

Acting Associate Commissioner for Health Affairs, HFY-1

Report of a Disqualification Hearing for John H. Hopkinson III, M.D.--  
Recommendation for Action

The Commissioner

Through: The Deputy Commissioner \_\_\_\_\_

SUMMARY

This document is the Report of the Presiding Officer in the Part 16 hearing concerning the eligibility of John H. Hopkinson III, M.D., to receive and use investigational new drugs. Based on the record of the hearing, I recommend that Dr. Hopkinson be found ineligible to receive and use investigational new drugs.

BACKGROUND

In 1976, Dr. John H. Hopkinson III, (sometimes referred to hereafter as "respondent") participated in two multiple-dose clinical studies. One of the studies involved an investigational new drug, \_\_\_\_\_ and was sponsored by \_\_\_\_\_ the other involved

\_\_\_\_\_ and was sponsored by \_\_\_\_\_

In October 1976, Dr. Hopkinson submitted a Form FD-1572 to \_\_\_\_\_

the sponsor, Ortho, as a condition for conducting clinical pharmacology testing with [redacted] It is not clear why Dr. Hopkinson signed and

submitted a Form FD-1572 instead of an FD-1573 prior to conducting the study. The [redacted] study was designed as a clinical trial and an

FD-1573 should have been submitted. The Bureau charges, however, address conditions agreed to by an investigator as listed in an

FD-1573. The requirements set forth in FD-1572 and FD-1573 do not differ in substance with regard to the conduct of the study. In any

case, Dr. Hopkinson was required to comply with the conditions of the exempting regulations for the kind of study he was doing. Thus, he was

bound by the conditions set out in Form FD-1573, whether or not he signed that form. (Neither a Form FD-1572 nor a Form FD-1573 for the

[redacted] study was submitted for the record.) The monitor of these

studies was

In November 1978 and July 1979, FDA investigators conducted an inspection of Dr. Hopkinson's study. Prior to inspection, FDA

personnel asked Dr. Hopkinson to make patient records and case report forms (CRFs) for the [redacted] and [redacted] studies available. The

record shows that Dr. Hopkinson fully cooperated with FDA inspectors.

The FDA inspectors reviewed patient records (also known as patient charts) and CRFs and compared entries on the CRFs to entries in the

medical records. A subject's medical record could include patient records and charts, nurses notes, pharmacy drug orders, etc. During

the inspection, FDA investigators found what they believed to be

several significant violations of the FDA regulations governing

clinical investigations. Dr. Hopkinson was informed of the results of the investigation by letter in December 1979 and was offered an

opportunity for an informal conference.

In February 1980, an informal conference took place. According to the memorandum of the informal conference, Dr. Hopkinson explained that he had delegated complete responsibility for the \_\_\_\_\_ and \_\_\_\_\_ studies to his residents. He attributed every regulatory violation discovered by FDA investigators to his misplaced trust and confidence in the residents who performed the study and to the monitor of the study-

Dr. Hopkinson noted that he did not know of any errors in the case report forms or in his conduct of the study, in general, until he received the invitation to the informal conference.

The memorandum of the meeting notes that Dr. Hopkinson did not refute any findings of FDA investigators.

In April 1980, Dr. Hopkinson was provided a notice of opportunity for a hearing on the basis that his explanation at the informal conference was insufficient and bespoke an inappropriate attitude and approach for an investigator of investigational new drugs. In May 1980, Dr. Hopkinson requested a hearing. The date was set for September 4, 1980. Dr. Hopkinson subsequently requested that the hearing not be commenced until mid-October 1980. The hearing was held on October 14, 1980, November 5, 1980, and January 14, 1981. Dr. Hopkinson requested that the hearing be closed, and was granted the request.

The Bureau of Drugs presented charges individually with respect to each study cited. The Bureau's testimony regarding the \_\_\_\_\_ study was presented by Dr. Michael Hensley, who conducted the inspection of Dr. Hopkinson's data. The charges regarding the \_\_\_\_\_ study were presented by Dr. Gurston Turner, who conducted the inspection of

Dr. Hopkinson's data. Drs. Hensley and Turner compared information entered on patient charts, pharmacy orders, nurses reports and other documents from each subject's medical records to entries on case report forms (CRFs) submitted by Dr. Hopkinson. The Bureau offered 10 exhibits to support these charges. The testimony and cross-examination regarding charges on the study were conducted during the first two days of the hearing. The charges were discussed during the third day of the hearing.

After the conclusion of the Bureau's testimony on each specific study, Dr. Hopkinson's attorney cross-examined the Bureau's witnesses. Following the completion of the Bureau presentation, Dr. Hopkinson's attorney asked that I conclude that the Bureau had not met its burden of showing that Dr. Hopkinson should be disqualified. I explained that I was reserving that judgment until the completion of the hearing and a review of the written record and testimony.

Dr. Hopkinson's attorney called Dr. Frances Kelsey as the first witness. Dr. Kelsey did not wish to testify and I refused to require her to testify. Dr. Hopkinson then testified in his behalf. He presented 2 exhibits for the record.

The hearing closed with summary statements from both attorneys. I offered both parties the opportunity of making post hearing submissions. Both sides submitted post hearing submissions. Both sides were provided with copies of the three volumes which constitute the transcribed record of the hearing and both submitted lists of corrections (mostly typographic) to the transcript. These corrections were made.

Preliminary Issues

During the course of the hearing and in the respondent's post hearing memorandum, Dr. Hopkinson's attorney presented several due process issues for my consideration. Dr. Hopkinson's attorney stated that the Bureau of Drugs repeatedly failed to comply with the provisions of 21 CFR §16.24(g), which require that the parties, at least one day before the hearing, provide to each other written notices of any published articles or written information to be presented or relied on at the hearing. The respondent felt that the Bureau of Drugs made copies of selected parts of case report forms and patient records for both studies available to Dr. Hopkinson, while the charges that the Bureau was attempting to make related to information that appeared on pages of the medical records or case report forms which the Bureau turned over after the hearing had commenced.

21 CFR §16.24(g) states, "FDA and the party requesting the hearing will, if feasible, at least 1 day before the hearing provide to each other written notice of any published articles or written information to be presented at or relied on at the hearing. A copy will also be provided in advance if the other participant could not reasonably be expected to have or be able to obtain a copy. If written notice or a copy is not provided, the presiding officer may, if time permits, allow the party who did not receive the notice or copy additional time after the close of the hearing to make a submission concerning the article or information." (Emphasis added.) I note that the copies in question

should have been provided at least one day before the hearing, but only if "the respondent could not reasonably be expected to have or be able to obtain a copy."

Thus, there are two elements to the requirement of this regulation. First, notice must be provided. Second, a copy must be provided if the other participant could not reasonably be expected to be able to obtain a copy. Here, through what the Bureau describes as clerical error, only the first pages of case report forms were provided to Dr. Hopkinson's counsel prior to the hearing. I believe it was or should have been obvious to Dr. Hopkinson's counsel that the Bureau intended to rely on more than those first pages. Thus, despite the clerical error,<sup>1</sup> I find that Dr. Hopkinson was provided sufficient notice of the material on which the Bureau intended to rely at the hearing.

Because the full CRFs that were not provided were obtained through Dr. Hopkinson, I believe it is fair to conclude that Dr. Hopkinson could reasonably have obtained full copies.<sup>2</sup> Therefore, in the absence of any evidence to the contrary, I find that Dr. Hopkinson could have obtained copies of the full documents. Accordingly, I do not find a violation of 21 CFR §16.24(g) in this incident.

---

<sup>1</sup> Dr. Hopkinson does not argue that there was bad faith on the part of the Bureau in this instance.

<sup>2</sup> Also it seems clear that Dr. Hopkinson's counsel could have obtained full copies simply by asking the Bureau for them at the point when counsel realized that the full documents had not been provided. Dr. Hopkinson's decision not to ask for the full CRFs from the Bureau or to produce them himself apparently reflected a tactical judgment by his counsel that his cause was better served by contending that the Bureau had not proved its case than by an attempt to show that the Bureau's allegations were wrong.

Dr. Hopkinson's attorney also argued that Dr. Kelsey's refusal to testify and my unwillingness to order Dr. Kelsey to testify as a condition of her employment detracted from the fair hearing that should have been provided Dr. Hopkinson. Furthermore, he argued that the Bureau's failure to present Dr. Kelsey as a witness denied Dr. Hopkinson the right to confront his accuser.

Dr. Hopkinson's arguments on this issue are unconvincing. There is no more right to have Dr. Kelsey as a witness simply because she initiated the action by a letter stating charges or because she had supervisory responsibility for the investigation of Dr. Hopkinson than there would be, in a judicial enforcement action, to call FDA enforcement officials or the FDA Chief Counsel, who initiates for the agency court cases brought on its behalf. What is relevant in this proceeding is not the reasons why the Bureau sought to disqualify Dr. Hopkinson, but rather whether there is a basis for that disqualification.

Dr. Hopkinson's counsel states in his post-hearing brief that he intended to question Dr. Kelsey about whether she or the Bureau had issued prior warnings to Dr. Hopkinson. That is information that obviously could have been elicited from Dr. Hopkinson himself. Dr. Hopkinson's counsel also wished to inquire whether lesser sanctions than disqualification had been considered and, if so, why they were rejected. The contention that such questioning must be allowed is analogous to a contention in a court case that either the recommending enforcement officials or the prosecuting United States Attorney should be subjected to questioning concerning the exercise of discretion in

choosing to initiate a case. Neither a fair hearing nor the right to confront one's accuser requires such testimony. Nor do those concepts require testimony concerning the other subject about which

Dr. Hopkinson's counsel wished to inquire, i.e., whether Dr. Kelsey still supported the charge outlined in her letter "in light of the fact that more than half of the specifications were clearly unproven or erroneous" (Hopkinson Post-Hearing Brief ("PHB") at 47). Again, the analogy to court proceedings, in which a recommending or prosecuting official would not be required to respond to this type of questioning, is persuasive. There is thus no basis for Dr. Hopkinson's contentions on this subject.

Dr. Hopkinson's attorney also suggested that the presiding officer of a Part 16 Hearing is not assisted by a clear definition of what constitutes a sufficient degree of dereliction or wrongful action to warrant disqualification. The respondent argued that the "repeated or deliberate" charge does not provide standards by which the Part 16 Hearing should be conducted.

The Bureau has interpreted the term "deliberately" to mean "willfully" or "intentionally," and cites a definition in which "willfulness" includes "reckless disregard for the law's requirements" and "closing of the eyes or deliberate indifference or refusal to be informed" United States v. Ottley, 509 F.2d 667, 672 (2nd Cir. 1975). The Bureau interprets "repeatedly" to mean more than once.<sup>3</sup>

I agree with the Bureau's interpretation of repeatedly to mean more than once. I do not interpret the regulation as allowing an investigator any number of violations in one study so long as he does not repeat those violations in another investigation.

A more difficult question is raised by the term "deliberate" in the regulation. There is, so far as I am aware, no instructive precedent in the Commissioner's decisions in previous disqualification proceedings that would help define this term. I did, however, address this issue in my report to you concerning the disqualification hearing for Dr. Martin Mok.

---

<sup>3</sup> During his testimony (Tr. Volume III, page 102), Dr. Hensley discussed the standards used by Bureau investigators with respect to the interpretation of "repeatedly and deliberately":

The prevailing standard would appear to be "repeatedly" means more than one study, in other words, observing violations within more than one study. Cases have, however, gone through and actions have been brought against physicians on the basis of one study. In those particular instances 'repeatedly' was held to mean within a study. In those instances, however, there was I believe uniformly also--there was also acts or apparent acts of commission on the part of the clinical investigator.

With respect to the word "deliberately" I go back to a hearing that I participated in in 1977 wherein a member of general counsel offered a definition of deliberate. His definition was that a deliberate act may be one of commission or one of omission.

The term "deliberately," as applied to the disqualification of clinical investigators, was used when the regulation dealing with investigational new drugs was first published on January 8, 1963, 28 Fed. Reg. 179, 182. The word did not appear in the proposal to that regulation, 26 Fed. Reg. 7990, 7992 (August 10, 1962); there is no explanation of the term in the short preamble to the final rule. Thus, this term is open for interpretation.

There are two possibilities. First, deliberate could be interpreted to mean intentional, or as involving a knowing intention to violate the regulations. Second, the term could be interpreted to encompass the concept of "reckless" disregard for the regulations' requirements. The latter definition, which has also been described as "closing of the eyes or deliberate indifference or refusal to be informed," United States v. Ottley, 509 F.2d 667, 672 (2nd Cir. 1975), comes from the criminal law's definition of the term "willfully" as that term appears in various statutes. The term "deliberately" has been viewed by courts as equivalent to "willfully," see, e.g., Wehr v. The Burroughs Corporation, 619 F.2d 276, 283 (3d Cir. 1980); Soweco, Inc., v. Shell Oil Co., 617 F.2d 1178, 1193 (5th Cir. 1980); United States v. Gregg, 612 F.2d 43 (2nd Cir. 1979).

In the report concerning Dr. Mok, I defined deliberate to include both of these concepts, as follows: "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" (Mok report at 6). Based on the purpose of the regulation, i.e., to protect

patients and the quality of drug research by assuring that deviations from the regulations do not occur, I believe that it is, as I stated in the Mok report, appropriate to interpret "deliberately" to encompass violations of the regulations that are in "reckless disregard" of the regulations' requirements. Because the question is unsettled, however, I will make alternative findings with respect to the deliberateness of any violations covering both interpretations of the term "deliberate."

One of Dr. Hopkinson's basic contentions has been that information entered on the CRFs may be more reliable than that entered on the subject's medical records. I would like to address this question before considering any of the specific examples.

Dr. Hopkinson argues that the entries on the medical records could be made by "numerous people, such as ward nurses. . ." who were ". . . not specifically trained to participate in [clinical] studies." The respondent notes that "errors in routine hospital records are not uncommon as Drs. Turner, Hensley and Hopkinson agree" (Hopkinson PHB 24-25). The respondent argues that the residents who completed the CRFs were specifically paid for conducting the studies and could do so with greater attention than nurses. The respondent argues that the benefit of the doubt as to which of the two records (the medical records or the CRF) is accurate should go to Dr. Hopkinson.

Although these inconsistencies do raise questions, they do not demonstrate that Dr. Hopkinson either repeatedly or deliberately submitted false information to the sponsor or that he repeatedly or deliberately violated FDA's regulations. Id. at 25.

The Bureau characterizes Dr. Hopkinson's contention that the information entered on the CRFs ought to be considered as reliable as that entered on the patient charts as disingenuous and preposterous (Bureau PHB at 26-27). The Bureau further states that "if [Dr. Hopkinson] were as unfamiliar with the records as he admitted he is, he can't possibly know which set of records is more reliable." During cross-examination (Tr. Vol. III at 254-255), the question of reliability of patient charts and CRFs was discussed.

Mr. Blyveis: But I gather then that your opinion is that between the patient charts and the case report forms the charts are more reliable?

Dr. Hopkinson: I didn't say that at all.

Mr. Blyveis: What would you say?

Dr. Hopkinson: I said you have to use both of them. Many times the case report form is more reliable than the chart because of the interpretation of the person interpreting the chart. . . .

Whether or not the medical records or CRFs are more reliable depends on the drug administration procedures routinely used at the

as well as the procedures developed by Dr. Hopkinson for the conduct of the studies. There was no concise testimony on how entries on the CRFs were made. In response to a questioning, Dr. Hopkinson testified as follows (Tr. Vol. III at 217-218):

Mr. Blyveis: Was anything written on the case report forms while the study was going on or was the study completed before anybody started filling in the case report forms?

Dr. Hopkinson: Once the individual patient had completed the study, then the case report form was filled out. They took the necessary history information first; then the patient got the medication and then the patient was evaluated.

Dr. Hopkinson also testified that for the study

Dr. added information to the CRFs once the patient finished the 24-hour time requirement.

Both the studies discussed were 24-hour studies. It seems reasonable to conclude that at least some of the entries on the CRFs were based on information on patient charts as entered by nurses or residents. If this were not the case, entries on the CRFs would have had to be made each time a drug was administered to the subject and, unless the resident was present 24 hours, the entries on the CRFs would have been made by nurses. Dr. Hopkinson testified otherwise.

Dr. Hopkinson suggests that the inconsistency in recordkeeping may be the result of inaccurate reporting in the subject's medical records. The medical records would be the responsibility of the hospital, but not necessarily Dr. Hopkinson's responsibility. I cannot discount totally the possibility that the medical records may be wrong and the CRFs may be right. Records kept in the normal course of business at a

hospital are, however, entitled to some presumption of accuracy. (That presumption would allow such records to be admitted into evidence in a court case despite their status as hearsay.) I agree with Dr. Hopkinson's testimony that both the patient charts and the CRFs need to be used to determine the reliability of data. This is, in fact, what FDA inspectors did during the conduct of the inspection. It is the inconsistencies in the records that are troubling and suggests that at least one of the records is inaccurate. It may be that the inconsistencies could have been explained by a written comment by the resident. However, this was not usually the case. In general, I have found, on the basis of the evidence I have seen, that the medical records are accurate and the CRFs are inaccurate in those instances where they conflict. My opinion is bolstered by the fact that Dr. Hopkinson did not submit any evidence that would show that the medical recordkeeping at the hospital was inaccurate. In any case, I find that failure to provide in the CRFs an explanation of why the CRFs varied from the medical records would render recordkeeping inadequate.

#### Charges brought by the Bureau of Drugs

The charges, as set forth in Dr. Kelsey's letter of December 21, 1979, were modified at the outset of and during the hearing. The modifications consist of withdrawal of specific examples of alleged violations of the regulations. No reason was given by the Bureau of Drugs for the withdrawal of specific allegations at the outset of the hearing. In its Post-Hearing Brief, the Bureau explained that it had

withdrawn other specific allegations where Dr. Hopkinson's counsel had uncovered inaccuracies in the Bureau's data during the course of the hearing (Bureau PHB at 15). The charges relating to the study were modified at the outset of the third day of hearings.

Exhibit G5 outlines all charges, and supporting allegations, as modified by the Bureau of Drugs at the outset of the second day of the hearing as they related to the study. The charges addressed here in my report are those specified in Dr. Kelsey's December 21, 1979, letter. I address individually the examples the Bureau cited in support of its charges. I also point out the specific examples of alleged violations which have been withdrawn.

The charges as they related to the two studies are presented and discussed separately.

Charges related toStudyCharge #1: Failure to maintain adequate and accurate case histories  
(312.1(a)(13) Item 4.c)

"The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the drug or employed as a control in the investigation."

The Bureau presented thirty-four examples of its allegations.

Charges Involving the Study  
(Thirty-four specific allegations identified by patient number)

## Unreported Prior Analgesia (4):

2 - Darvon with aspirin	13 - Darvon with aspirin
12 - Darvon with aspirin	19 - Darvon with aspirin

## Unreported Concomitant Analgesia (8):

1 - Demerol	12 - Darvon with aspirin
5 - Tylenol with codeine	13 - Darvon with aspirin
6 - Tylenol with codeine	17 - Tylenol with codeine
7 - Darvon with aspirin	19 - Tylenol

## Unreported Symptomatic Treatment (14):

1 - Nupercainal	9 - Nupercainal
2 - Nupercainal	9 - Sitz bath
5 - Dermoplast	12 - Nupercainal
6 - Sitz bath	12 - Sitz bath
7 - Sitz bath	13 - Nupercainal
7 - Dermoplast	13 - Sitz bath
7 - Ice packs	17 - Ice pack

Inaccurate Medical History (8):

- 1 - 4th dose separated by 36 hours from 3rd
- 2 - natural birth vs. epidural anaesthesia
- 2 - inaccurate reporting of time of birth
- 5 - unreported probable adverse effect
- 7 - misrepresentation of reason for stopping study
- 12 - unreported urinary retention
- 14 - unreported CNS adverse effect
- 19 - unreported fever

All allegations involving subjects 9 and 13 (6 specific instances) were withdrawn at the onset of the hearing. Six other specific examples were withdrawn at the onset or during the hearing. The Bureau presented CRFs and medical records for the subjects cited and the testimony of Dr. Michael Hensely in support of the remaining 22 charges. The charges, Dr. Hopkinson's response, my discussion and my findings are presented below.

- Four subjects received unreported prior analgesia (2, 12, 13 and 19)

The charge regarding subject 13 was withdrawn.

Dr. Hopkinson's Response

The respondent argued that for subjects 12 and 19, the absence of an entry of prior analgesia administration was not a protocol violation and that the validity of the study was not affected. The respondent showed that the CRF for subjects 2 and 12 showed entries mentioning Darvon as a prior drug administration.

### Discussion

In the case of subject 2, as the respondent pointed out during cross-examination, the CRF stated that when the test drug failed, the subject resumed prior medication of Darvon with aspirin. However, that reference to the Darvon with aspirin administration did not specify when the Darvon with aspirin had been administered, and whether it was prior to the test or was concomitant administration. Therefore, although reference to the Darvon was made in the CRF, the reference does not provide enough information to make it useful.

The box marked "none" had, in fact, been checked on the CRF for subject 2 at the point where prior medication should have been identified. The CRF for subject 12 showed only one of three prior administrations of Darvon with aspirin and did not list the administration closest to the test itself.

The respondent's argument that administration of the prior analgesia was not a protocol violation does not address the charge. The Bureau was not charging that the drug should not have been given, as the protocol allows for a 3 hour wash-out period. Instead the charge is that the administration of analgesia prior to the test should have been reported accurately. Although entries showing that prior analgesia was administered are present in the CRF, the correct time of administration is not noted.

Findings

The three examples that were not withdrawn support the Bureau's charge.

Conclusions related to the Prior Analgesia Allegations

The allegation that subjects received unreported prior analgesia is supported for three of the four subjects originally cited. For these three the Bureau showed that prior analgesia was administered, but was not accurately reported.

- Eight subjects received unreported concomitant analgesia (1, 5, 6, 7, 12, 13, 17, 19)

The charge as it pertains to subject number 13 was withdrawn at the outset of the hearing. The charge with respect to subject number 19 was withdrawn after cross-examination (Tr. Vol. III, page 188).

Dr. Hopkinson's response to the charge related to subject 1

The respondent argued that two separate dose administration series of the test drug were given to the subject. In the Post-Hearing Brief (PHB at 28), the respondent stated:

Although the CRF did not precisely reflect the events, the subject did receive four consecutive doses of the study medication without concomitant medication or interruption.

### Discussion

It is impossible to tell with certainty what happened with respect to this subject. Probably there were two separate series of test medications so that the medication alleged to have been concomitant was administered after the first series and before the second. If this is so, the dates on the CRF are in some places inaccurate.

### Findings

The unreported concomitant analgesia allegation is not supported by the records concerning subject 1. The medical record does not show that the allegedly concomitant medication was administered at any time during the full sequence of test drug administration, i.e., the second series. The appearance of concomitant medication seems to be a result of unclear reporting on the CRF.

### Dr. Hopkinson's response to charges related to subjects 5, 6, 7, 12 and 17

The respondent argued that each of the alleged unreported concomitant medications were administered either toward the end of the study or after the final dose of medication was given. Several of the studies (for subjects 6 and 7) were reported as failures. The respondent argued that the unreported drug administrations were minimal intrusions into the study and affected only one or a few of the final pain ratings.

### Discussion

In each of the cases, the administration of the allegedly unreported medication was toward the end of the study and affected few of the pain ratings. However, the administration of the concomitant medication was a violation of the protocol. Also, the CRF was inaccurate in that it had no record of the medication being administered.

### Findings

These five examples support the charge.

### Conclusions related to the unreported concomitant analgesia allegations

Five of the eight examples of alleged violations cited by the Bureau in support of the allegation that unreported concomitant analgesia was administered were supported. The allegation is substantiated.

- Nine subjects received unreported symptomatic treatment  
(1, 2, 5, 6, 7, 9, 12, 13, 17)

The Bureau cited fourteen specific examples of this allegation. Of these, ten examples involving seven subjects were withdrawn during the course of the hearing (2, 5, 7-ice packs, 9, 12, 13, 17).

Dr. Hopkinson's response to charges relating to examples 1, 6,  
7-Sitz bath, Dermoplast

The respondent's argument in the case of subject 1 was the same as the one he made concerning the allegation of concomitant analgesia. His position was that there were two separate series of test drug administrations interrupted by a tubal ligation and that the symptomatic treatment came between these series and thus was not concomitant. For subject 6, the respondent argued that the unreported symptomatic treatment could have affected only one or two of the pain ratings and that the bulk of the study was not affected. For subject 7, the respondent argued that the alleged symptomatic administration could have occurred before the study began.

Discussion

The conduct of the study on subject 1 has been discussed above (page 19). The circumstances of the study are not clear from a review of the CRF. There is a reference to "Nuper" on the CRF but the medical record does not show that Nupercainol was administered.

Subject 6 received an unreported Sitz Bath during the last part of the study. The respondent agreed that this was technically a protocol violation. Although the bulk of the study pain ratings were not affected, the CRF did not contain a reference to the symptomatic treatment, as is required by the protocol.

For subject 7, the Bureau was unable to establish conclusively the time the allegedly unreported symptomatic treatment was given. Furthermore, entries in the CRF indicate that the subject requested symptomatic treatment, implying that it had not been administered.

#### Findings

The example involving subject 6 supports the charge. Examples involving subjects 1 and 7 do not support the charge.

#### Conclusions related to the allegation that nine subjects received unreported symptomatic treatment.

Most of the examples the Bureau cites in support of the allegation were either withdrawn or did not support the allegation. The Bureau's evidence does not support the charge that nine subjects received unreported symptomatic treatment but does show a violation with respect to one subject.

- Medical histories for seven subjects were inaccurately reported (1, 2, 5, 6, 12, 14, and 19).

In support of the allegation, the Bureau presented seven specific examples of alleged violations.

The charge regarding subject 1

The Bureau charged that inaccurate medical history was provided in the CRF because the fourth dose of \_\_\_\_\_ was separated by 36 hours from the third. The Bureau submitted medical records and the case report form in support of the allegations.

Dr. Hopkinson's response to the charge involving subject 1

As discussed above, the respondent argued that subject 1 received two separate sequences of test drug administration on two separate days. He suggested that the information entered on the CRF was based on the second continuous sequence of study drug administration. The respondent also noted that this was the first multi-dose study he had conducted and acknowledged that start up problems existed.

Discussion

There appears to be no clarification on the CRF of the circumstances of the study on this subject. Entries on the CRF do not correspond with those in the medical records and a valid explanation of the events which apparently existed was not in the CRF. The fact that the subject received two sequences of test drug administration is pertinent medical history and should have been reported in the CRF.

Findings

The Bureau's charge is supported.

The allegation regarding subject 7

The Bureau charged inaccurate reporting of medical history (misrepresentation of reason for stopping study) in the CRF. The Bureau cited entries in the medical record which allegedly indicated that the subject was in pain, while the CRF noted otherwise.

The Bureau misrepresentation charge centered on several entries in the CRF. One read "was satisfied with pain relief of medicine given, but also wished to receive Dermoplast spray and anaesthetic suppositories" (G7(i)(5)).<sup>4</sup> The pain ratings in the CRF were at the "pain absent" level.

Dr. Hopkinson's response to the charge as related to subject 7

The respondent argued that the CRF entry indicating that the subject was satisfied with pain relief (G7(i)(5)) represented how the patient felt. Dr. Hopkinson also argued that the subject could have been referring to pain in different areas.

---

<sup>4</sup> Documents in the record will be cited by the letter designations given them at the hearing.

## Discussion

The CRF is supposed to represent the medical judgment of the physician, based on his interpretation of various input and should, therefore, be consistent with the medical records. The CRF and the medical records are contradictory in several places where reference to the subject's level of pain is made (G7(i)(5)). Some entries suggest that pain relief was adequate and that the patient requested to be taken off the test drug for reasons other than pain relief. The medical record indicates that pain relief was not obtained and that concomitant medication was administered.

The argument that the subject could have been referring to pain in different areas of the body is not compelling as this supposition was not supported with any evidence such as an adequate description of the situation in the CRF. The entry on the CRF (G7(i)(5)) is itself contradictory and confusing and adds no useful information to the pain ratings which, in themselves, misrepresent the subject's degree of pain, documented in the medical records.

## Findings

The example supports the Bureau charge.

The allegation regarding subject 2

The Bureau presented two examples of how inaccurate medical records were kept: the birth was described as "natural childbirth" when, in fact, epidural anaesthesia was used, and the birth occurred 15 hours before the time stated in the case report form. In support of the allegations, the Bureau presented the medical record and CRF for subject 2.

Dr. Hopkinson's response related to subject 2

The respondent argued, and Dr. Hensely agreed, that the protocol did not preclude use of a subject when epidural anaesthesia was used and that the quality of the study was not affected. The respondent's counsel described the extent to which Dr. Hopkinson would have had to look within the medical records to determine that epidural anaesthesia was used. The respondent argued, and Dr. Hensely agreed, that the time of birth was not important to the protocol.

Discussion

The respondent's argument that the inaccuracies charged by the Bureau were not violations of the protocol was compelling only to the extent that inclusion of the subject in the study is not a violation of the protocol. This, however, is not the allegation. The inaccuracies do represent inaccurate reporting of medical histories and are in violation of the regulations.

The respondent's argument that ascertaining the validity of the entries of the CRF would have required significant effort on the part of Dr. Hopkinson may be true. However, the argument is irrelevant, since the respondent agreed to undertake the responsibility, regardless of the effort it would entail.

### Findings

The Bureau's charges are supported.

### The allegations regarding subjects 5, 12, 14, and 19

The Bureau charged that probable adverse effects (in subjects 5, 12, and 14) or a fever (subject 19) were unreported in the CRF. In support of the charge involving subject 12, the Bureau presented the CRF for subject 15, noting that the same adverse effect (urinary retention) was reported for that subject.

### Dr. Hopkinson's response

The respondent argued, and Dr. Hensley agreed, that medical judgments regarding adverse effects were to be made by the doctor, and pointed out that the Bureau's evidence relied on a nurse's notation based on the subject's statement.

For subject 12, the respondent argued that the degree of seriousness of urinary retention varies, and may have been different in subjects 12 and 15. The investigator's medical judgment is involved in determining whether or not to include the condition in the CRF.

The respondent did not address subject 14 in his post-hearing brief. It was, however, unclear during the hearing whether the medical records on which the Bureau was basing its charge were those of the subject.

For subject 19, the respondent argued that the protocol did not require reporting a temperature if it occurred prior to or after the study. The respondent showed that Tylenol was administered for fever eighteen hours before the study began.

### Discussion

The physician's medical judgment is crucial in determining adverse effects of a test medication. Possible adverse effects, as noted by the patient and supporting personnel, are evaluated by the physician and many factors may affect the physician's judgment. Absence of an entry describing "heartburn" in subject 5 seems justifiable, assuming that the physician considered the nurse's notation and judged it not an adverse effect.

For subject 12, the Bureau argued that because the test of subject 15 was stopped as a result of urinary retention, urinary retention should have been listed as an adverse effect for subject 12. This charge fails for two reasons. First, urinary retention was not listed as an adverse effect for subject 15. Second, urinary retention can vary in severity and its listing is ultimately based on the medical judgment of the clinical investigator that determines whether an occurrence is a drug related adverse effect.

For subject 14, the Bureau was unable to show that the medical records on which the Bureau's testimony was based in fact belonged to subject 14.

For subject 19, the respondent established that the reported time of temperature entered in the record was prior to the study. Dr. Hensley testified that, in his opinion, the sponsor would have wanted to know about that fever, but the protocol does not require that prior fever be reported. For that reason, the charge cannot be supported.

#### Findings

The examples presented by the Bureau do not support the Bureau's charge.

Conclusions related to the allegation that medical histories for seven subjects were inaccurately reported

Of the eight specific allegations of inaccurate medical history cited by the Bureau, four supported the charge and four did not. The substantiated allegations, however, were serious enough to support the charge.

Conclusion related to the charge -

The charge that Dr. Hopkinson failed to maintain adequate and accurate case histories as required by 312.1(a)(13), Item 4.c is substantiated. The evidence presented by the Bureau supported the charge that Dr. Hopkinson repeatedly failed to maintain adequate and accurate case histories for a significant number of subjects entered in the study. Dr. Hopkinson's violations of the regulations in this study demonstrate a lack of care on the part of the investigator in producing reliable study results. I do not believe, however, that the evidence shows deliberate violations of the regulations, whether or not "deliberate" is defined to include the concept of reckless disregard of the regulation's requirements.

Charges related to                      Study

Charge #1: Failure to maintain adequate and accurate case histories.

21 CFR 312.1(a)(13)4.c

"The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the drug or employed as a control in the investigation."

In support of the charge, the Bureau presented examples of six types of alleged violations. Instances the Bureau presented as supporting the allegations are discussed below.

- 28 subjects received unreported prior or concomitant CNS medication while receiving the test medication.

The specific instances are summarized below.

FAILURE TO MAINTAIN ADEQUATE AND ACCURATE CASE HISTORIES

Unreported prior or concomitant CNS medication while receiving the test medication (Thirty-seven specific instances)

Prior:	1601 - Codeine	1618 - Darvon
	1603 - Codeine	1620 - Codeine
	1608 - Codeine	1626 - Codeine
	1611 - Demerol	1628 - Percodan
	1617 - Codeine	1632 - Darvon

Concomitant:	1601 - Dalmane	1636 - Codeine
	Tylenol	1643 - Darvon
	1606 - Percodan	1646 - Percodan
	1607 - Darvon	1650 - Darvon
	Seconal	1652 - Dalmane
	1608 - Codeine	1667 - Percodan
	1618 - Darvon	1671 - Dalmane
	1622 - Nembutal	1675 - Aspirin
	1623 - Codeine	1676 - Tylenol
	1626 - Dalmane	1677 - Percodan
	1631 - Dalmane	Nembutal
	1632 - Seconal	1678 - Codeine
	Darvon	1679 - Codeine
	1633 - Percodan	

### Bureau

In support of this allegation, the Bureau cited 37 instances where a single drug was given to a subject while in the study. The administration of the drug was allegedly unreported as either a prior or concomitant medication. The number of instances cited is greater than the number of subjects because administration of more than one unreported drug per subject, or both prior and concomitant administration of drugs, was alleged. Of these 37 instances, 10 (1601-Tylenol/concomitant; 1603-codeine/prior; 1606-Percodan/concomitant; 1607-Darvon, Seconal/concomitant; 1618-Darvon/concomitant; 1623-codeine/concomitant; 1628-Percodan/Prior; 1643-Darvon/concomitant; 1646-Percodan/concomitant) were withdrawn during the course of the hearing. In support of the allegation, the Bureau submitted medical records and case report forms for the subjects.

### Respondent's Arguments

The respondent presented arguments against the Bureau's charges on a case-by-case basis. The responses have been summarized, based on the similarity of the responses and charges. Dr. Hopkinson's response for each group of specific allegations is followed by a discussion and my findings with respect to those allegations. My conclusion about the Bureau charges is based on the findings.

Contention that the additional medication was administered after the last dose of the test drug: 1608-codeine/concomitant; 1620-codeine/prior; 1633-percodan/concomitant; 1636-codeine/concomitant; 1650-Darvon/concomitant.

In these five instances, the respondent claimed that the drugs were administered to the subject after the last dose of test drug

Therefore, the respondent argued, the drug administration occurred following the conclusion of the study for each subject. The study, in each case, was reported a failure. The respondent argued that any discrepancies in time of drug administration between the subject's medical records and the CRF did not affect the validity of the study because the study was completed at the time of drug administration and was correctly reported as a failure.

## Discussion

The Bureau of Drugs argued that all cases, even those charged as failures, remain an integral part of the study and also need to be evaluated. In the Post-Hearing Brief, the Bureau of Drugs stated that when a subject was not getting relief from a drug, the respondent termed the situation a "patient failure" (Bureau PHB at 30). The Bureau argued that the "failure" of a drug remains an integral part of the study and that "[t]he patient may have felt no relief because she received only a placebo, or the pain medication being tested failed to provide the expected relief" (id. at 30-31).

## Findings

I find that the alleged violations have occurred. The regulations require accurate reporting of case histories, whether or not the study is a failure and whether or not the reporting of the study as a failure is accurate. The respondent's argument is essentially that the violations of the protocol that occurred in fact caused no harm. We do not know how, or if, later analyses of the data from this investigation might be skewed by the inaccuracy of the CRFs that resulted from the failure to report required information. It is for that reason, I believe, that the regulation's requirement of accurate reporting must be complied with even when a test is judged a treatment failure. With the exception of subject 1620,<sup>5</sup> for which the charge was not supported, the examples support the allegation.

---

<sup>5</sup> During the course of the hearing, Bureau witness Dr. Turner agreed that there was not a prior administration of codeine to subject 1620, but rather that codeine was administered concomitantly and not reported (Tr. Vol. II at 58). Because the latter charge was not made prior to the hearing, I do not find this instance to be supportive of the Bureau's overall charge.

Contention that Bureau may have relied on inadequate hospital records (1632-Darvon/prior, Seconal, Darvon/concomitant; 1618-Darvon/prior; 1631-Dalmane/concomitant; 1677 Percodan/concomitant, Nembutol/concomitant).

In the instances involving subject 1632, the respondent suggested during cross-examination that one page of the records on which the Bureau relied may not have belonged to the subject. In the examples involving subjects 1618, 1631 and 1677, the respondent suggested at the hearing that the medical records against which the CRFs were compared were incomplete or were misinterpreted. The respondent did not address any of these charges in his Post-Hearing Brief.

#### Discussion

Dr. Hopkinson apparently made the tactical decision not to present evidence from these records, which were available to him, that might clarify whether or not there was a mistake on the part of the Bureau. As noted, he did not argue in his Post-Hearing Brief that there was such a mistake with respect to these subjects.

Although there was confusion, I conclude that, with respect to subject 1632, the entire medical record, including the one page in dispute, does refer to the patient in question. The difference in the patient name on the last page can be explained as an omission due to the difficulty in embossing the patient's name on the medical record.

Although Darvon administration was reported as prior analgesia in the CRF for this subject, the time reported is inaccurate and, therefore, the unreported prior analgesia charge is supported. Review of the medical records and CRF establishes that both Seconal and Darvon were administered as unreported concomitant medications and those charges are, therefore, also supported.

With respect to subject 1618, the Bureau's charge was that prior administration of Darvon was not reported in the CRF was substantiated by the medical records.

With respect to subject 1631, the respondent argued that the initials in the medical records that indicate administration of Dalmane, an administration not reported in the CRF, may have been erased, thus indicating that Dalmane was not in fact administered. Although the initials do appear to be lighter than other markings on the medical report form, there is not, as there is elsewhere in the records, either initialing by a person who corrected an error or the circling of the entry that would indicate that the medication was not given. I thus find the Bureau's charge with respect to this subject to be supported as well.

With respect to subject 1677, the evidence shows unreported concomitant Percodan administration. The Bureau did not present evidence on the Nembutol concomitant administration charge for this subject.

Findings

With the exception of the allegation of unreported concomitant administration of Nembutol in subject 1677, the examples cited by the Bureau support the charge.

Charges Dr. Hopkinson did not address: 1608-codeine and other medications/prior; 1622-Nembutal/concomitant; 1626-Dalmane/concomitant; 1652-Dalmane/concomitant.

In these four instances, the respondent did not address the Bureau's allegations either in cross-examination or in his Post-Hearing Brief. Throughout the hearing, however, the respondent argued that the burden of proof is with the Bureau which is making the charges.

Discussion

The burden of proof is, of course, with the Bureau. The evidence submitted by the Bureau satisfied that burden. Lacking any refutation by the respondent, I have considered the Bureau's charges and evaluated the medical record and CRF in the context of the charges.

Findings

The evidence presented by the Bureau in these four instances supports the charges.

Contention that the alleged concomitant drug administration did not occur: 1671-Dalmane/concomitant; 1676-Tylenol/concomitant.

In these two instances, the respondent argued that several of the entries in the medical records on which the Bureau based its allegations could have been erased or were unclear. Thus, the lack of clarity could indicate that drug administration did not actually occur, and the entry on the medical record showing this could have been erased. If the drug administration did not occur, it did not need to be reported in the CRF.

#### Discussion

I believe the entries in the medical records are reasonably clear. The concomitant drug administrations that they record thus should have been reflected on the CRFs. With respect to subject 1676, Dr. Hopkinson suggested that the entry may have been erased. Yet, other entries on the medical records showing drugs which were refused were not erased, but circled and noted as "ref" (refused).

#### Findings

The Bureau's evidence in these two instances supports the allegation.

Contention that prior medication was in fact reported: 1601-codeine/  
prior; 1617-codeine/prior; 1626-codeine/prior.

In these instances, the respondent claimed that the prior medication was reported as such, although the time of medication administration as reported on the CRF was different from that recorded on the medical records. The respondent discussed nurses' practice of recording time of drug administration after they have completed their rounds, and implied that this may have been the case in subject 1617. Charges involving prior medication to subject 1617 were not included in the Bureau's revised chart of allegations in the post-hearing brief (PHB at 6). However, no record of the allegation being withdrawn during the course of the hearing was noted, and the example is discussed in Dr. Hopkinson's post-hearing brief (PHB at 18). Thus, it is possible that this example was inadvertently omitted from the revised Bureau chart. Because the example was presented and discussed, and because Dr. Hopkinson had the opportunity to respond to the charge as it pertains to subject 1617, I am considering it.

#### Discussion

The regulations require accurate reporting of case histories, including accurate reporting of time of drug administration, when this information is required. Although, technically, codeine was reported as a prior drug administration in all cases, the time at which the drug

administration occurred was inaccurately reported. The respondent's argument that the time reported on the medical history may have differed from the time of actual drug administration is not compelling because there is no reason to believe that the CRFs accurately reflect the actual time of administration.

#### Findings

The allegations support the Bureau's charges.

Attempt to blame Dr. \_\_\_\_\_ for violation: 1601-Dalmane/concomitant.

Dr. Hopkinson argued that Dalmane was part of the standard medication order, and argued that there was no evidence that he "deliberately or not, allowed the administration of Dalmane." Respondent's counsel suggested during cross-examination that Dr. \_\_\_\_\_ a resident who worked for Dr. Hopkinson in this study, was responsible for recording data from the medical records on the case report forms and for placing the standard medication order.

### Discussion

The Bureau argued that because Dalmane was given to the subject during the course of the study, it is irrelevant who ordered the drug and who recorded the drug's administration (Tr. Vol. I at 45). The charge is that the case report forms were inaccurate. It does not matter who actually recorded entries on the subject's medical records.

Ultimately, the responsibility for assuring the accuracy of the subject's medical history is the clinical investigator's.

### Findings

The evidence supports the Bureau's charge.

Contention that failure to report prior medication was not important because the study was a treatment failure: 1611-Demerol/Prior.

The respondent argued that the study was a treatment failure and that that fact was accurately reported.

### Discussion

The medical records show Demerol was administered an hour before the time when the CRF reports the test drug was administered and thus the Bureau's charge is substantiated.

As discussed above, the fact that a study is a treatment failure does not justify inaccurate reporting of the subject's medical history. In this instance, the patient's medical records do not indicate that the patient took the study medication. If the study medication was not given, but reported in the CRF as given, then the respondent falsely reported a study subject. This, however, was not charged by the Bureau. Based on the CRF notation that this study medication was administered an hour later than was actually the case, I conclude that the charge of unreported prior analgesia should be considered.

#### Findings

The Bureau charge is substantiated.

Contention that the medical records relied on by the Bureau were not complete records for the subjects covered by the CRFs: 1667-Percodan/concomitant; 1675-Aspirin/concomitant; 1677-Codeine/concomitant; 1678-Codeine/concomitant; 1679-Codeine/concomitant.

The respondent suggested that the medical records in several of the cases were incomplete. In other cases, the respondent argued that the CRF may have been a more accurate representation of the facts than the medical records made available by the Bureau.

Discussion

For each of these subjects, the Bureau charges consist of allegations that a drug was administered concomitantly and unreported. As discussed later in this report, the Bureau also charges that no record of administration existed in the medical record. The allegations are related, and address the same charge - inaccurate recordkeeping - from both ends: the accuracy of the medical records and the accuracy of the case report form. Supporting one of the allegations necessitates not supporting the other. There are essentially three possibilities--the medical records are inaccurate, the case report forms are inaccurate, or the medical records identified by the Bureau are not in fact records for the patients whose data are reflected on the case report forms.

Dr. Hopkinson ordered that the medical records be provided to inspectors when they visited the hospital. The inspectors then linked the medical records to the case report forms by comparing initials and dates. Dr. Hopkinson has never, either at the informal hearing held before the hearing or at this hearing, corrected a misidentification of medical records with CRFs or shown that medical records were incomplete by producing appropriate records. Rather, he has simply raised the question whether the medical records may have been misidentified or incomplete. Dr. Hopkinson, in fact, testified that he did not question the accuracy of the Bureau's reproduction of records (Tr. Vol. III, page 230).

After review of the records themselves, I conclude that the medical records relied on by the Bureau are the records of the patients in question. Thus, either the medical records or the CRFs are inaccurate. For the reasons discussed below, I find that it is the CRFs that are in error.

### Findings

Because I conclude that the records show that no investigational drug was administered to these patients, I do not find that the charge that other drugs were unreported concomitant medications is supported. I recognize, however, the Bureau's intent in alleging both types of deficiencies, as doing so points out the inaccuracies in record keeping. Because of the confusion about this issue, however, I make the finding, in the alternative, that if the test drug was administered to these patients, the charge of unreported concomitant medication would be established.

Therefore, although the specific allegations are not supported, the examples cited by the Bureau lend credence to the overall charge.

Conclusions related to the allegation that 28 subjects received unreported prior or concomitant CNS medication while receiving the test medication.

Of the thirty-seven instances presented by the Bureau as examples of the alleged violation, ten were dropped before or during the study. Of the remaining twenty-seven instances, I found five not to be supported because of my judgment that the test drug was not administered to these patients. Of the remaining twenty-two charges, eighteen examples supported the charge. Four of the examples did not support the charge.

In summary, the Bureau established that eighteen subjects received unreported or concomitant CNS medication while receiving the test medication.

- Two subjects received unreported symptomatic treatment  
(1632, 1633)

### Bureau

In support of this violation, the Bureau cited two deficiencies, 1632-Topical Ointment; 1633-Sitz Baths, Topical Ointment, and pain medications. The Bureau's charges concerning one of the deficiencies (1632) were withdrawn by the Bureau during the course of the hearing.

### Discussion

The charge regarding the second deficiency (1633) was changed from an instance of unreported symptomatic treatment to an instance of inaccurate medical history in the Bureau's Post-hearing brief. The charge was changed following the hearing and, as a result, the respondent was unable to respond to the charge. For this reason, I did not consider this charge.

### Findings

The Bureau's allegation that two subjects received unreported symptomatic treatment is not supported.

Conclusion related to the allegation that two subjects received unreported symptomatic treatment

The charge is not supported by the examples cited by the Bureau.

- Medical histories were inaccurately reported for five subjects (1604, 1607, 1613, 1634, 1676)

Bureau

In support of this allegation, the Bureau presented five subjects for which a total of eight deficiencies were alleged:

1604 - Inaccurate reporting of surgery date.

1607 - No record of first dose of investigational drug.

Inaccurate medical history.

1613 - Inaccurate medical history.

Unreported Dalmane after study was completed.

1634 - Inaccurate reporting of surgery date.

1676 - Inaccurate report of surgery time.

Unreported adverse reaction.

The Bureau withdrew three of the examples for which the deficiencies were alleged (1604, 1607, 1634) during the course of the hearing. Although the "unreported adverse reaction" allegation for subject 1676 appears in the Bureau's post-hearing brief (at 7), Bureau witness Dr. Turner stated at the hearing that the Bureau was not pursuing that allegation (Tr. Vol. II, pages 161-162) and I, thus, consider that allegation to be withdrawn.

The Bureau charged that medical history for subjects 1613 and 1676 was inaccurately reported. The Bureau alleged that the subjects' surgery times were inaccurately reported. The times of surgery reported on the CRFs were different from the times reported in the medical records. Furthermore, the Bureau charged that Dalmane was administered to subject number 1613 after the study was completed and that the administration was unreported. The Bureau's charge that Dalmane was administered but unreported was based on the fact that Dalmane administration was noted in the medical records for this subject, but there was no notation of Dalmane administration in Box 31 of the CRF. (Box 31 was for listing concomitant drugs.)

Dr. Hopkinson's Response

The respondent questioned whether the reported time of surgery affected reporting of pain ratings required by the protocol. The respondent, in the Post-hearing brief, stated:

There was, indeed, a discrepancy in the reporting of the surgery time on the case report form and the patient chart. This discrepancy, however, did not affect the patient's eligibility to participate in the study or the validity of the study results and, therefore, is irrelevant. (Hopkinson PHB 20-21).

The respondent established that the Dalmane administration was, in fact, reported on a later page of the CRF. (Tr. Vol. II, pages 26-27 and Hopkinson PHB 16-17).

Discussion

Whether or not accurate reporting of the time of surgery affects the pain ratings required by the protocol is not at issue here. The protocol required reporting of time of surgery; that time is a critical aspect of a subject's records and it should be accurately reported.

Dalmane administration was reported in the CRF, although not in the box for that purpose on the CRF.

Findings

The Bureau's evidence supports the charge that the times of surgery were incorrectly reported. The unreported Dalmane administration allegation is not substantiated and the evidence on that allegation does not support the charge.

Conclusions relating to allegation that medical histories were inaccurately reported for five subjects

Of the eight specific examples, the Bureau withdrew five. Of the remaining three examples, two supported the charge. One allegation did not support the charge. The examples which were supported, however, are serious and in themselves show a violation of the regulations.

- Ten patient case reports indicate inaccurate time and dates of the administration of the investigational medication

At the onset of the hearing, the Bureau cited ten patient case reports which allegedly indicated inaccurate times and dates of administration. During the course of the hearing, the Bureau withdrew seven of the examples of allegations (1601, 1607, 1611, 1623, 1626, 1628, 1644).

The Bureau presented medical records and case report forms for subjects #1610, 1615 and 1642 which allegedly showed inaccuracies in reporting the time of administration.

#### Dr. Hopkinson's response

The respondent did not refute the Bureau's assertion that inconsistencies between the medical records and CRFs existed.

In all of the examples, the respondent argued that entries on the medical records and CRFs could have been made by Dr. The respondent argues that the residents who completed the CRFs were specifically paid for conducting the studies and could do so with greater attention than nurses and that the benefit of the doubt as to which of the two records (the medical records or the CRF) is accurate should go to Dr. Hopkinson.

In addition, the respondent argued that the medical records for subject number 1610 may have been incomplete. The respondent pointed out that in order to verify the accuracy of Dr. [redacted] entries on the CRF for subject number 1610, Dr. Hopkinson would have had to review each notation on the medical records and compare to the CRF. Respondent pointed out during cross-examination that Dr. [redacted] initials appeared on several CRF entries for subject number 1642. It is unclear what relevance that fact is supposed to have.

#### Discussion

In all three examples, the time of drug administration recorded on the CRF differed from the recorded entry in the subject's medical records.

I have discussed the question of inconsistency between the CRF and the subject's medical records above (pages 11-14). In this case, as in general, I find, on the basis of the evidence I have seen, that the medical records are accurate and the CRFs are inaccurate in those instances where they conflict. In any case, I find that Dr. Hopkinson's failure to provide in the CRFs an explanation of why important discrepancies between the CRFs and the medical records renders Dr. Hopkinson's recordkeeping inadequate.

Findings

The examples of subjects 1610, 1615 and 1642 support the allegation.

Conclusion relating to allegation of inaccurate time and dates of administration of the investigational medication

Of the ten examples of the allegations, the Bureau withdrew seven during the hearing. The remaining three examples support the Bureau's charge.

- Six subjects were reported to have received the investigational drug but this fact was not recorded in the patient case histories.  
(1667, 1675, 1677, 1678, 1679, 1680)

The charge for all subjects, except 1680, was discussed above. (Pages 44-45). Information presented at the hearing for subject 1680 is similar to the information on the other five subjects, except that the unreported administration of a concomitant drug was not charged.

Respondent

As discussed above, the respondent's arguments did not address the absence of a record of study drug administration in the subject's medical records. Rather he argued that the CRF, rather than the medical records, may have been the accurate representation of the facts.

Discussion

For the reasons discussed above on page 52, I find that the medical records which do not show administration are accurate. The CRFs are thus inaccurate. Even if was administered as stated in the CRF, Dr. Hopkinson's recordkeeping was inadequate because it failed to explain the discrepancy between the medical records and the CRFs on this important point.

Findings

The examples cited by the Bureau support the allegation.

Conclusion related to the allegation

The allegation is supported by the examples presented by the Bureau. This particular allegation is very serious, as it casts doubt on whether or not these studies were in fact conducted.

- Ten subjects were found to have been entered and not reported into a clinical study of another investigational drug within one day of their participation in the clinical trial (1604,1608,1613,1621,1622,1623,1642,1652,1679,1680).

Charges regarding two of the subjects (1623 and 1642) were dropped during the course of the hearing. For subjects 1679 and 1680, the Bureau alleged that the test drug was not actually administered. In support of the charge, the Bureau presented medical and CRF records of the subjects. The medical records included pharmacy orders, patient charts and, in two cases (1604,1621), consent forms.

#### Dr. Hopkinson's Response

Dr. Hopkinson argued that these charges constituted a violation of neither FDA regulations nor the study protocol. He pointed out that the Bureau's charge was that the subjects were entered into another study within one day of their participation in the study. The respondent argued that neither the protocol nor the regulations required that participation in other drug studies be mentioned unless participation occurred within 4 hours of the study. Dr. Turner's testimony was cited (Tr. Vol. I, 129, 186-7, 188)

as a concession on the Bureau's part that not reporting participation in another drug study in the circumstances at issue was not a violation of the protocol. The respondent argued that the regulations (21 CFR and 312.1(a)(13) Item 4.c) required the investigator to "record all observations and other data pertinent to the investigation," and that Dr. Turner was interpreting the regulations on the basis of his personal preferences on what should have been included. Dr. Turner, under cross-examination, stated that the Bureau cited investigational studies "performed on the same patient within 12 hours." The respondent noted the discrepancy between Dr. Turner's 12 hour figure and Dr. Kelsey's use of one day (24 hrs.), as a criterion for citing subjects' participation. The respondent argued that even if subjects participated in studies within 24 hours of the study, the Bureau had failed to establish that the protocol or regulations were violated. For two of the subjects, (1652 and 1679), the respondent argued that involvement with other investigational drugs was subsequent to participation in the study.

The respondent argued that, for subject 1604, there is no record that medication for the other study was ever administered.

#### Discussion

The protocol (G-3) does not specifically address participation in another drug study. It does, however, exclude from participation "Patients having taken interfering or interacting medication, i.e.,

other analgesics within 4 hours of entry into the study, or any psychoactive medication, until effects have dissipated." None of the examples cited involved use of test drugs within 4 hours of the study. The investigator should have considered whether or not other investigational drugs were psychoactive, and whether effects would have dissipated, particularly if the other investigational drug was prescribed for the same episode. The case report form, box #30, provides the format for listing "Medication for this episode taken prior to this study." Since patients taking medication within four hours of the study were to be excluded, the prior medication presumably refers to medication taken for the same episode prior to four hours before the study.

Determination of what cut-off time to use in deciding what should be listed was left to the investigator. The Bureau used 24 hours (one day) as the "cut off" time.

In two of the examples, 1608 and 1622, the records shows that participation in the other study occurred within 24 hours of the study. In a third example, 1613, the participation occurred 28 hours prior to the study. In all three cases, the study drugs were prescribed for the same episode as the other test drug. In examples 1652 and 1680, alleged participation in the other study occurred following the study.

On review of the record, I conclude that no record of other study medication administration is present for subjects 1604, 1621 and 1652. The factors that I considered for each subject are summarized in the table below.

Subject Number

	1604	1608	1613	1621	1622	1623	1642	1652	1679	1680
Allegation Withdrawn						X	X			
Record of Administration Challenged?									X	X
Other Test Drug Ordered	X	X	X	X	X			X	X	X
Other Test Drug Administered?	?	X	X	NO	X			NO	X	X
Consent Form ?	X			X						
Time Between Other Test Drug & Administration (Hrs.)	16	16	28		20			5*	17	5*
Support Charge	NO	YES	YES	NO	YES	W	W	NO	YES	NO

\* Subsequent to Study

Findings

Although the protocol and the CRFs are admittedly not clear on the issue, I believe that a test medication used for the same episode prior to the study is a significant prior medication. Furthermore, reporting the use of such a medication is certainly within the intent of the protocol and, thus, within the requirement of the regulations. Even if the lack of specificity of the protocol and CRF is taken into account, a subject's use of another investigational drug prior to the study is certainly . . . "data pertinent to the investigation . . ." and thus, should be reported.

I find that examples involving subjects 1604, 1621 and 1652 do not support the charge, since only other study medication orders, not evidence of actual administration of other study medication was presented. The examples involving subjects 1652 and 1680 do not support the charge because alleged administration of other study drugs occurred following the conclusion of the study.

Allegations involving subjects 1608, 1613, 1622 and 1679 are substantiated and support the charge.

Conclusion related to the allegation

The examples presented by the Bureau support the allegation.

Conclusions related to Charge #1 -

The charge that Dr. Hopkinson failed to maintain adequate and accurate case histories as required by 312.1(a)(13), Item 4.c is substantiated. That charge would be substantiated even if I did not consider the failure to list participation in a different drug study to be a violation.

Charge #2:Failure to Maintain Adequate Drug Accountability Records312.1(a)(13), Item 4.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 investigation is terminated, suspended, discontinued, or completed, to return to the sponsor any unused supply of the drug.

Bureau Presentation

The Bureau charged Dr. Hopkinson with not maintaining adequate drug accountability records for the study.

The Bureau testified that no shipping records were kept, either for the receipt or for the shipment for return of excess drugs. The Bureau noted that these records by Bureau investigators were requested from Dr. Hopkinson, but the records were not provided.

Dr. Hopkinson's Response

Dr. Hopkinson has stated that he "may not have maintained separate drug accountability records," believing that dispensing records satisfy the requirements (PHB at 21 and 22). The respondent argued that case report forms and the patient's hospital records account for the drugs . . . "in that they reflect the 'dates, quantity, and use' of the drug

by the subject," and that the regulations allow dispensing records to satisfy the requirement for drug accountability records. The respondent cited FDA's proposal to amend the regulations involving clinical investigations (43 FR 35210-August 8, 1978) and specifically noted that FDA recognized "that there existed a misunderstanding on the part of clinical investigators about the requirements for drug accountability" (Hopkinson PHB at 22). The respondent argued that the new proposed regulations represent a higher standard than that which existed when the study was conducted. The respondent also argued that the protocol specifically provided for returning all bottles of study medication to the study monitor, thus allowing for drug accountability. Dr. Hopkinson does not contend that he kept records of the amount of drugs received or returned.

#### Discussion

The regulations require that adequate records of drug accountability be kept by the investigator and be made available to the FDA.

Dr. Hopkinson contends that his dispensing records satisfy that requirement. However, the Bureau has shown that no record of administration was available in the medical records of six subjects (1667, 1675, 1677, 1678, 1679, 1680). If this indeed was the method of drug accountability used by the investigator, these examples verify the inadequacy of this system of recordkeeping. Thus, I need not decide whether individual dispensing records may satisfy the requirement for drug accountability records.

Dr. Hopkinson states that he returned all unused bottles to the monitor, as required by 312,1(a)(13) Item 4.b. However, no records for drug receipt or return to the sponsor or to \_\_\_\_\_ were presented.

### Findings

The Bureau's charge that inadequate drug accountability records were kept is supported.

### Conclusion related to Charge #2 -

The Bureau's charge that Dr. Hopkinson failed to maintain adequate records of the disposition of the test drug as required by 312(a)(13), Item 4.b is substantiated.

### Conclusion related to the                      Charges

The Bureau charges that Dr. Hopkinson failed to maintain adequate and accurate case histories and adequate drug accountability records were supported. The substantiated examples and allegations relied on by the Bureau were sufficient to show that during the conduct of the study, Dr. Hopkinson repeatedly and deliberately violated the regulations pertaining to the proper conduct of a clinical study. The number of supported examples of violations show that the violations were repeated. Repeated violations of a similar nature resulting in case

report forms showing no evidence of protocol deviation or violation when medical records show that such deviations and violations have occurred are evidence that the violations were indeed deliberate, if "deliberate" is defined to include the concept of "reckless" disregard for the regulation's requirements. The unexplained discrepancies between medical records and CRFs on the question of whether the test drug was actually administered are, I believe, particularly telling evidence of "deliberate" action under this standard. Certainly, the failure to keep adequate records of receipt, dispensation, and return of the investigational drug shows a reckless disregard of the requirements of 21 CFR 312.1(a)(13) item 4.b. On the other hand, if deliberate is defined to mean "intentional" (see page 9, above), there is insufficient evidence to find that Dr. Hopkinson's violations were deliberate.

#### Sufficiency of Violations to Warrant Disqualification

I find that Dr. Hopkinson has repeatedly violated the regulations in the study and repeatedly and deliberately violated the regulations in the study. In summary, this constitutes repeated and deliberate violation of the regulations. I have considered whether his non-compliance with the regulations was so significant as to require disqualification in the absence of an adequate assurance of future compliance. This does not suggest that I consider any violation of the regulations acceptable. In the Commissioner's decision in the Gelfand matter, Commissioner Hayes stated that:

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

On the basis of my review of Dr. Hopkinson's violations, and in the absence of adequate assurances, I conclude that Dr. Hopkinson should be disqualified. Dr. Hopkinson's non-compliance with the regulations was severe enough to compromise the integrity of the data. The violations were repeated and on-going. Dr. Hopkinson did not exercise adequate supervision over the conduct of the studies. In fact, the violations in the study became more serious as the study progressed. The seriousness of the violations, particularly those showing no record of study drug administration to subjects and unreported concomitant medication, make those violations inexcusable.

I recognize that these violations were observed in the only two multiple-dose studies done by Dr. Hopkinson, but find that the nature of the deficiencies is not particular to this study design. Therefore, I conclude that disqualification is necessary absent a showing of adequate assurance.<sup>6</sup>

---

<sup>6</sup> My conclusion on this subject, and on the question of whether Dr. Hopkinson's assurances are acceptable, is not dependent upon my findings that some of Dr. Hopkinson's violations of the regulations were "deliberate." Because those violations were clearly "repeated," I would reach the same conclusion even if I found the violations were not deliberate.

Dr. Hopkinson's Assurances

21 CFR 312.1(c)(2) states: "After evaluating all available information, including any explanation and assurance presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the conditions of the exempting regulations in the section or has repeatedly or deliberately submitted false information to the sponsor of an investigation and has failed to furnish adequate assurance that the conditions of the exemption will be met, the Commissioner will notify the investigator and the sponsor of any investigation in which he has been named as a participant that the investigator is not entitled to receive investigational-use drugs with a statement of the basis for such determination." (Emphasis added.)

Dr. Hopkinson has provided the following assurances and announced the steps he has taken to insure that the studies he conducts are in full accordance with FDA's "expectations":

- He testified that he now exercises much more immediate supervisory control over the people who assist him in conducting clinical investigations than he did in the                      and                      studies.
- He reviews each case report form and each patient's hospital chart with his resident to ensure that there are no inconsistencies between the two documents.

- He no longer accepts multiple dose studies because of the difficulty of exercising proper supervisory control.
  
- He recognizes that it is the ultimate responsibility of the principal investigator to insure that studies are conducted properly in accordance with the protocol.

Dr. Hopkinson also submitted a list of studies which he had successfully conducted since 1970. He also submitted a letter from stating that there was no evidence of any inappropriate procedures being used or of breaking the double blind code in the three studies he conducted for

In the post-hearing brief (at 37), Dr. Hopkinson notes that the FDA has no regulations or guidelines specifying what an appropriate assurance is, and submits that the presiding officer should look at at least two things in determining whether there are adequate assurances that the conditions of FDA's regulations will be complied with in the future. Dr. Hopkinson asks that I look at: 1) his written or oral assurances; and 2) the overall quality of the work he has performed, particularly studies performed after he had received notice from FDA that previous studies were not, in FDA's view, in full compliance with "FDA's expectations." I have reviewed Dr. Hopkinson's explanations and assurances as provided for by the regulations. However, it would not be appropriate for me to address the quality of other investigational work he has conducted, as the only information submitted for the record is inadequate for a full review. My decision on the adequacy of Dr. Hopkinson's assurances is based on the submitted assurances and on whether the record supports that Dr. Hopkinson will meet his assurances that the conditions of FDA's

The Bureau of Drugs, in its post-hearing brief, argues that Dr. Hopkinson's assurances are inadequate because he did not display sufficient interest to review the records to determine how the problem arose so that he could prevent its reoccurrence. Dr. Hopkinson was unable to answer pertinent questions about the studies in question during the course of the hearing. The record clearly shows that Dr. Hopkinson was not prepared to discuss the patient records relied upon by the Bureau in support of the charges. The Bureau argued (Bureau PHB at 26) that "[t]o accept the assurances of a man who . . . admitted that he has never examined the hospital patient charts and compared them to the CRFs in order to ascertain the cause of the deficiencies, and thereby be prepared to prevent their recurrence, is to vitiate the Bureau's efforts to ensure that clinical studies are performed with a modicum of care."

During cross-examination, Dr. Hopkinson stated that the FDA never provided an opportunity for him to review records to explain problems with the records. The informal conference and the Part 16 hearing are the opportunities provided for such discussions to occur. Yet, during this hearing, and the informal hearing with the Bureau that preceded the hearing, Dr. Hopkinson did not care to personally discuss the records. At this hearing he stated that he felt that review of the records was "what my attorneys were for." (Tr. Vol 111 at 246). Dr. Hopkinson's inability or unwillingness to substantively discuss the deficiencies of the                      and                      studies causes me to question both his awareness of what is required of a clinical investigator and his credibility in assuring that the conditions of the regulations will be met in the future.

Dr. Hopkinson's assurance that he will no longer conduct multiple dose studies because of the difficulty in exercising proper supervisory control does not prevent similar problems in supervision from occurring in single dose studies. Although the studies he conducted were his first, and only, multiple dose studies, the charges, as supported by the Bureau of Drugs, could apply to single dose studies as well. The principles of the conduct of clinical investigations are the same, whether the study is single or multiple dose.

Dr. Hopkinson's assurances state that he will conduct his studies in full accordance with FDA's "expectations" and in accordance with the protocol. In addition to adhering to the protocol, the clinical investigator needs to conduct a study in accordance with FDA regulations, not expectations. Dr. Hopkinson seems unaware of his responsibilities as a clinical investigator as required by the regulations on the conduct of clinical investigations and his apparent lack of interest in understanding the specific problems in the studies discussed during the course of this proceeding lends doubt to the assurance that the future conduct of his studies will be in accordance with FDA regulations. Although Dr. Hopkinson states that he recognizes the principal investigator's ultimate responsibility in assuring that studies are conducted in accordance with the protocol, he does not provide an assurance that the FDA regulations will be met by simply his adherence to the protocol.

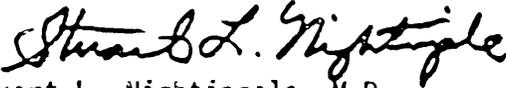
Dr. Hopkinson's contention that other studies conducted by him should serve as an assurance that in the future he will conduct studies in accordance with the regulations is not adequate to ensure his conduct in the future. If, as he has asserted during this proceeding (Tr. Vol. III at 203), he delegated a great deal of the day-to-day activities of these studies to the residents, however well-qualified, for the conduct of his studies, the quality of other studies he submitted as assurance of his qualifications may vary with the capabilities of his former staff. Dr. Hopkinson's increased supervision over those conducting his studies may not result in studies meeting regulatory requirements if Dr. Hopkinson is unaware of appropriate regulations. Finally, Dr. Hopkinson does not provide any indication that adequate drug accountability records will be kept. His assurances in this regard are inadequate.

In summary, I find that Dr. Hopkinson has not presented adequate assurances that he understands his obligations as a clinical investigator and that those obligations will be met in the future. My decision in not accepting Dr. Hopkinson's assurances is based not only on their inadequacy, but also on his inability to demonstrate his understanding of violations of the FDA requirements in his studies and of the requirements imposed on clinical investigators. Dr. Hopkinson did not demonstrate that he, personally, was aware of the nature of his deficiencies or that he became aware of them during the course of the proceedings.

I have, on occasion, as presiding officer, recommended acceptance of assurances from clinical investigators found to violate the regulations. In those cases, however, the assurances were supported by showing the clinical investigator's awareness of the nature of the previous deficiencies, the requirements of the regulation for performance of clinical trials, and his ultimate responsibility as a clinical investigator. All these factors contribute to support specific assurances as reasonable and credible. In Dr. Hopkinson's case, I do not feel that the assurances are adequate.

Conclusions Regarding Dr. Hopkinson's Eligibility to Receive  
Investigational Drugs

I conclude that Dr. Hopkinson repeatedly and deliberately violated regulations pertaining to the proper conduct of clinical studies involving investigational new drugs. These violations are of sufficient significance to warrant disqualification in the absence of adequate assurances that Dr. Hopkinson will comply with the regulations in the future. The assurances provided by Dr. Hopkinson are not adequate to assure that Dr. Hopkinson will conform to the conditions of the IND exemption in the future.

  
Stuart L. Nightingale, M.D.  
Presiding Officer