DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

January 17, 2001

[redacted], Esq.
Esq.

Ann Wion, Esq.
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Food and Drug Administration
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Counsel:

I have reviewed the record of the regulatory hearing involving James A. Halikas, M.D., the summary decision of the Presiding Officer, the parties' summary decision memoranda with attachments, and Dr. Halikas' submission requesting review of the summary decision. Based upon my review, I have concluded that Dr. Halikas repeatedly and deliberately violated 21 CFR § 50.20 in connection with an investigational new drug study of [redacted]. Consistent with 21 CFR § 312.70(b), I have determined that Dr. Halikas is no longer entitled to receive investigational drugs. The reasons for my decision are set forth in the enclosed decision.

Dr. Halikas may seek to have his eligibility to receive investigational drugs reinstated pursuant to 21 CFR 312.70(f) upon presentation of adequate assurances that the investigator will employ investigational drugs solely in compliance with the provisions of 21 CFR Parts 50, 56, and 312.

Sincerely,

Jane E. Henney, M.D.
Commissioner of Food and Drugs

Enclosure

cc: Linda Ann Sherman, M.D., M.P.H.
Presiding Officer (w/enclosure)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

REGULATORY HEARING ON THE PROPOSAL TO DISQUALIFY

JAMES A. HALIKAS, M.D.

FROM RECEIVING INVESTIGATIONAL NEW DRUGS

COMMISSIONER'S DECISION

The purpose of this proceeding is to determine, pursuant to 21 CFR § 312.70(b) and 21 CFR Part 16, whether James A. Halikas, M.D., a clinical investigator, should be disqualified from receiving investigational new drugs. Linda Ann Sherman, M.D., M.P.A., serves as the presiding officer for this disqualification. Dr. Sherman issued a summary decision in favor of the Center for Drug Evaluation and Research (CDER or the Center) and recommends that Dr. Halikas be disqualified.

Based upon my review of the administrative record in this matter, including Dr. Sherman's summary decision and the parties' submissions, I conclude that Dr. Halikas repeatedly and deliberately failed to obtain legally effective informed consent, in violation of 21 CFR § 50.20. Therefore, I am disqualifying Dr. Halikas from receiving investigational drugs. The reasons for my decision follow.

I. PROCEDURAL BACKGROUND

On June 22, 1992, FDA received an Investigational New Drug Application ("IND") (No. [ ]), from Dr. Halikas, which proposed a study of [ ] as a treatment for alcohol withdrawal syndrome. Studies under this protocol were never initiated. On August 3, 1992, FDA received three amendments to the original protocol from Dr. Halikas. The first of these, the [ ] Amendment 1 Study, is at issue here.

The [ ] Amendment 1 Study proposed a Phase 1 open-label dosing study to investigate the use of [ ] in the treatment of opiate addiction in a population of Hmong patients. Beginning on June 11, 1993, nine Hmong subjects were enrolled in the Amendment 1 Study.[1] On August 3, 1993, Dr. Halikas learned that signed, written informed consent forms had not been obtained from the Hmong study subjects. Dr. Halikas voluntarily stopped this study on August 5, 1993.

In a letter dated April 2, 1997, FDA's Associate Commissioner for Regulatory Affairs informed Dr. Halikas that he would be given an opportunity for a regulatory hearing under 21 CFR Part 16 to determine whether he should be disqualified from receiving investigational drugs. The notice of opportunity for a hearing (NOOH) was issued pursuant to 21 CFR §§ 312.70 and 16.22. The NOOH alleged violations of 21 CFR Parts 50 and 312. Dr. Halikas

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[1] One other subject was enrolled in the [ ] IND No. [ ]; study, under Amendment 3 on May 10, 1993. This subject was a non-Hmong, English speaking, heroin-addicted subject who signed the informed consent form for the study before [ ] was administered. Only one of the nine Hmong subjects enrolled in the Amendment 1 Study signed an informed consent form on the day that he or she first received treatment with [ ].

requested a hearing in a letter dated April 16, 1997. On January 16, 1998, the Center moved for summary decision on five charges:

1) the failure to obtain informed consent, in violation of 21 CFR § 50.20;

2) the failure to obtain timely informed consent, in violation of 21 CFR § 50.20;

3) the failure to provide informed consent in a language understandable to study subjects, in violation of 21 CFR § 50.20;

4) the failure to minimize or reduce the risk of coercion to the study subjects to enroll in the study, in violation of 21 CFR § 50.20; and

5) the failure to adhere to the study dosing limits in the study protocol, in violation of 21 CFR §§ 312.50 and 312.60.

On March 2, 1998, Dr. Halikas submitted a Memorandum in Opposition to the Center's Motion. On March 17, 1998, the Center submitted a Memorandum in Reply to Dr. Halikas' Opposition to its Motion.

Under 21 CFR § 16.26(b), the presiding officer may issue a summary decision on any issue when there is no genuine and substantial issue of fact respecting that issue. Based upon the evidence presented in and attached to the Center's summary decision motion, Dr. Halikas' opposition to the Center's motion, and the Center's reply to Dr. Halikas' opposition, Dr. Sherman issued a summary decision on two of the issues in favor of the Center on May 3, 2000.

Dr. Sherman found that there were no genuine and substantial issues of fact with regard to Charges 1 and 2, and issued summary decision in favor of the Center on those charges. Regarding Charge 1, Dr. Sherman found that Dr. Halikas repeatedly and deliberately failed to

obtain legally effective informed consent from five of the nine Hmong subjects in the study, in violation of 21 CFR § 50.20. Dr. Sherman relied on (1) Dr. Halikas' statement to FDA investigators that he was not involved in obtaining informed consent from any of the study subjects prior to their involvement in the [ ] Amendment 1 study, (2) FDA interviews with a study subject and staff of the Chemical Dependency Treatment Program where the study took place, in which the subject and staff indicated that informed consent was not obtained from the subjects, and (3) Dr. Halikas' statements in two letters stating essentially that he had failed to ensure that signed, written informed consent was obtained from the five Hmong study subjects and that he had failed to ensure that anyone had obtained any form of informed consent from the subjects.

Regarding Charge 2, Dr. Sherman found that Dr. Halikas repeatedly and deliberately failed to obtain timely legally effective informed consent from three additional Hmong study subjects. Relying on her findings under Charge 1, Dr. Sherman found that as a matter of law Dr. Halikas committed these violations repeatedly and deliberately.

Dr. Sherman found that it was unnecessary to address Charge 3 because she had already found, under Charges 1 and 2, that Dr. Halikas repeatedly and deliberately failed to obtain legally effective informed consent from eight of the Hmong study subjects, and it was irrelevant whether the informed consent forms were understandable to the study subjects. With regard to Charge 4, Dr. Sherman stated that since she had found that Dr. Halikas did not obtain legally effective informed consent from eight of the Hmong subjects, there was no reason to address a violation concerning the circumstances under which consent was sought. Finally, on Charge 5, Dr.

Sherman found that a final determination as to whether Dr. Halikas violated 21 CFR §§ 312.50 and 312.60 could not be made without evidence regarding the significance of the dosage changes, and therefore denied the Center's motion for summary decision on that charge. Based upon these findings, Dr. Sherman recommended that Dr. Halikas be disqualified from receiving investigational drugs.

In a letter dated June 6, 2000, Dr. Halikas requested that I review the summary decision and not concur in Dr. Sherman's recommendation. Dr. Halikas requested review of Dr. Sherman's summary decision stating (1) the Presiding Officer ignored inferences favoring Dr. Halikas; (2) Dr. Sherman gave the terms "repeatedly" and "deliberately" meanings that are inconsistent with their common legal meanings, and that the meanings given these words effectively violate the Administrative Procedure Act; and (3) a general reiteration of each of the arguments presented in his opposing pleadings and incorporation of those pleadings by reference. Dr. Halikas also requested that the Commissioner not concur in Dr. Sherman's recommendation that Dr. Halikas be disqualified, arguing that he has been effectively disqualified for seven years.

II. DECISION

In order to conclude that a clinical investigator is no longer eligible to receive investigational drugs, I must find that the investigator repeatedly or deliberately violated FDA regulations, or repeatedly or deliberately submitted false information to FDA or to the sponsor. Section 312.70(b) of Title 21 of the Code of Federal Regulations provides, in relevant part, that:

> [a]fter evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately

> failed to comply with the requirements of this part, Part 50, or Part 56, or has deliberately or repeatedly submitted false information to FDA or to the sponsor in any required report, the Commissioner will notify the investigator and the sponsor of any investigation in which the investigator has been named as a participant that the investigator is not entitled to receive investigational drugs. The notification will provide a statement of basis for such determination.

Therefore, a determination that an investigator either repeatedly or deliberately failed to comply with the regulations or submitted false information is a sufficient basis for disqualification.

A. Repeatedly or Deliberately Failing to Comply with 21 CFR Parts 50 and 312

In this proceeding, Dr. Halikas is charged with repeatedly or deliberately failing to comply with 21 CFR Parts 50 and 312. I will, as Dr. Sherman did in her summary decision, separately address each of the charges briefed in the parties' summary decision memoranda.

1. The failure to obtain informed consent, from five study subjects, in violation of 21 CFR § 50.20.

The Center charged that Dr. Halikas failed to obtain informed consent from five Hmong study subjects who received [redacted], in violation of 21 CFR § 50.20. As support for this charge, the Center referred to a statement Dr. Halikas made in a July 20, 1994, letter to FDA investigators, that he takes and "continue[s] to take primary responsibility for failure to obtain signed consent from five of the ten subjects" (emphasis in the original). The Center also referred to a similar statement Dr. Halikas made in a February 17, 1994, letter to the administrator of the Committee on the Use of Human Subjects in Research (the Institutional Review Board or IRB

for the [ ] study), that "I, as Principal Investigator, bear the ultimate responsibility for the failure to obtain written signed consents on the five . . . patients." The Center noted that in addition to being the sponsor and principal investigator of the [ ] IND study, Dr. Halikas was also the Director of the University of Minnesota's Chemical Dependency Treatment Program (CDTP), a member of the University of Minnesota's IRB, and an experienced clinician who had previously worked with the Hmong population.

In response, Dr. Halikas stated that the Center was relying exclusively on his acknowledgment that he accepted primary responsibility for not obtaining signed, written informed consent from the subjects. Dr. Halikas argued that 21 CFR § 50.20 requires only legally effective informed consent and does not require signed, written informed consent. Dr. Halikas argued that to be legally effective, the patient must understand the nature of the treatment, the potential risks and benefits, alternative treatments, and that the patient has the right to discontinue at any time.

Additionally, Dr. Halikas asserted that under Minnesota law, it is the hospital's responsibility to ensure that the patient understands the treatment, the potential risks and benefits of the treatment, and his or her right to discontinue treatment. Dr. Halikas stated that each patient had acknowledged in writing that he or she understood these matters. Further, Dr. Halikas stated that the record demonstrates that hospital staff did discuss with each patient the [ ] regimen and the right to discontinue treatment. Dr. Halikas argued that every patient thus received the information necessary to make an informed decision as to whether to take the [ ].

In her summary decision, Dr. Sherman agreed that the two letters cited by the Center did not support the Center's assertion that Dr. Halikas admitted that he never obtained any consent from the five Hmong subjects. Dr. Sherman found that although the record did show that Dr. Halikas had admitted that neither he nor anyone else obtained signed, written informed consent from the five Hmong subjects, he did not specifically admit that legally effective informed consent was not obtained. Dr. Sherman stated, however, that upon review of all the evidence submitted in support of the motion for summary decision, she found that the Center "presented sufficient evidence to show that there is no genuine issue that Dr. Halikas did not obtain legally effective informed consent from the five subjects."

As the basis for this finding, Dr. Sherman cited FDA's Establishment Inspection Report Summary of Findings (EIR) dated October 21, 1993 through April 7, 1994, which included a statement by Dr. Halikas to FDA investigators that he was not involved in subject intake/obtaining consent. The EIR also included a statement from one of the study subjects that he or she was never informed that he or she was being included in a drug study. Dr. Sherman also noted that the EIR states that the FDA investigators interviewed several individuals who worked at the University of Minnesota's CDTP at the time of the study. The interviewees included a resident, a fellow, and a medical student at the University of Minnesota; the clinical director of the University of Minnesota's CDTP; and the interim director at the University of Minnesota's CDTP According to the EIR, these individuals confirmed that informed consent was not obtained from the five Hmong study subjects. Additionally, Dr. Sherman found that the letters cited by the Center, when reviewed in their entirety, contained evidence that Dr. Halikas

failed to ensure that anyone obtained any form of informed consent. Dr. Sherman found that Dr. Halikas' statements, as noted in the letters to the FDA investigators and the Committee on the Use of Human Subjects in Research, demonstrated that Dr. Halikas failed to obtain legally effective informed consent from the five Hmong study subjects.

In response to Dr. Halikas' arguments, Dr. Sherman found that she could not equate a patient's reading and understanding of the Minnesota Patients' Bill of Rights with ensuring that the Hmong study subjects gave legally effective informed consent to participation in the [ ] Amendment 1 Study. Dr. Sherman also found that it was irrelevant whether the Hmong study subjects may have signed statements that "they understood their State statutory rights" because the provisions of the bill of rights did not fulfill the requirements of 21 CFR § 50.20. Dr. Sherman continued by stating that in the absence of any evidence that legally effective informed consent was actually obtained by the staff from the Hmong study subjects, a genuine and substantial issue of fact as to whether Dr. Halikas obtained informed consent was not created. Dr. Sherman noted that under FDA regulations it was Dr. Halikas' responsibility, not the University of Minnesota Hospital's, to ensure that legally effective informed consent was obtained from the Hmong study subjects before their involvement in the [ ] Amendment 1 Study.

With regard to Dr. Halikas' argument that patient records reflect that hospital staff discussed with each study subject the proposed [ ] Amendment 1 Study and his or her right to discontinue treatment, Dr. Sherman noted that Dr. Halikas had provided the records for only one of the Hmong study subjects, and that the records did not establish a dispute as to whether

informed consent was obtained from even the one subject. Dr. Sherman found that the records simply established that the subject received doses of [ ] and was informed regarding this new medication for withdrawal. Dr. Sherman noted that the information that would have been discussed at daily meetings was insufficient to overcome a motion for summary decision in view of the lack of any statements from staff that legally effective informed consent was actually obtained.

Dr. Sherman then continued by finding that Dr. Halikas had violated 21 CFR § 50.20 both repeatedly and deliberately.

Dr. Sherman noted that FDA interprets the term repeatedly as meaning "more than once." Dr. Sherman found that Dr. Halikas' failure to obtain legally effective informed consent from five Hmong study subjects was a repeated violation of 21 CFR § 50.20.

Consistent with findings in previous disqualifications, Dr. Sherman found that Dr. Halikas had also deliberately violated 21 CFR § 50.20 because the violations were committed "with a reckless disregard for the rights of the Hmong study subjects to not be involved in the [ ] Amendment 1 Study without giving their informed consent." As the basis for this finding, Dr. Sherman noted that the record established that Dr. Halikas, both as a clinical researcher with many years of experience and as a member of an IRB, was well aware of the requirement to obtain legally effective informed consent from study subjects. Dr. Sherman also noted that Dr. Halikas knew, and had described, the Hmong population as a particularly vulnerable population.

Although Dr. Halikas had argued that to establish "deliberate," testimony as to his state of mind was necessary, Dr. Sherman found that a credibility assessment was unnecessary to resolve

the issue. Dr. Halikas also argued that the Center failed to allege that Dr. Halikas acted deliberately, as the term is commonly understood, and that even if deliberate conduct could be defined as including a reckless disregard of obvious and known risks, the factual record dispels the suggestion that Dr. Halikas acted in this manner. Dr. Sherman found, however, that reckless disregard was the appropriate standard to apply. Finally, as noted earlier, Dr. Sherman found that the record, which included information as to Dr. Halikas' experience as a clinical investigator, membership on an IRB, and his awareness of the vulnerability of the Hmong population, did establish that "Dr. Halikas acted with reckless disregard of the rights of the Hmong study subjects to not be involved in the [ ] Amendment 1 Study unless and until they gave their legally effective informed consent."

In summary, Dr. Sherman found that the Center met its initial burden on this charge and that, in response, Dr. Halikas failed to establish that a genuine and substantial issue of fact existed. Dr. Sherman noted that Dr. Halikas proffered no statements from any staff that legally effective informed consent was actually obtained from the five Hmong study subjects, and that he never contended that he obtained legally effective informed consent from the five Hmong study subjects. Thus, Dr. Sherman issued a summary decision in favor of the Center on this issue.

I am persuaded by the evidence in the record that Dr. Sherman's finding on this charge was appropriate. As discussed above, the record contains an FDA EIR that summarizes the interviews FDA investigators had with Dr. Halikas and staff (see page 8 of this Decision) who assisted with the study. Not one of these individuals states that legally effective informed consent, consistent with the requirements of 21 CFR § 50.20, was ever obtained from the five

Hmong study subjects. On the contrary, according to the EIR, staff confirmed that informed consent was not obtained from these subjects. Additionally, the 1994 letters from Dr. Halikas to FDA investigators, and to the administrator of the University of Minnesota Committee on the Use of Human Subjects in Research, both include statements from Dr. Halikas that he failed to obtain signed, written informed consent from five of the Hmong study subjects, and also statements indicating that he failed to ensure that someone else obtained legally effective informed consent from the five Hmong subjects. This, despite the fact that Dr. Halikas had extensive experience in the area of clinical investigations and human subjects research, including membership on the Committee on the Use of Human Subjects in Research. Finally, there is evidence in the record that Dr. Halikas was aware that the Hmong population was an especially vulnerable population. For all these reasons, I find that Dr. Sherman's conclusion that there is no genuine and substantial issue of fact that Dr. Halikas violated 21 CFR § 50.20 by failing to obtain legally effective informed consent from five Hmong study subjects is appropriate and affirm it.

Additionally, I affirm Dr. Sherman's finding that Dr. Halikas violated 21 CFR § 50.20 repeatedly and deliberately.[2] Thus, consistent with 21 CFR § 312.70, I determine that Dr. Halikas repeatedly and deliberately failed to comply with 21 CFR § 50.20 and is no longer entitled to receive investigational drugs.

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[2] The issues Dr. Halikas has raised regarding the appropriate meanings of repeatedly and deliberately are discussed in depth in Section II.B.2 of this decision.

2. The failure to obtain timely informed consent, from three additional study subjects, in violation of 21 CFR § 50.20.

The Center charged that Dr. Halikas also violated 21 CFR § 50.20 by failing to obtain legally effective informed consent from three additional Hmong study subjects before they received [ ]. The Center again relied upon statements made in the July 20, 1994, letter from Dr. Halikas to FDA investigators. In response, Dr. Halikas made the same arguments he made in response to Charge 1: that although signed, written informed consent was not obtained before these three study subjects received [ ], state law required the University of Minnesota Hospital to present the Minnesota Patients' Bill of Rights to the Hmong study subjects, as part of the general admissions process; that others would have obtained informed consent; and that portions of one patient (subject) record evidenced that timely legally effective informed consent was obtained from all three of these Hmong subjects. Dr. Sherman noted that the fact that the three subjects had signed informed consent forms after they received [ ] was irrelevant because 21 CFR 50.20 requires that legally effective informed consent be obtained before involving any human being in research. Dr. Sherman stated that she found Dr. Halikas' response to Charge 2 insufficient to withstand a summary judgment motion for the same reasons as discussed under Charge 1, and found that Dr. Halikas had committed the violation repeatedly and deliberately.

Similarly, I affirm Dr. Sherman's finding on this charge for the reasons discussed in my analysis of Charge 1. The fact that informed consent was eventually obtained is immaterial here; the informed consent was only obtained for these three Hmong study subjects after they received their first dose(s) of [ ].

3. The failure to provide informed consent forms in a language understandable to four study subjects, in violation of 21 CFR § 50.20.

The Center also charged that Dr. Halikas failed to provide informed consent forms in a language understandable to the four Hmong study subjects who signed informed consent forms (three of whom had already started receiving [ ]), in violation of 21 CFR § 50.20. The Center supported this charge with statements made by Dr. Halikas in a February 17, 1994, letter to the administrator of the Committee on the Use of Human Subjects in Research, and an August 13, 1992, letter to an FDA employee in FDA's Office of Pilot Drug Evaluation. In the February 17 letter, Dr. Halikas stated "that a signed, written consent form, not even [one] understood by the interpreter, added nothing to these patients' actual understanding of informed consent." In response to this allegation, Dr. Halikas argued that the Center had misinterpreted his statements and that he was simply stating that the verbal informed consent obtained from each subject was understandable and that a written informed consent added nothing.

Dr. Sherman observed that she had already found that Dr. Halikas failed to obtain legally effective informed consent from five of the Hmong study subjects, and timely legally effective informed consent from three additional Hmong study subjects. Thus, Dr. Sherman found that it did not matter whether the informed consent forms given to four of the Hmong study subjects were understandable to them, and did not reach the issue.

Based upon my review of the record in this case, I find that Dr. Sherman acted appropriately by not reaching this charge. Because the record demonstrates that Dr. Halikas failed to obtain legally effective informed consent from five of the Hmong study subjects, and

failed to obtain timely legally effective informed consent from three additional Hmong study subjects, it is unnecessary to determine whether the forms that were eventually provided to the three Hmong study subjects--after they had already received [ ] –were understandable to them. I note that there is a ninth Hmong study subject from whom signed, written informed consent was apparently obtained on the same day he or she received the first dose of [ ]; had this disqualification proceeded to an oral hearing, it might have been appropriate to receive testimony as to whether the form was understandable to this Hmong study subject. Since, however, Dr. Halikas is disqualified because of my findings under Charges 1 and 2, it is unnecessary to determine whether oral testimony on this charge would have been of value.

4. The failure to minimize or reduce the risk of coercion to the study subjects, in violation of 21 CFR § 50.20.

The Center charged that Dr. Halikas failed to minimize or reduce the risk of coercion when he failed to obtain legally effective informed consent from the Hmong study subjects before involving them in the [ ] Amendment 1 Study and by failing to provide informed consent in a language understandable to the Hmong study subjects. The Center relies upon Dr. Halikas' statement in an August 10, 1993, memorandum to the administrator of the Committee on the Use of Human Subjects in Research as supporting evidence. Dr. Halikas argues that the Center's argument is premised upon the conclusion that no informed consent was obtained, but that his statements merely show that he acknowledged that the absence of signed, written informed consent raises the possibility of coercion, but that he has not admitted that there had been coercion.

Dr. Sherman found that because she had already determined that Dr. Halikas repeatedly and deliberately failed to obtain legally effective informed consent from five of the Hmong study subjects, and timely legally effective informed consent from three additional Hmong study subjects, there was no reason to address a violation concerning the circumstances under which consent was sought.

I find Dr. Sherman's decision on this charge appropriate and affirm her finding.

5. The failure to adhere to the study dosing limits in the study protocol, in violation of 21 CFR §§ 312.50 and 312.60.

The Center charged that Dr. Halikas, as a sponsor-investigator, violated 21 CFR §§ 312.50 and 312.60 because he failed to adhere to the protocol on file with FDA, in that he exceeded the dosage regimen and subjected his patients to unacceptable and unnecessary risk. The Center supported this charge with statements made by Dr. Halikas in a May 3, 1994 (corrected July 20, 1994), letter to the Center, an April 11, 1994, letter to FDA investigators, and Patient Discharge Summaries.

In response, Dr. Halikas argued that he did not improperly modify the dosing requirements and that the Center inappropriately charged him with violating 21 CFR § 312.50, which applies only to sponsors. Dr. Halikas questioned the agency's authority "to disqualify a sponsor-investigator for actions taken by the individual in his capacity as a sponsor, not investigator." Dr. Sherman noted that because the Center charged Dr. Halikas with violating both 21 CFR § 312.50 (applicable to sponsors) and 21 CFR § 312.60 (applicable to

investigators),[3] it was unnecessary to further address Dr. Halikas' arguments on this point. Dr. Sherman continued by finding that although there was no factual dispute that Dr. Halikas deviated from the dosing regimen established in the protocol on file with FDA, she believed it would be appropriate to determine the significance of the dosage changes Dr. Halikas made, before deciding whether he violated 21 CFR §§ 312.50 and 312.60. Therefore, Dr. Sherman stated that she could not make a determination on this charge without further evidence and denied the Center's motion for summary decision on this charge.

The Center has not requested that I review Dr. Sherman's decision on this charge and I, accordingly, have not done so.

6. Summary of Findings

Based upon the above analysis, I conclude that there is no genuine and substantial issue of fact with regard to whether Dr. Halikas repeatedly and deliberately failed to obtain legally effective informed consent from five Hmong study subjects, and timely legally effective informed consent from three additional Hmong study subjects, in violation of 21 CFR § 50.20. Under 21 CFR § 312.70, my findings on Charges 1 and 2 are sufficient to disqualify Dr. Halikas.

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[3] At the time of the alleged violations, the regulations did not explicitly address the status of sponsor-investigators, although FDA's longstanding interpretation of 21 CFR 312.70(b) was that it did encompass the disqualification of sponsor-investigators. The regulation was amended in 1997 to clarify the agency's authority to reach sponsor-investigators. See 62 Fed. Reg. 46875 (1997).

B. Dr. Halikas' Request for Review of the Summary Decision

As noted earlier, Dr. Halikas requested that I review Dr. Sherman's summary decision on several grounds. First, Dr. Halikas argues that Dr. Sherman ignored inferences favoring him and embraced attenuated inferences supporting the Center, contrary to caselaw holding that in deciding summary judgment motions, all reasonable inferences must be drawn in favor of the non-moving party. Second, Dr. Halikas argues that Dr. Sherman gave meanings inconsistent with common usage to the terms "repeatedly" and "deliberately." Finally, Dr. Halikas asked for review based on a general reiteration of "each of the arguments presented in his opposing pleadings."

1. Reasonable Inferences Must be Drawn in Favor of the Non-Moving Party

Dr. Halikas argues that Dr. Sherman was willing to accept evidence from the Center even though it could be considered double or triple hearsay under the Federal Rules of Evidence (FRE), but was unwilling to entertain Dr. Halikas' evidence even though that evidence would have been admissible under the FRE. Dr. Halikas further asserts that Dr. Sherman did not review documentary evidence supporting his opposition. Therefore, Dr. Halikas' argument seems to be that if the evidence he cites as supporting his arguments had been given the appropriate weight, the Presiding Officer could not have issued summary decision in favor of the Center. Dr. Halikas implies that this evidence should be given more weight than the evidence relied on by the Center because his evidence would allegedly be admissible under the FRE, and the Center's evidence would not.

Arguments based on the FRE are irrelevant in the context of a Part 16 hearing. A longstanding principle of regulatory hearings is that the hearing is informal in nature and the rules of evidence do not apply. See, e.g., 41 Fed. Reg. 48258, 48260 (1976) (preamble states technical rules of evidence are not applicable). This principle is codified at 21 CFR 16.60(c), and was re-emphasized in the preamble to the summary decision regulation, which states that the information that is submitted to show that there exists a genuine and substantial issue of fact "is not limited to evidence that is admissible under the Federal Rules of Evidence." 53 Fed. Reg. 4613, 4614 (1988). This preamble further states that "none of the information submitted . . . is required to meet those standards of admissibility." Id.

Dr. Halikas also states that Dr. Sherman dismissed arguments made in his opposition as "supposition or speculation." In his opposition, Dr. Halikas argued that the patients "would have" been asked if they wanted to continue with the treatment and "would have been" repeatedly provided with all of the information that appeared on the printed informed consent form before receiving any [ ]. Dr. Sherman determined that such speculation was inadequate to overcome the Center's motion for summary decision, which was supported by the EIR. The EIR included summaries of FDA interviews with staff (see page 8 of this Decision) who worked at the University of Minnesota's Chemical Dependency Treatment Program and on the study. According to the EIR, these individuals confirmed that informed consent was not obtained from the five Hmong study subjects, and one of the subjects stated that he or she was never informed that he or she was being included in a drug study. Dr. Sherman also noted that Dr. Halikas failed to proffer statements by the staff involved with the study that informed consent was actually

obtained from the subjects. Under the circumstances, this failure is fatal to his claim of what staff "would have" done.

In his request for my review, Dr. Halikas argues that Dr. Sherman ignored his citations to pages three and six of a letter that supported his claims as to "what was done" and "what was said." Thus, Dr. Halikas implies that if Dr. Sherman had reviewed the citations she would have found that the subjects were asked if they wanted to continue with the treatment and were repeatedly provided with all the information that appeared on the printed consent form. The citations in question appear in a July 20, 1994, letter from Dr. Halikas to FDA investigators. I reviewed the citations and found that they do not create reasonable inferences that must be drawn in favor of Dr. Halikas. The letter simply does not support a finding that the subjects were actually asked if they wanted to continue with the treatment and provided with all the information that appears on the printed informed consent form.

First, it is not clear what statements on pages three and six Dr. Halikas views as supporting his argument that the subjects were asked if they wanted to continue the treatment and provided with the information on the printed informed consent form. There is nothing on either of the cited pages of this letter that actually states that the subjects were given the information required under 21 CFR § 50.20 or that the investigator obtained legally effective informed consent from the subjects. One excerpt from page three that seems most related to the argument Dr. Halikas attempts to make is as follows: "[e]ach weekday morning, all chemical dependency team patients met with the physicians, nurses, social workers, interpreters, and allied health personnel, in a group where the treatment plan of each patient was discussed . . . [t]his daily

educational activity included repeated explanations about [ ] and all other medications used" (emphasis omitted). This excerpt says nothing about whether as part of the treatment plan discussion the patients were asked if they wanted to continue with the treatment and provided with the other information related to informed consent. Second, Dr. Halikas apparently was not present at these meetings, and as noted by Dr. Sherman in her summary decision, Dr. Halikas has not proffered statements from other staff that they provided the subjects, in the treatment plan discussions or at any other time, all the information that appeared on the printed informed consent form.

Third, there is nothing on page six of the letter to demonstrate "what was done" and "what was said" at the daily team meetings. Further, nothing on page six demonstrates or supports Dr. Halikas' argument that the subjects were informed of the investigational nature of the treatment and that the investigator obtained legally effective informed consent from the subjects. Rather, on page six of the letter, Dr. Halikas states that the record of one patient showed that the patient refused a "variety of specific hospital activities." Dr. Halikas inferred from this that the subject "did not feel himself in a coercive situation and felt free to refuse activities at will."

By contrast, there is significant information in the record demonstrating that Dr. Halikas failed to obtain legally effective informed consent from five of the Hmong study subjects, and timely legally effective informed consent from three additional Hmong study subjects. in violation of 21 CFR § 50.20. First, the FDA EIR notes that Dr. Halikas stated to FDA investigators that he was not involved with subject intake/obtaining consent and that he thought this would be "taken care of by other people via standard operating procedures." Second, the EIR

also includes summaries of interviews with staff (see page 8 of this Decision) who worked at the University of Minnesota's Chemical Dependency Treatment Program and on the study as well as an Hmong study subject from whom legally effective informed consent was not obtained; staff confirmed that informed consent was not obtained from the five Hmong study subjects. Third, as Dr. Sherman noted in her summary decision, when reviewed in their entirety, a July 20, 1994, letter from Dr. Halikas to FDA investigators, and a February 17, 1994, letter to the administrator of the Committee on the Use of Human Subjects, contain evidence that Dr. Halikas failed to ensure that anyone obtained any form of legally effective informed consent.

Other than the letter cited by Dr. Halikas and already discussed in detail above, Dr. Halikas provides no information that even allows for an inference that timely and legally effective informed consent was obtained from the eight Hmong study subjects, and mere allegations are not enough to overcome a properly supported motion for summary judgment. See First Nat'l Bank v. Cities Serv. Co., 391 U.S. 253, 289 (1968).

Therefore, the record supports Dr. Sherman's summary decision that there was no genuine and substantial issue of fact that Dr. Halikas failed to obtain to legally effective informed consent from five of the nine Hmong study subjects and failed to obtain timely legally effective informed consent from an additional three Hmong subjects. I affirm Dr. Sherman's findings.

2. Meaning of "Repeatedly" and "Deliberately"

Dr. Halikas also requested review on the ground that the Presiding Officer's interpretation of the words "repeatedly" and "deliberately" are inconsistent with common usage and the Administrative Procedure Act (APA). As Dr. Halikas states, under the APA, interpretive rules

must be published in the Federal Register. Decisions in investigator disqualification matters, however, are not interpretive rules. Thus, Dr. Halikas' statutory argument is beside the point.

A determination that the investigator either repeatedly or deliberately failed to comply with the regulations is enough to disqualify an investigator from entitlement to receive investigational new drugs. See 21 CFR § 312.70. Dr. Sherman found that Dr. Halikas both repeatedly and deliberately failed to comply with the regulations.

In her decision, Dr. Sherman stated the meaning of repeatedly as "more than once." Dr. Halikas maintains that repeatedly must mean transgressions in more than one study. Dr. Sherman's interpretation of repeatedly is consistent with the meaning of repeatedly given in previous disqualifications.[4]

Even without this precedent, however, it is wholly reasonable to interpret "repeatedly" as meaning more than once. The plain meaning of "repeatedly" is again and again. See Webster's Ninth New Collegiate Dictionary, 1991, Merriam-Webster, Inc. There is no reason to assume that in the context of a disqualification proceeding, repeatedly should bear other than its plain meaning. In fact, to interpret repeatedly to mean transgressions in more than one study would permit an investigator to commit as many violations of the regulations as he/she wished without possibility of disqualification as long as that investigator limited his/her violations to one study. Such a result--and the interpretation offered by Dr. Halikas–would be absurd.

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[4] See e.g., Reports of the Presiding Officer: In the Matter of Chaovanee Aroonsakul, M. D. (1990); In the Matter of Ronald R. Fuller, D.V.M. (1987); In the Matter of John H. Hopkinson III, M.D. (1982); and In the Matter of Michael C. Gelfand, M.D. (1980).

In his request for my review, Dr. Halikas also refers to the discussion in his opposition, stating that it explained in detail why the term "repeatedly" must mean transgressions in more than one study. Dr Halikas asserts that the agency had taken this position in rulemakings, citing the preamble to one proposed rule. See 43 Fed. Reg. 35210, 35217 (1978).[5]

The preamble to which Dr. Halikas cites is to a proposed rule that was withdrawn in 1991. See 56 Fed. Reg. 67440, 67446 (1991). The notice of withdrawal specifically states that the withdrawn proposals do not bind or commit the agency to the views expressed. Id. at 67440-441.

Dr. Sherman found that there was no genuine and substantial issue of fact as to whether Dr. Halikas repeatedly violated 21 CFR § 50.20. Dr. Sherman further found that Dr. Halikas failed to obtain legally effective informed consent from five Hmong study subjects, and failed to obtain timely legally effective informed consent from three additional Hmong study subjects. Dr. Halikas' failures to obtain legally effective informed consent and timely legally effective informed consent represent repeated violations of 21 CFR § 50.20. I reiterate my earlier affirmation of Dr. Sherman's findings on these issues.

Dr. Halikas also argues that Dr. Sherman inappropriately found that Dr. Halikas acted deliberately because Dr. Sherman did not make any assessment of Dr. Halikas' state of mind. Dr. Halikas refers to his opposition in which he emphasized the "traditional meaning of the term

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[5] In his opposition, Dr. Halikas incorrectly cites this as 52 Fed. Reg. 35210.

'deliberately' and the fact that assessments of state of mind cannot be made in the course of summary proceduring [sic]."

Dr. Sherman found that Dr. Halikas acted deliberately because he acted with a reckless disregard for the rights of the study subjects to not be involved with the study unless and until they gave their legally effective informed consent. Dr. Sherman's interpretation of deliberately is consistent with the interpretation of "deliberately" given in previous disqualifications.[6] Even without this precedent, however, it is wholly reasonable to view deliberate as being established when it is shown that the clinical investigator engaged in reckless conduct.

Deliberately is defined as including willfully See Black's Law Dictionary 427 (6th ed. 1990). In McLaughlin v. Richland Shoe Co., 486 U.S. 128, 133 (1988), the Supreme Court stated that "[i]n common usage the word 'willful' is considered synonymous with . . . 'deliberate' . . . ." In McLaughlin, the Court was trying to give meaning to the word "willful," which was used in a particular statute. Id. The Court found that although willful could not be viewed as conduct that is merely negligent, it could be viewed as conduct demonstrating reckless disregard. Id. See also Wehr v. Burroughs Corp., 619 F.2d 276, 283 (3d Cir. 1980) (willful "is used to characterize conduct marked by careless disregard"); United States v. Ottley, 509 F.2d 667, 672 (2d Cir. 1975) (an act is committed willfully, if one acts in reckless disregard of the law's requirement). Willful or reckless conduct tends to "take on the aspect of highly unreasonable

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[6] See e.g., Reports of the Presiding Officer, In the Matter of John H. Hopkinson III, M.D. (1982); In the Matter of Martin S. Mok, M.D. (1982).

conduct, involving an extreme departure from ordinary care." W. Page Keeton et al., Prosser and Keeton on Torts § 34 at 214 (5th ed. 1984).

Dr. Sherman found that Dr. Halikas acted deliberately based on evidence in the record that demonstrated that Dr. Halikas was well aware of the requirement to obtain informed consent from subjects before involving them in clinical research. The record included evidence that showed that Dr. Halikas had been involved in clinical research for twenty years, was the principal investigator for twenty-one studies, and served on a committee addressing issues involving the use of human subjects in research

In addition, included in the record is an August 13, 1992, letter written by Dr. Halikas to an FDA employee, in which Dr. Halikas acknowledges that "this is a 'vulnerable' population . . . . [t]hey are, rather, intimidated by all of western authority." Thus, despite his experience with human subject research and the requirements of the regulations, and his knowledge of the vulnerability of this particular population, Dr. Halikas failed to ensure that legally effective informed consent was obtained. It was unnecessary for Dr. Sherman to hold an oral hearing to determine that Dr. Halikas' failures were "deliberate" because Dr. Halikas' conduct and failure to act demonstrated reckless disregard. Under the circumstances, Dr. Halikas' actions were highly unreasonable and an extreme departure from ordinary care, and his failure to ensure that legally effective informed consent was obtained could appropriately be viewed as deliberately failing to comply with 21 CFR Part 50.

Dr. Sherman found that there was no genuine and substantial issue of fact as to whether Dr. Halikas deliberately violated 21 CFR § 50.20. Based upon the above discussion, I affirm Dr. Sherman's findings on this issue.

3. General Reiteration of the Arguments

Dr. Halikas' final basis for his request for my review is a general reiteration of all the arguments he made in his pleadings. I reviewed Dr. Halikas' pleadings in order to evaluate and respond to his request for my review and in the course of reaching my decision. I find the arguments in question to be without merit.

III. CONCLUSION

I find that Dr. Halikas repeatedly and deliberately failed to comply with the requirements of 21 CFR Part 50, in connection with the clinical investigation of the investigational drug [ ]. I also find that the violations are sufficiently serious so as to require disqualification.

I note that Dr. Halikas argues, in his request for my review, that I should not concur in Dr. Sherman's recommendation that he be disqualified because he has been effectively disqualified for seven years. Dr. Halikas states that the University of Minnesota IRB (Dr. Halikas has been a faculty member of the University of Minnesota during the pendency of the FDA action) has taken the position that he could not participate in any human subject research during the pendency of this FDA action.

Once a finding is made that an investigator has repeatedly or deliberately failed to comply with the applicable requirements, disqualification generally must follow. In the preamble to 21 CFR § 312.70, FDA rejected the option of lesser sanctions, providing instead that disqualification

would be the general response to violations. 52 Fed. Reg. 8798, 8826 (1987). However, the preamble does provide that the Commissioner always retains the discretion not to disqualify if the Commissioner believes the violations are insignificant or lesser sanctions would be adequate. Id. The preamble makes clear that this discretion should be exercised only in extraordinary circumstances (e.g., where the violations are truly insignificant, or where disqualification would be truly unjust or would accomplish nothing). Id.

Given the findings in this matter, such extraordinary circumstances do not exist. Dr. Sherman found, and I concur, that Dr. Halikas both repeatedly and deliberately failed to obtain any legally effective informed consent from five of the nine Hmong subjects, and failed to obtain timely legally effective informed consent from an additional three of the nine Hmong subjects, in a study involving an experimental drug. Further, the subject population was one generally considered to be, as Dr. Halikas himself stated, a vulnerable population

Therefore, I conclude that Dr. Halikas is no longer entitled to receive investigational drugs. Dr. Halikas may seek to have his eligibility to receive investigational drugs reinstated pursuant to 21 CFR § 312.70(f).

Jane E. Henney, M.D.
Commissioner of Food and Drugs

Dated: January 17, 2001