not to attempt a detailed refutation of the allegations. Although Dr. Lippmann made the pro forma statement that the Bureau has not

proved repeated and deliberate violations, he apparently concedes that nearly all of the alleged violations actually occurred.

> In this memorandum respondent will not address the specific inaccuracies and discrepancies between patient records and case report forms alleged in the NOH. Indeed, Dr. Lippmann has conceded that there were many inaccuracies. Respondent will rely on the record made at the hearing for his response to those charges. Respondent addresses here the more general concerns of the Bureau that patients in these studies did not participate as reported in the case report forms, as well as the steps Dr. Lippmann has taken to prevent future errors.

Lippmann post-hearing memorandum at 4.

Because I, as presiding officer, must make detailed findings, conclusions, and recommendations, I will first state my findings as to which violations of FDA regulations that occurred in the study might have occurred and then proceed to do the same thing as concerns the study.

II. THE STUDY

Dr. Lippmann's study, for which the sponsor was was an oral, double-blind, placebo-controlled study of the analgesics, and , in patients with moderate to severe post-operative pain.

The Bureau audited the case report forms and in-patient hospital records of twelve subjects selected at random. It alleges that it found significant discrepancies between case report forms and hospital in-patient records for

every one of the twelve patients audited. The Bureau classified these violations in five groups: (1) failure to accurately report concomitant and other medication in the case report forms; (2) failure to accurately report significant surgical information such as type and date of surgery and whether surgery was performed at all; (3) failure to obtain informed consent of subjects; (4) non-existence of appropriate patient hospital records by which data could be validated; and (5) failure to enter into the hospital records the administration of the study drug. The deficiencies and discrepancies which the Bureau alleged are listed in tabular form at pp. 10-13 of the Bureau's post-hearing brief. I will discuss in order by group each set of alleged violations.

A. Failure To Accurately Report Concomitant Or Other Medication

The Bureau alleges that, for nine of the twelve subjects audited, Dr. Lippmann failed to report accurately concomitant or other medication. In all nine instances, the Bureau alleges, Dr. Lippmann reported that the subject received medication other than the test drug, whereas hospital records showed either that the drug was never given or it was given at a time significantly different from that reported on the case report forms. In four instances, the Bureau alleges, Dr. Lippmann failed to report medication that the hospital records showed that the subject received within one and one-half hours of the time when the study drug was reportedly administered.

I make the following findings as to the patients indicated:

1. Patient No. 1:

(a) Patient No. 1 received at 0815, according to Dr. Lippman's report, which also stated that no additional pain medication was requested during the four-hour observation period. However, the nursing notes state that the patient was medicated for pain at 0930 on the same day, well within the four-hour period. Dr. Lippman did not report that concomitant medication.

(b) Dr. Lippmann reported that Patient No. 1 received general anesthetics, while the discharge summary states that only local anesthesia was used. G-9, p. 1, 11. Dr. Lippmann reported Tylenol #3 as having been given at 0130 on the day of surgery (as previous analgesic medication), whereas the medication record shows that Tylenol #3 was given at 1700 and 2130 on that day but not at 0130. G-9, p. 1, 5; T. I-41.

(c) Dr. Lippmann reported that Patient No. 1 received the study drug only once, on the date of surgery, while the medication record shows that the study drug was also administered the day before and the day after. G-9, pp. 1, 5.

2. Patient No. 11:

(a) Dr. Lippmann reported that this patient received at 0900 on August 11, 1978. However, the hospital medication records reflect that this patient received aspirin at 1000 on the same day. G-10, pp. 2-3, T. I-46. Dr. Lippmann did

not report this concomitant medication even though the protocol required him to do so. G-10, pp. 1-2.

(b) Dr. Lippmann failed to report that this patient had a history of alcoholism and "DTs" when the protocol called for exclusion of persons who had a history of "developed tolerance or addiction to drugs, including alcohol." G-4, p. 8. G-10 at 1, 5; T. I-48. Although the Bureau did not allege this violation of the protocol, failure to report this history represents a failure to keep accurate case histories.

3. Patient No. 18: Dr. Lippmann reported that this patient received the test drug at 0900 on August 16, 1978, and that she received concomitant medication in the form of Rheomacrodex at 0800 on the same day. He further reported that a pre-operative medication, morphine, was administered at 0600 on August 15. However, hospital medication records do not show administration of either Rheomacrodex or morphine. G-11, pp. 1, 2, 5; T. I-51-2.

4. Patient No. 20: Dr. Lippmann reported that patient No. 20 received the test drug at 0825 on August 18 and was remedicated for pain with Tylenol #3 at 1025. However, the hospital's medication record shows that the patient was given Tylenol # 3 at 1200 and at 2015. G-12, pp. 2, 4.

5. Patient No. 33: Dr. Lippmann reported that this patient received the test drug at 0930 on September 13 and was given the previous analgesic medication, Tylenol #3, at 0430 as well as a

concomitant medication, Gentamicin, at 0600, following which the patient was remedicated for pain with Tylenol #3 at 1230. G-13 at 1. However, the medication record and nursing notes show that Tylenol #3 was given only at 1215 and 2200 on September 13 but do not show that Gentamicin was ever administered. G-13, pp. 1-3; T. I-54-6.

6. Patient No. 38: This patient received at 1000 on September 19. Although Dr. Lippmann did not report any concomitant medication, hospital medication records reflect that this patient received aspirin at the same time. G-15, pp. 1-3; T. I-61-2. Although Dr. Lippmann reported that the previous analgesic medication was Harbogesic B (acetominophen), administered at 0330 on September 19, the medication records show that this drug was given at 0100. G-15 at 1, 3.

7. Patient No. 48: This patient received at 0900 on September 28. Hospital records and nursing notes show that this patient received Harborgesic A (ASA), an analgesic, at 0810 and 1030 on the same day, but Dr. Lippmann did not report any interfering concomitant medication. G-17, at 1-3, 10; T. I-70-1. Dr. Lippmann also reported that the patient received Tylenol #3 at 0430 and concomitant medication, Rheomacrodex, at 0900, but the medication record again does not show that these drugs were given. G-17, pp. 1, 3; T. I-69-70.

8. Patient No. 58: This patient had an analgesic, Tylenol #3, at 2330 the night before the patient received the

the test drug. However, the medication record shows that Tylenol #3 was only given at 0100 on October 4. G-18 at 1, 3, 6.

9. Patient No. 73: This patient, who received [redacted] at 1400 on October 11, had previous concomitant medication, Rheomacrodex, at 0800 and a previous analgesic medication, Tylenol #3 at 1000. G-20 at 1. However, hospital medication records do not show that either of these drugs was given. G-20 at 3.

The Bureau correctly points out that Dr. Lippmann offered no defense or explanation concerning these allegations, either at the hearing or in his brief. Therefore, I deem them admitted, and I find that the Bureau of Drugs has sustained its burden of proof on all of them. Dr. Lippmann does not argue that the hospital records were incorrect, nor does he attempt to advance any reason for these discrepancies.[1/] Thus, I find that, with respect to the allegation that he failed to note certain interfering concomitant medication and that he noted otner medication that was not in fact given, I find that Dr. Lippmann failed to keep adequate and accurate case histories.

1/ As I found in my decision regarding the disqualification of Dr. Mok (p. 12), the existence of significant unexplained discrepancies between case reports and hospital records constitutes a failure to keep accurate and adequate case histories.

B. Failure To Report Accurately Significant Surgical Information

The Bureau alleges that, for nine of twelve subjects whose records were audited, Dr. Lippmann failed to report adequately important surgical information such as type of surgery, date of surgery, and whether surgery was performed at all.

1. Patient No. 1: According to Dr. Lippmann, this patient had an incision and drainage of an abcess on the left arm, but the patient's hospital record shows that the lesion was on the hand, not the arm, and does not indicate that any surgery was performed. G-9, pp. 1, 8, 9. Because the protocol calls for the inclusion in this study of subjects who are experiencing postoperative pain, this subject was not suitable for the study. G-4, P. 9.

2. Patient No. 18: Although hospital records show that this patient had surgery on August 18, Dr. Lippmann reported surgery as occurring on August 15. Moreover, the patient was evaluated on August 16, indicating that, unknown to the sponsor, this patient was not evaluated for pain postoperatively. G.-11, P. 1, 2, 3.

3. Patient No. 34: Again, the hospital records and Dr. Lippmann's reports show that surgery was performed on different dates, in this case almost a week apart, August 29, 1978 and September 4, 1978 respectively. Dr. Lippmann reported the study drug was administered on September 14, 1978. G-14, P. 1, 2, 4, 7. Therefore, if the hospital records are correct, Dr. Lippmann's description of the date of surgery caused the time

of administration of the drug to appear to be closer to the time of surgery than it really was.

4. Patient No. 38: There is no evidence whatever that this patient had surgery at all, other than Dr. Lippmann's report, which dated surgery as September 15. Neither the Bureau nor Dr. Lippmann could produce any records to confirm any surgery although the hospital consent form for surgery was signed and dated August 23, 1978. The hospital recovery room log has no record of this patient being there on September 15, 1978. G-21, P. 20.

5. Patient No. 45: Dr. Lippmann's report that patient No. 45 had surgery on September 22 is contradicted by the hospital's discharge summary, which shows that he was not admitted to the hospital until September 25. The hospital summary indicates that he was discharged without ever having had surgery. Obviously, this patient could not have been evaluated for pain postoperatively.

6. Patient No. 48: Again, although Dr. Lippmann notes performance of surgery (a left medial meniscectomy), hospital records do not show that any surgery was ever performed. G-17 at 8-9; G-21 at 29; T. I-67-8.

7. Patient No. 58: Dr. Lippmann reported that this patient had surgery on October 2 and received on October 5. G-18, pp. 1, 3. However, the hospital records show that he was admitted on October 3 and had surgery and was discharged on October 5. G-18, pp. 4-5; T. I-72-3.

8. Patient No. 68: Hospital records for this patient show that surgery was performed on October 3, whereas Dr. Lippmann reported the surgery as having occurred on October 5. G-19, pp. 1-2, 7-8; G-21, p. 31; T. I-76.

9. Patient No. 73: Whereas hospital records for this patient show that surgery was performed on September 26, Dr. Lippmann reported that surgery occurred on October 6 and that the study drug was administered on October 11, fifteen days after hospital records record that surgery was performed. Dr. Lippmann's description of the date of surgery made the time of administration of the drug appear to be closer to the time of surgery than it apparently was. G-20, pp. 1-2, 5-6; G-21, p. 26; T. I-78-9.

Once again, for all of these discrepancies, Dr. Lippmann made no explanation and offerred no defense. Therefore, with respect to all, the discrepancies constituted the preparation and/or maintenance of inadequate case histories in violation of 21 CFR 312.1(a)(12)(6c).

C. Failure To Obtain Informed Consent

The Bureau alleges that Dr. Lippmann failed to obtain the informed consent of eleven subjects. It presented a great deal of evidence to show that patient signatures on study consent forms were different from signatures for the same persons on various hospital records. G-134-45. Mr. Nelson attempted to locate and interview twelve subjects to ascertain whether their signatures were genuine and whether their informed consent had

been obtained. T. II-6-9, G-133-45. Mr. Nelson testified that, of the twelve persons interviewed, ten did not recall participating in the study and stated that the signatures on the consent form were not theirs. Patient No. 26, in a signed affidavit, stated that the signature on the consent form was not his and that he was never asked to participate in a drug study during his hospitalization. G-134, pp. 9-10. T. II-9.

Also in a signed affidavit, patient No. 27 stated that the signature on the study consent form was not hers, that she did not remember reading a consent form or discussing a pain study during her hospitalization, and that she did not give her consent to try a new drug. This patient did identify her signature on the surgery consent form, which signature was significantly different from the signature on the study consent form. G-135, pp. 10-11, T. II-9-10.

Patient No. 29 also signed an affidavit to the effect that the signature on the study consent form was not his, that he did not have a middle initial (which appeared in the signature on the study consent form), and that he was not asked to participate in the study. G-136, pp. 12-13. T. II-11.

Patient No. 36 also signed an affidavit to the effect that the signature on the study consent form was not his, that the middle initial appearing on the form was not his, that no one discussed a drug study with him during his hospitalization, and

that he did not consent to participate in a study. G-137, pp. 9-10, T. II-11-12.

Patient No. 47 told Mr. Nelson that the signature on the study consent form was not his, that the signature on that form included the wrong middle initial, and that he did not use "Jr.," which appears in the consent form signature. G-138, pp. 13-14, T. II-12.

The Bureau adduced evidence to the effect that the consent forms for patient Nos. 50 and 54 were for the same patient. G-139 at 8-11. The patient agreed that one consent form does bear his signature but denied that the other form, which bears his signed name in other handwriting, bears his signature. T. II-12-14. However, the Bureau fails to support with evidence its argument that the patient's alleged mental impairment vitiates his valid consent.

Patient No. 62 signed an affidavit to the effect that the consent form signature is not his and that no one asked him to participate in a drug study. G-140, pp. 9-10, T. II-14.

Although he could not say whether the initials on the consent form were his, patient No. 67 stated that no one asked him to participate in the study and that he did not consent to do so. G-141, pp. 8-9, T. II-14.

Patient No. 68 stated that the signature on the study consent form was not hers and that she does not use the middle initial that appears on the form. Further, she stated that she was not asked to participate in the drug study. G-142, pp. 6, 7, 8 T. II-15.

Patient No. 79 stated that the signature on the consent form is not hers, that she signs her name, " not ," that the false signature misspells her last name, that no one had previously discussed this drug study with her, and that she did not consent to participate in it. G-143, pp. 10-11, T. II-15-16.

Patient No. 73 stated that the signature on the consent form attributed to her is not hers and that she had never before seen the consent form. G-145, at 8, T. II-17.

Dr. Lippmann presented no significant rebuttal to any of these allegations. Ms. , an associate in the firm of Hyman & Phelps, P.C., stated that she had interviewed three individual patients who either did not remember talking to Mr. Nelson or who did not remember signing an affidavit.

It is obvious that the signatures on the consent forms and on the affidavits provide convincing proof that these signatures are not those of the patients involved. Ms. 's statements are not an effective rebuttal to the allegations, which are well documented and completely convincing. The Bureau's evidence, on the other hand, is convincing. Therefore, I find that Dr. Lippmann failed to obtain informed consent for all of the above subjects in violation of 21 CFR 312.1(a)(12)(6g). These are extremely serious violations because they constitute the gravest kind of misrepresentation.

For all reported subjects, including the ones who denied signing consent forms, Dr. Lippmann attested by his signature to the following statement as it appears in paragraph 10 of each consent form:

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

Therefore, Dr. Lippmann attested that he personally obtained the consent and that he personally reviewed and explained the form to each subject. Despite this certification, Dr. Lippmann denied that he personally participated in the consent process or that he spoke to any of the patients. Instead, he said that he signed paragraph 10 on the consent forms in batches during meetings with the study nurse. In many instances, he said, he backdated his signature. T. II-153-6.

Therefore, I find that Dr. Lippmann falsely certified to the facts in paragraph 10, thus submitting false information to the sponsor. Dr. Lippmann counters that he was permitted to delegate the duty to obtain informed consent to his study nurse, Miss . True, he may delegate the duty to obtain informed consent, but he cannot delegate the responsibility for doing so. The existence of an agency relationship here is irrelevant. The

fact is that Dr. Lippmann certified that he himself had obtained informed consent, and that was a false certification.

D. Failure To Verify Participation In The Study.

The Bureau alleges that in two instances, patients reported to have been in the study were not at Hospital during the time when Dr. Lippmann reported that they were on the study at that hospital. G-16, 18. Also, in five additional instances, the Bureau alleged that no records could be found to the effect that five of the reported subjects were ever patients at the hospital at all. Finally, in nine additional instances, the Bureau alleges, patients were never asked to participate in the study. G-134-45.

With respect to patients Nos. 45 and 48, hospital records show that they were discharged home before study evaluations could have been completed.

In addition, Mr. Nelson testified that for five reported subjects of the study, patients No. 52, 69, 71, and 82, he was unable to find any hospital record that shows that they ever entered Hospital. T. II-32-40. Because these subjects were not identified in the Notice of Opportunity for Hearing, I am unable to take cognizance of these allegations insofar as my determination as to whether or not violations of FDA regulations occurred.

Circumstantial evidence proves conclusively that the absence of these records cannot mean that the hospital simply lost them.

, Assistant Director of the Medical Record Service at the hospital, signed an affidavit (G-162, pp. 25-31) to the effect that the surgical procedures described in the case report forms for these patients would have required hospitalization and assignment of a unique hospital patient number. Further, she stated that the hospital can retrieve records if an accurate name and date of birth are provided. She noted that the hospital is accredited by the Joint Commission on Accreditation of Hospitals, and that accreditation implies satisfactory record keeping. She concluded that the hospital's medical record system is accurate and well maintained.

Because hospital records are important parts of case histories, Dr. Lippmann failed to prepare and maintain adequate and accurate case histories. I find that, although an occasional record can be lost, the chances of losing an entire case history are small. The availability of other patient records at Hospital as attested to by Ms. and Mr. Nelson provides adequate evidence of the general trustworthiness of Hospital's record keeping. I would grant benefit of the doubt to Dr. Lippmann if only a record or two were

missing, but all evidence of the hospitalization of five subjects was absent. This record's absence is circumstantial evidence that Dr. Lippmann prepared case reports for patients that never existed. Therefore, Dr. Lippmann either 1) failed to prepare and maintain adequate case histories or 2) submitted false information to the sponsor in that the case report forms misrepresent patients as actual participants in the study when they were not. I find that the latter conclusion is more probably correct.

E. Failure To Chart The Study Drug .

For patients Nos. 11, 18, 20, 38, 48, 58, and 73, the Bureau alleges that Dr. Lippmann failed to record the administration of the study drug in the patients' hospital charts. Thus, he failed to prepare and maintain adequate case histories. The medication records and nursing notes for these subjects do not contain entries for the administration of a fact that Dr. Lippmann does not contest. Indeed, Dr. Lippmann admitted that he did not instruct his nurse to chart the study medication. T. II-145-6.

The importance of charting the patients' medication is to assure that medical staff know of potentially interfering or even life-threatening medication. Further, study personnel must bear the burden of carrying out this responsibility. T. I-141-2, 193-9; T. II-218-20.

Therefore, either Dr. Lippmann failed to chart the study drug or he did not administer the study drug at all. In either

case, he failed to prepare and maintain adequate and accurate case histories. If the drug was not administered, then Dr. Lippmann made false statements to the sponsor.

F. Conclusion for Study

For the reasons stated above, I find that Dr. Lippmann failed to keep adequate and accurate case histories in that he failed to report accurately concomitant or other medication; he failed to report accurately significant surgical information; he failed to verify participation in the study; and he failed to chart the study drug. In addition, he failed to obtain informed consent and, by signing paragraph 10, submitted false information to the sponsor.

The Bureau argues that these violations were deliberate within the meaning of United States v. Monday, 421 F.2d 1210 (7th Cir. 1970), cert. denied 400 U.S. 821, in that they were willful and showed a careless disregard for FDA's regulations. According to the Bureau's position, 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 reckless disregard for obvious or known risks. Dr. Lippmann argues for a much narrower definition of "deliberate," that is, having knowledge of and intent to violate the law. In my opinion in the Mok hearing (p. 6), I stated that a "deliberate" violation could include a reckless disregard for obvious or known risks. I reaffirm this definition. Dr. Lippmann, an experienced investigator, was

admittedly grossly negligent in his choice and supervision of a study nurse. Lippmann post-hearing memorandum at 4 and 15. Therefore, I agree with the Bureau that, with respect to the study, the violations were deliberate. Certainly, his signing of paragraph 10 of the consent forms (the making of a false report to the sponsor) constituted a deliberate violation within the meaning of Monday. The statement of Nurse to the effect that Dr. Lippmann had instructed her not to inform potential subjects of the risks or of the experimental nature of the study (G-154) is evidence of the deliberate nature of his failure to obtain informed consent even under a narrow definition of "deliberate." Therefore, with respect to the study, I find that violations involving failure to obtain informed consent were deliberate.

III. THE STUDY

The second study at issue is Dr. Lippmann's study, a phase-three, double-blind, single-dose parallel study designed to determine the relative analgesic efficiency of orally administered , Darvocet-N100, and placebo in patients with moderate to severe post-operative pain following back, abdominal, pelvic, chest, limb, or plastic surgery.

The Bureau's charges on the study closely parallel those which it brought for the study: (1) failure to report adequately and accurately concomitant or other medication in the case report forms; (2) failure to report adequately and accurately significant surgical information such as type of

surgery, date of surgery, or whether the surgery was performed at all; (3) failure to obtain informed consent; (4) the non-existence of appropriate patient hospital records by which study data could be validated; and (5) failure to chart in hospital records the administration of the study drug. As with the study, I will review each of these classes of allegations in turn.

A. Failure To Accurately Report Concomitant or Other Medication

The subject-selection criteria in the protocol for the cac study required that "aspirin, non-steroidal anti-inflammatory agents, and analgesics including propoxyphene, codeine, acetaminophen, and pentazocine will be discontinued approximately four hours prior to the study." The protocol also provides that

> Throughout the study, all concomitant medications such as nonsteroidal anti-inflammatory agents, salicylates, and analgesics, including propoxyphene, acetaminophen, codeine, hydroxyzine, and pentazocine will be excluded. If other conditions, present at the start of the study, require drug therapy during this study, those conditions and any concomitant medication prescribed will be recorded on the case report form in the "Concomitant Medication section." G-5 at 8.

The Bureau alleges that, for eleven of the fifteen subjects whose records were audited, Dr. Lippmann failed to report adequately and accurately concomitant or other medication:

1. Patient No. 10052: This patient received at 1030 on November 13, according to Dr. Lippmann's report, which

stated that the most recent post-operative analgesic was Tylenol #3 at 0600 on the same day. However, hospital medication show that the most recent post-operative analgesic was Tylenol #3, was administered at 0130 on November 9 and that Tylenol #3 was next given at 1300 on November 13. G-81, p. 6. Dr. Lippmann did not report the Tylenol #3 given at 1300 on November 13 as concomitant medication.

2. Patient No. 10053: This patient received at 0900 on November 14. Dr. Lippmann reported that the most recent precperative analgesic was Darvocet-N-100 at 0330 on the same day following which the patient was remedicated for pain with Darvocet-N-100 at 1400. G-82, pp. 1-2. However, hospital medication records show that the only Darvocet administered was at 1800. T. I-92-3.

3. Patient No. 10054: Dr. Lippmann reported that this patient received at 1000 on November 14 and that the most recent post-operative analgesic was Tylenol #3, given at 0400 of that day. Further, he lists as a concomitant medication. G-83, p. 1. However, the hospital medication record shows that Tylenol #3 was not given at 0400 but at 0630, less than four hours prior to administration of the study drug. Dr. Lippmann did not report that concomitant medication. Further, the hospital records do not show that the patient received G-83, p. 9; T. I-96-7.

4. Patient No. 10055: According to Dr. Lippmann, this patient received at 1200 on November 16, whereas the

most recent post-operative analgesic administered was Tylenol #3 at 0800 on the same day. The hospital's records, however, show that the patient was discharged the previous day and received no medication as an in-patient on November 16. G-84 at 5-6, 10; T. I97-101.

5. Patient No. 10056: The study case report form shows that this patient received at 0845 on November 16, that the most recent post-operative analgesic was Tylenol #3 at 0100 on the same day, and that the patient was later remedicated at 1350 with Tylenol #3. G-85, pp. 1-2. On the other hand, the hospital records show that Tylenol # 3 was only given at 1115 on November 16, 1978, less than three hours after administration of the study drug, and that, further, Demerol 50 mg. was given at 0030 on that date, thus making it a prior unreported concomitant medication. T. I-101-3.

6. Patient No. 10060: This patient received at 1200 on November 18, according to Dr. Lippmann, and received the post-operative analgesic, Talwin 50 mg. at 0730 that day. The patient was later given Talwin 50 mg. again at 1400. G-86, pp. 1-2. On the other hand, hospital records show that Talwin was not given the patient on November 18 at all, but that Tylenol #3 was given at 1125, less than an hour prior to the alleged administration of the study drug. Dr. Lippmann did not report the Tylenol #3 administration. G-86 at 1, 4-5.

7. Patient No. 10065: This patient received at 1100 on November 22, according to Dr. Lippmann, who also reported

that the patient received Tylenol # 3 at 0630 that day and later again at 1500. G-87, pp. 1-2. However, the hospital records do not show administration of Tylenol #3 at any time on that day. G-87, p. 6.

8. Patient No. 10081: Whereas the hospital records show that Tylenol #3 was given this patient at 0830, only two hours prior to Dr. Lippmann's reported time of administration of the study drug, Dr. Lippmann did not report that concomitant medication at all. T. I-109-10.

9. Patient No. 10091: This patient received at 1000 on December 15 according to Dr. Lippmann and received as a postoperative analgesic Tylenol #3 at 0430 that day and the patient was again given Tylenol #3 at noon. However, hospital records show that Darvocet NT was given at 0940, a mere twenty minutes prior to alleged administration of the study drug, and that Tylenol #3 was not given at any time on that date. Dr. Lippmann did not report the Darvocet administration. G-89 at 1, 16.

10. Patient No. 10102: Dr. Lippmann reported that this patient received at 0900 on January 2, 1979, and that the patient had received Tylenol #3 at 0030 and 1300. G-90 at 1-2. However, the hospital records show that the patient received Tylenol at 0030, 0800, and 1100. Dr. Lippmann did not report as the administration of Tylenol at either 0800 or 1100 as concomitant medication. G-90, pp. 1-2, T. I-14-15.

11. Patient No. 10126: This patient received at 1230 on January 23 and Tylenol # 3 at 0800 and again at 1730,

according to Dr. Lippmann. G-94 at 1-2. However, hospital medication records do not show that Tylenol #3 was given on January 23 at all but do show that the patient received Demerol 50 mg. at 0930 and Valium 5 mg. at 1100, but Dr. Lippmann did not report the administration of either Valium or Demerol. G-94 at 1, 5.

Dr. Lippmann did not seek to rebut any of these allegations. Therefore, with respect to the patients listed above, I find that Dr. Lippmann failed to keep adequate and accurate case histories. The records of Dr. Lippmann and those of the hospital differ markedly. Dr. Lippmann has failed to keep adequate and accurate case histories with respect to all of these patients and has submitted false information to the sponsor.

B. Failure to Report Accurately Significant Surgical Information

The Bureau alleges that, for seven of the fifteen subjects whose records were audited, Dr. Lippmann failed to report adequately and accurately significant surgical information such as type of surgery, date of surgery, and whether surgery was performed at all.

1. Patient No. 10052: For this patient, hospital records show that surgery took place November 14, whereas Dr. Lippmann reported surgery as taking place on November 10. Furthermore, the study drug was reportedly administered on November 13, the

day before surgery, indicating that the patient could not have been evaluated for pain post operatively. G-81, pp. 1, 14, 15, T. I-88-90.

2. Patient No. 10053: Whereas hospital records show that surgery was performed on November 4, Dr. Lippmann reported surgery on November 9 and the study drug having been administered on November 14. Dr. Lippmann's incorrect statement of the date of surgery makes the time of administration of the drug appear closer to that of surgery. G-82, pp. 1, 3, T. I-91.

3. Patient No. 10054: The hospital records for this patient show that surgery was performed on November 9, while Dr. Lippmann reported surgery as having occurred on the next day. G-83, pp. 1, 5, 6, T. I-95-6.

4. Patient No. 10065: Although Dr. Lippmann reported that this patient had surgery on November 19, there is no evidence in the hospital records showing surgery for this patient on that date. Rather, the hospital's recovery room log records the patient as having had surgery on November 21. G-67, p. 7, T. I-107-8.

5. Patient No. 10091: Hospital records for this patient show that surgery was performed on December 18, but Dr. Lippmann reported surgery as occurring on December 14. Moreover, Dr. Lippmann reported having administered the study drug on December 15, showing

evaluated for pain post operatively. G-89, pp. 1, 3, 4, T. I-111-12.

6. Patient No. 10102: Dr. Lippmann reported this patient as having had surgery on December 31, but hospital records show that the patient was not admitted until the next day. Furthermore, hospital records do not show that surgery was ever performed on this patient. G-90, pp. 1, 3, T. I-113-4.

7. Patient No. 10104: This patient had surgery on December 30, according to Dr. Lippmann, but the hospital records show that surgery had been performed ten days previous to that and that the patient was discharged on December 23. Moreover, the study drug was reportedly administered on January 2, ten days after the discharge date. G-91, pp. 1, 5, 10, 11.

As with most of the Bureau's allegations, Dr. Lippmann did not attempt to reconcile the discrepancies concerning the dates of surgery for the seven patients which reportedly exist between the hospital records and his reports. Therefore, with respect to all of the above patients, I find that Dr. Lippmann failed to maintain adequate and accurate case histories. Furthermore, I find the discrepancies between Dr. Lippmann's case report forms and the hospital records to be so serious as to call into question whether these patients ever actually participated in the study. At the very least, Dr. Lippmann has failed to prepare and maintain adequate and accurate case histories and has supplied false information to the sponsor. Because of the widespread

nature of the discrepancies, I do not accept the argument that the hospital records are wrong and Dr. Lippmann's are correct.

C. Failure To Obtain Informed Consent

The Bureau alleges that Dr. Lippmann failed to obtain the informed consent of eight patients. Mr. Nelson testified that all of the eight patients he interviewed either did not recall participating in the study or stated that the signatures on the study consent form were not theirs.

Patient No. 10055 signed an affidavit to the effect that the signature on the consent form was not his, that he did not have a middle initial (one appeared on the consent form), that he did not recall participating in the study, and that he was unable to take capsules after surgery because his jaw was wired shut. G-146, pp. 15, 16, T. II-20-1. Ms. testified that , patient 10055, told her that he neither remembered being visited by an FDA investigator nor signing an affidavit for an FDA investigator. T. III-5, 6.

Patient No. 10076 stated that he had never before seen the consent form that Mr. Nelson showed him and that he did not recall participating in the study. However, he could not positively state that the initials appearing on the consent form were not his. G-147, p. 12, T. II-21. Ms. testified ., patient 10076, told her that he remembered the FDA investigator but did not remember whether or not he signed an affadavit for the investigator. T. III-6.

Patient No. 10079 stated that no one discussed the study or the consent form with her and that she did not give her consent, although the consent form bears the notation by Dr. Lippmann to the effect that both arms were "casted" and that the patient was unable to sign. G-148 at 4. However, the patient told Mr. Nelson that she did have the use of her fingers and could have signed her name at the time. G-148, pp. 10, 11, T. II-21-2.

Patient No. 10081 stated that the signature on the consent form was not hers and that she did not recall reading the consent form or discussing it with anyone or even being on the drug study. G-149, pp. 10, 11, T. II-22.

Patient No. 10084 stated that she verbally agreed to participate in the drug study, but signed an affidavit to the effect that the signature on the consent form is not hers. G-150, pp. 11, 12, T. II-22-3.

Also in a signed affidavit, patient No. 10088 stated that the signature on the consent form was not his, that he had never before seen the form, that he did not recall discussing the drug study with anyone during his hospitalization, and that he did not consent to participate in it. G-151, p. 8, T. II-23-4.

Patient No. 10104 likewise denied that the signature on the consent form was his, that he had ever seen the consent form, that anyone had ever discussed the study with him, and that he

had agreed to participate in a study. The patient also stated that he was discharged from the hospital on December 23, whereas the consent form is dated January 2. G-152, pp. 7, 3, T. II-24. The hospital's discharge notes show that he was discharged on December 23. G-152, p. 12.

Patient No. 10115 signed an affidavit stating that the signature on the consent form was not hers, that she never saw the consent form, that no one had discussed the study with her, and that she did not consent to participate in a drug study. G-153, p. 10, T. II-24-5.

Ms. 's attempt, on Dr. Lippmann's behalf, to contact the eight patients, although successful in two instances, did not produce information sufficient to refute the affidavits subscribed to and sworn before Kenneth Nelson.

Therefore, I find that Dr. Lippmann failed to obtain informed consent of these eight patients in violation of 21 CFR 312.1(a)(13)(4g). As with the study, he made false statements in the certification paragraphs of all of the consent forms regarding his role in the consent process (see discussion at pp. 14-15).

D. Failure To Verify Participation In The Study

In three instances, the Bureau alleges, patients were not at Hospital at the time that Dr. Lippmann reported that they were in the hospital and on the study. In nine

additional instances, the Bureau alleges that, after a thorough and good faith search, no hospital records could be found that showed that the subjects were ever in the hospital. In six additional instances, the Bureau alleged that the patients were never asked to participate in the study. These patients were as follows:

1. Patient No. 10055 received the drug on November 16 according to Dr. Lippmann, and gave written consent on the same day. However, hospital records show that he was discharged from the hospital the day before. G-146, pp. 5, 11, T. I-99-100.

2. Patient No. 10104 received the study drug on January 2 and gave written consent on the same day, according to Dr. Lippmann. However, the hospital records show that he was discharged from the hospital on December 23. G-152, pp. 3, 4, 5, 12, T. I-115-6.

3. Patient No. 10106 received the study drug at 1445 hours on January 3 with observation for two hours thereafter, but hospital records show that he was discharged home with no medication at 1500 hours on the same day and that the last time of administration of medication was at 1000 hours. G-92.

Mr. Nelson searched the hospital records for nine reported subjects: patients Nos. 10071, 10073, 10075, 10085, 10090, 10092, 10094, 10096, 10097. Unlike the study, the case report forms identify subjects by both name and hospital number, and Mr. Nelson searched for the hospital

records by both means of identification. T. II-33, 42. Mr. Nelson stated that he requested and obtained from the Medical Records Department hospital charts corresponding to the hospital numbers reported in Dr. Lippmann's case report forms. In every case, he said, the chart showed that the hospital number belonged to someone other than the person described in the case report form. G-157, pp. 5, 6, 7, T. II-42-5. In six of the nine instances, Mr. Nelson testified that even the sex of the person whose chart was provided was different from the sex of the person whom Dr. Lippmann reported as a subject with that hospital number.

As with most of the allegations, Dr. Lippmann has attempted no refutation, nor has he attempted to show that any of these nine patients existed.

Finally, Mr. Nelson testified to having interviewed six patients who stated that they did not give their informed consent and did not participate in the study (patients Nos. 10055, 10076, 10079, 10088, 10104, 10115).

Therefore, with respect to all of the patients discussed in this section, I find that Dr. Lippmann failed to prepare and maintain adequate and accurate case histories. Again, as with the study, I find that it is necessary to the adequate maintenance of case histories to assure the existence of hospital records for the patients allegedly participating in the study or at least to explain why these records are absent. (See

Gelfand hearing decision, pp. 8-9.) I also find that, by failing to obtain informed consent while purporting to do so and by submitting consent forms with apparently forged signatures, Dr. Lippmann submitted false information to the sponsor.

E. Failure To Chart The Study Drug

As with the study, the Bureau alleged that Dr. Lippmann failed to prepare adequate and accurate case histories in that he failed to record in the patients' hospital charts the administration of the study drug (patients Nos. 10052, 10053, 10054, 10055, 10060, 10065, 10081, 10091, 10102, 10104, 10106, 10115, and 10126.) As with the study, I find that it was Dr. Lippmann's obligation to assure that administration of the study drug was reflected in the hospital records of each patient who received it.

F. Conclusion: Study

Therefore, with respect to the study, I find that Dr. Lippmann failed to prepare and maintain adequate and accurate case histories in that he failed to report accurately concomitant and other medication; failed to accurately report significant surgical information; failed to verify patient participation in the study; and failed to chart the study drug. Also, I find that Dr. Lippmann failed to obtain informed consent as required by 21 CFR 312.1(a) and that he submitted false information to the sponsor when he submitted the case report forms which did not include concomitant medication and had erroneous dates of surgery and administration of the drug, and falsified informed consent forms.

IV. ASSURANCES

Dr. Lippmann has reported the following actions and given the following assurances:

1. He has replaced Ms. with a different nurse observer who, he states, is "professional in every sense of the word ...." T. II-185.

2. He examines the hospital records of patients to verify the accuracy of information on case report forms.

3. Dr. Lippmann personally selects the patients who are asked to participate in the study.

4. He explains the study and obtains the patient's signature on the consent form. T. II-186.

5. He signs the informed consent form twice--once as witness to the patient's signature and once as clinical investigator attesting to his explanation of the nature of the study to the patient.

Dr. Lippmann states that he continues and will continue to delegate to the study nurse certain tasks such as drawing of blood, charting of medication, rating pain severity, and completing case report forms. T. II-187-8. In addition, Dr. Lippmann contends that he has implemented all of the steps suggested by Dr. in the latter's testimony at the hearing. T. II-244. Dr. Lippmann contends that, given the measures he has taken and promises to take, it is highly unlikely that the violations that I have found occurred in the and studies would occur again. Dr. Lippmann points to the parenteral studies as evidence that he can be a

thorough and diligent clinical investigator. Without hesitation, he blames his study nurse for all violations and recognizes, he says, that reliance on her was a mistake and a result of "overdelegation of responsibility." Lippmann brief at 15. He promises that this delegation will not occur again.

V. DISCUSSION

It is important to remember that, whereas the Bureau has the burden of proof of showing that violations of the FDA IND exemption regulations occurred, the investigator has the burden of proof of showing the adequacy of assurances. Under 21 CFR 312.1(c)(2),

> 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 this 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 ... that the investigator is not entitled to receive investigational-use drugs ....

Thus, if an investigator's assurances are adequate, the Commissioner may not disqualify him. However, the regulations do not say that assurances must be taken at face value because the word, "adequacy," is a broad term which allows the Commissioner to consider many factors such as the seriousness of the violations that the investigator committed as that reflects on his credibility and the sincerity with which the assurances are offered.

I consider the following facts paramount in my recommendations:

1. Based upon the evidence and testimony presented, Dr. Lippmann has not persuaded me that all of the blame (much less the responsibility) can be placed on his nurse. Without either the active encouragement or the tacit approval of Dr. Lippmann, it is unclear what motive Ms would have had to produce fraudulent studies such as the and studies were. Not only were signatures on consent forms apparently forged, but corroborative evidence of the existence of some alleged subjects was missing altogether.

2. Dr. Lippmann's many false statements made when he signed paragraph 10 for each of the consent forms constitute serious violations. This conclusion would obtain even if I were to assume that he really believed that he was telling the truth in signing the statements.

3. Nurse stated to Mr. Nelson that Dr. Lippmann had instructed her not to inform potential subjects of the risks or of the experimental nature of the drug study. G-154. Even though I understand that Nurse may have been making a self-serving exculpatory statement to avoid any blame, I still credit the statement somewhat in light of the fact that it is consistent with what we know about the way that these studies were conducted.

4. In my judgment, Dr. Lippmann's attitude toward obtaining informed consent in the and studies not only

compromised the integrity of the study but actually presented a danger to the patients and infringed upon their rights to know that they were being given experimental drugs.

5. Dr. Lippmann points with pride to his parenteral study as evidence of the fine work that he is capable of doing. However, an audit of this study by the sponsor, , found instances where Dr. Lippmann failed to report a patient's history of alcoholism, failed to chart administration of the study drug, failed to report concomitant medication, and failed to document the obtaining of informed consent. These irregularities closely parallel problems that we have seen in greater abundance in the studies under consideration here. Also, as with these two studies, some records were not available during audit. G-164.

VI. RECOMMENDATION

Therefore, I am recommending to the Commissioner that Dr. Lippmann be disqualified from receiving investigational-use drugs. I conclude that Dr. Lippmann's assurances are not adequate; that he made many false statements to the sponsor; that, by failing to obtain informed consent, he endangered the safety of his patients; and that he is responsible for two fraudulent studies. Dr. Lippmann must accept the responsibility and blame for the violations of FDA's regulations.

Respectfully submitted

Stuart L. Nightingale, M.D.
Presiding Officer

Dated: