DEPARTMENT OF HEALTH AND HUMAN SERVICES

U.S. FOOD AND DRUG ADMINISTRATION

REGULATORY HEARING ON THE PROPOSAL TO DISQUALIFY

JAMES ANASTASIO HALIKAS, M.D.

FROM RECEIVING INVESTIGATIONAL NEW DRUGS

SUMMARY DECISION OF THE PRESIDING OFFICER

I. INTRODUCTION

Pursuant to Title 21 of the Code of Federal Regulations ("C.F.R.") Parts 16 and 312, I have reviewed (1) the Motion for Summary Decision and supporting affidavits and exhibits submitted by the Center for Drug Evaluation and Research ("CDER" or the "Center"), Food and Drug Administration ("FDA"), (2) the Memorandum in Opposition to the Center for Drug Evaluation and Research's Motion for Summary Decision and exhibits submitted by James A. Halikas, M.D., and (3) the Memorandum in Reply to Dr. Halikas' Opposition to the Center's Motion for Summary Decision submitted by the Center, in response to Dr. Halikas' request for a hearing to consider CDER's proposal to disqualify him from being eligible to receive investigational new drugs pursuant to 21 U.S.C § 355(I) and 21 C.F.R. § 312.70.

Pursuant to 21 C.F.R. § 16.26(b), this summary decision constitutes my ruling on the Center's motion. This decision will be referred to the Commissioner of Food and Drugs for a final determination on this matter, in accordance with 21 C.F.R. §§ 16.95 and 312.70.

2. 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.[1] *See* Center Motion at Tab F. Studies under the original IND protocol were never initiated. On August 3, 1992, FDA received three amendments to the original IND protocol from Dr. Halikas, only the first of which, Amendment 1 (hereafter referred to as the "[ ] Amendment 1 study"), is at issue here. *See* Center Motion at Tab S.

The [ ] Amendment 1 Study proposed a Phase I open-label dosing study to investigate the use of [ ] in the treatment of opiate addiction in a population of Hmong patients.[2] In the study protocol, the first three study subjects enrolled were to be given 5 mg/kg of [ ] four times a day ("q.i.d.") along with any needed methadone for five days of detoxification. If supplemental methadone were required at the 5 mg/kg dose, then the following three study subjects would receive 10 mg/kg of [ ] q.i.d. for five days, again with supplemental methadone as needed.

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[1] Because Dr. Halikas both initiated and conducted the [ ] IND study, he was a sponsor-investigator, as defined by 21 C.F.R. § 312.3 (b).

[2] The Hmong are an ethnic group of tribes people who originally resided in the rural mountainous regions of Laos, Cambodia, and Vietnam. Under threats against the Hmong by the North Vietnamese at the close of the Vietnam war, the United States offered to expatriate them to the United States. Those who accepted the offer were resettled by the government in the Minneapolis-St .Paul, Minnesota area. *See* Halikas Opposition at 7. Many of the Hmong who settled in the Minneapolis-St. Paul area are middle-aged and elderly adults who were former opium farmers and who used opium for the treatment of many somatic ailments.

The Hmong did not have a written language until one was developed for them by missionaries in the 1950s. Many Hmong are illiterate in both their own written language as well as English. In order to accommodate these patients, the State of Minnesota employs Hmong translators to communicate with those admitted to the hospital. *See* Halikas Opposition at n. 4.

This dose escalation procedure would continue until a maximum dosage of 15 mg/kg of [ ] q.i.d. was attained. If any untoward side effects, such as drowsiness, vertigo or nausea were observed in the initial 5 mg/kg q.i.d. group, the dosage of [ ] was to be adjusted downward, first to 2.5 mg/kg, and if necessary, to 1 mg/kg of [ ] for five days of detoxification. Once an appropriate dose that maximized efficacy and minimized side effects was determined, it was to be selected and carried forward into the outpatient setting. *Id.*

In response to a local newspaper article claiming that Hmong study subjects were being coerced into enrolling in the [ ] Amendment 1 Study, FDA investigators initiated an inspection on October 21, 1993. *See* Center Motion at Tabs M and N. The inspection disclosed that Dr. Halikas began enrolling study subjects under IND [ ], Protocol 1, Amendment 1, on May 10, 1993.[3] On August 3, 1993, Dr. Halikas learned that written informed consent forms had not been obtained from the Hmong study subjects. The study was stopped two days later. *See* Center Motion at Tab I, p. 2 and 11.

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[3] Ten study subjects were enrolled in the [ ] IND study, one under Amendment 3, and nine under Amendment 1. The first subject, a non-Hmong, English-speaking, heroin-addicted patient was enrolled in the study under Amendment 3. She signed the informed consent form for the study before [ ] was administered. Nine additional subjects, Hmong people, most or all of whom were non-English speaking, were enrolled under Amendment 1. Of these nine individuals, five never signed informed consent forms, and three did not sign informed consent forms until after they had begun receiving [ ]. Only the last Hmong subject signed an informed consent form on the day that he or she received treatment with [ ]. *See* Center Motion at Tab I, at 2.

3. PROCEDURAL HISTORY

Based on the FDA investigation, CDER concluded that Dr. Halikas had failed to comply with the requirements of 21 C.F.R. Parts 50 and 312, and that he should be disqualified from receiving investigational new drugs. 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 C.F.R. Part 16 to determine whether he should be disqualified from receiving investigational new drugs. *See* Center Motion at Tab C. This Notice of Opportunity for a Hearing ("NOOH") was issued pursuant to 21 C.F.R. §§ 312.70 and 16.22, and alleged violations of 21 C.F.R. Part 50, specifically, of § 50.20 (failure to obtain informed consent, failure to obtain timely informed consent, failure to minimize or reduce the risk of coercion of the study subjects, and failure to provide informed consent in language understandable to the study subjects); § 50.25 (failure to explain elements of informed consent to study subjects); § 50.27 (failure to document informed consent and provide copies to the study subjects); §§ 312.50 and 312.60 (failure to follow research protocol regarding dosing limits, patient qualifications for enrollment in the study, and to conduct baseline laboratory analyses of study subjects prior to involvement in the study); and § 312.53 (failure to notify colleagues of their duties under the IND).

In a letter dated April 16, 1997, Dr. Halikas requested a hearing. *See* Center Motion at Tab D. On January 16, 1998, CDER moved for summary decision based on the following violations: 1) failure to obtain informed consent from the first five Hmong study subjects who received the investigational new drug [ ] in violation of 21 C.F.R. § 50.20; 2) failure to obtain timely informed consent from three Hmong study subjects who received the investigational new

drug [ ] in violation of 21 C.F.R. § 50.20; 3) failure to provide informed consent to the three Hmong study subjects who signed informed consent forms in language understandable to them, in violation of 21 C.F.R. § 50.20; 4) failure to minimize or reduce the risk of coercion of the Hmong study subjects to enroll in the study of the investigational new drug [ ], in violation of 21 C.F.R. § 50.20; and 5) failure to adhere to the study dosing limits in the study protocol, in violation of 21 C.F.R. §§ 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, CDER submitted a Memorandum In Reply to Dr. Halikas' Opposition to its Motion.[4]

4. REGULATORY FRAMEWORK

FDA's regulations governing the clinical evaluation of investigational new drugs are set forth in 21 C.F.R. Part 312. FDA's regulations regarding informed consent and study protocols applicable to clinical investigators and sponsors are set forth in 21 C.F.R. §§ 50.20, 50.25, 312.50, and 312.60. Section 312.70 of the regulations provides for the disqualification of clinical investigators[5] for violations of these regulations.

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[4] Following receipt of Dr. Halikas' Memorandum in Opposition to the Center's Motion, the Center sought to supplement the record with information and documents regarding the outcome of certain actions taken by the University of Minnesota, to which Dr. Halikas objected. The information contained in the Center's supplemental response concerns events that occurred after the time of the alleged violations were committed. I find that these events are not relevant to the charges before me. I have, therefore, not considered this additional information in rendering my decision in this matter.

[5] Including sponsor-investigators. *See* 21 C.F.R. §312.70(a).

> After 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 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.
> 21 C.F.R. § 312.70(b).

Pursuant to 21 C.F.R. § 16.26, the Presiding Officer of a Part 16 hearing is authorized to issue a summary decision on any issue in the hearing[6] if the Presiding Officer determines from material submitted in connection with the hearing, or from matters officially noticed, that there is no genuine and substantial issue of fact respecting that issue. *See* 21 C.F.R. § 16.26(b). A summary decision may be issued any time after receipt by FDA of a request for a hearing submitted in response to a NOOH. *Id.*

The standard for administrative summary decision contained in 21 C.F.R. § 16.26(b) mirrors that contained in Rule 56 of the Federal Rules of Civil Procedure ("Fed.R.Civ.P."), which provides that summary judgment "shall be rendered ... if ... there is no genuine issue as to any material fact and ... the moving party is entitled to a judgment as a matter of law." Fed.R.Civ.P. 56(c). Therefore, the Presiding Officer may be guided by the body of law developed under Rule 56 in determining whether summary decision is warranted.[7]

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[6] For the purposes of 21 C.F.R. § 16.26(b), a hearing commences upon receipt by FDA of a request for a hearing submitted under 21 C.F.R. § 16.22(b). *See* 21 C.F.R. § 16.26(b).

[7] *Puerto Rico Aqueduct and Sewer Authority v. EPA*, 35 F.3d 600, 604-608 (1st Cir. 1994) (finding that "[f]rom its inception, the concept of administrative summary judgment has been linked inextricably to Fed. R.Civ.P. 56," and that "[m]any agencies habitually look to Rule 56 case law for guidance in respect to administrative summary judgments."); *John D. Copanos and Sons, Inc. v. FDA*, 854 F.2d 510, 523 (D.C. Cir. 1988) (finding that the principles of *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 247-248 (1986) "apply with equal force in the

In ruling on a summary judgment motion, the decision maker must determine whether there are issues of fact in dispute to be decided in a trial on the merits. *Celotex Corp. v. Catrett*, 477 U.S. 317 (1986). The party moving for summary judgment bears the burden of establishing the absence of a genuine issue of material fact. *Adickes v. S.H. Kress*, 398 U.S. 144, 157 (1970). A party opposing a properly supported motion for summary decision has the burden of showing that a rational trier of fact could find for the nonmoving party and that there is a "genuine issue for trial." *Matsushita Electrical Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586 (1986). Any doubts are to be resolved in favor of the non-moving party and the non-moving party is entitled to all justifiable inferences. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986). To fulfill this burden, the nonmoving party "must set forth specific facts showing that there is a genuine issue for trial." Fed.R.Civ.P. 56(e); *Matsushita Electrical*, 475 U.S. at 586; *First Nat'l Bank v. Cities Service Co.*, 391 U.S. 253, 289 (1968).

The mere existence of a scintilla of evidence in support of the non-moving party's position will be insufficient to overcome a motion for summary judgment. *Anderson*, 477 U.S. at 252. Further, the opposition to a properly supported motion for summary judgment "must do more than simply show that there is some metaphysical doubt as to the material facts," *Metsushita Electrical*, 475 U.S. at 586, and cannot rest on mere allegations. *First Nat'l Bank*, 391 U.S. at 289.

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context of administrative judgment."). *See* also 53 *Fed. Reg.* 4613, 4614 (February 17, 1988)(stating that the standard for summary decision set forth in 21 C.F.R. § 16.26 "conforms to well-settled law.").

5. ANALYSIS

Charge I. **Dr. Halikas violated 21 C.F.R. § 50.20 by failing to obtain informed consent from five study subjects who received [ ]**

As the party seeking summary decision, the Center bears the initial burden of submitting sufficient evidence to show that there is no genuine issue that legally effective informed consent[8] was not obtained from the first five Hmong subjects in the [ ] investigational new drug study. Fed.R.Civ.P. Rule 56(e). In its motion, the Center argues that Dr. Halikas admitted on several occasions that he failed to obtain informed consent from the first five Hmong study subjects and that, solely based on these admissions, there is no dispute that they did not receive legally effective informed consent. *See* Center Motion at 14-16.

The Center refers to certain statements contained in two letters from Dr. Halikas: one dated February 17, 1994, to the Administrator of the University of Minnesota Hospital's Committee On The Use of Human Subjects in Research; and another dated July 20, 1994, to FDA, attached as Tabs I and J to its Motion, respectively. Specifically, CDER quotes Dr. Halikas as follows:

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[8] FDA regulations define the elements of informed consent. *See* 21 C.F.R. § 50.25. They include, but are not limited to, a statement that the study involves research; an explanation of the purposes of the research and the expected duration of the subject's participation; a description of the procedures to be followed, identification of any procedures which are experimental; a description of any reasonably foreseeable risks or discomforts to the subject; a disclosure of appropriate alternative procedures or courses of treatment; a description of any benefits to the subject that may reasonably be expected from the research; a statement that notes the possibility that the FDA may inspect the records; an explanation of whom to contact for answers to pertinent questions about the research; and a statement that participation is voluntary. The regulations also require that this information be conveyed to the study subject, and that consent to participate in the study be obtained before the subject is involved in the study. *See* 21 C.F.R. § 50.20.

> With regard to the [ ] study, and the FDA audit, as Principal Investigator, I have taken and continue to take primary responsibility for failure to obtain signed consent from <u>five of the ten</u> subjects....(emphasis in the original)

See Center Motion, Tab I at p. 2.

and

> [A]ccording to the guidelines of the FDA, I, as Principal Investigator, bear the ultimate responsibility for the failure to obtain written signed consents on five ... patients.

See Center Motion, Tab J at p. 3.

In his response, Dr. Halikas argues that the Center's evidence shows only that he admitted that he did not obtain *written* informed consent from these subjects, and that 21 C.F.R. § 50.20, the regulation at issue in this charge, does not require that informed consent be in writing. Dr. Halikas argues that the Center failed to support its motion with any evidence that he violated §50.20, and therefore failed to meet its initial burden of showing the absence of a genuine dispute as to whether he obtained legally effective informed consent from the first five Hmong subjects. Halikas Opposition at 17.

Based on my review of the evidence cited in support of the Center's motion, I find that this evidence does not, in fact, support CDER's assertion that Dr. Halikas has *admitted* that he never obtained *any* consent from the five subjects at issue. Although the record clearly shows that he admitted that neither he nor anyone else obtained *written* informed consent from the first five Hmong study subjects involved in the [ ] Amendment 1 Study, he did not specifically admit that legally effective informed consent was not obtained.[9] Because the Center has moved for

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[9] 21 C.F.R. § 50.20 states that no investigator may involve a human being as a subject in research covered by FDA regulations unless the investigator has obtained the legally effective informed consent of the subject in writing or orally. Section 50.27 requires that informed consent be obtained in writing, and that if it is obtained orally, that it be reduced to writing, signed by the study subject, and witnessed by a third party. Furthermore, this regulation requires that a

summary decision on a violation of 21 C.F.R. § 50.20, which makes no reference to consent being obtained in writing,[10] Dr. Halikas' argument has some merit. [11]

Under 21 C.F.R. § 16.26(b), which governs my review of this matter, however, I have considered *all* of the evidence submitted in support of the motion for summary decision, as well other matters of which I may take official notice. Based on this review, I find 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 at issue in this charge.

First, the Center has attached to its motion a copy of the FDA inspection report ("FDA report") documenting the agency's investigation of Dr. Halikas' [ ] IND study. According to the FDA report, Dr. Halikas admitted to the FDA investigators that he was not involved in obtaining informed consent from any of the Hmong study subjects ***prior*** to their involvement in the [ ] Amendment 1 Study. *See* Center Motion at Tab N, p. 3. In addition, the FDA investigators interviewed study subject 9/[ ], one of the first five Hmong study subjects. This individual told the FDA investigators that he or she was never informed that he or she was being used in a drug study. *Id.* at 6. Finally, the FDA report states that the FDA investigators interviewed several individuals employed in the Chemical Dependency Treatment Program at the

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summary of what is to be said to the study subject must have been approved by the IRB beforehand.

[10] 21 C.F.R. § 50.20 states that, "No informed consent, whether oral or written, may include any exculpatory language...."

[11] Although the NOOH alleged that Dr. Halikas also violated 21 C.F.R. § 50.27, the failure to document informed consent, the Center has not moved for summary decision on this allegation. Further, the Center did not argue in its Motion for Summary Decision that to be legally effective, informed consent must be in writing. I, therefore, do not reach this issue.

Minnesota University Hospital where the [ ] Amendment 1 Study was conducted (the "program"). These individuals confirmed that informed consent was not obtained from the Hmong study subjects.[12]

Dr. [ ], Clinical Director of the program, told FDA investigators that Dr. Halikas had presented the use of [ ] to the program staff as an open trial for which informed consent was not needed. *Id.* at p. 6. [ ], M.D., Interim Director of the program, told FDA investigators that Dr. Halikas had told her that [ ] was a vitamin and that he did not need consent from the study subjects to use it. *Id.* at 6-7. Ms. [ ], a medical student who admitted several of the study subjects into the program, told FDA investigators that [ ] was not presented to the study subjects as an experimental drug, and that they were not told that there were alternative medications. *Id.* at 5. [ ], M.D., a Fellow on rotation at the program at the time of the [ ] study and who reported directly to Dr. Halikas, told FDA investigators that Dr. Halikas had told him that they were using a new drug, [ ], for the treatment of narcotic withdrawal symptoms. When he asked Dr. Halikas if informed consent was needed, Dr. [ ] said that Dr. Halikas told him that [ ] was an innocuous drug available on the open market in Europe and that they did not need anything other than the standard consent for hospitalization. *Id.* at 4.

Second, the July 20, 1994 and February 17, 1994 letters from Dr. Halikas,[13] in their entirety, contain sufficient evidence that, not only did Dr. Halikas admit that he did not obtain

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[12] The rules of evidence do not apply to Part 16 informal hearings. *See* 21 C.F.R. § 16.6(c).

[13] *See* Center Motion at Tabs I and J.

written informed consent from the first five study subjects, but that he did not ensure that anyone obtained any form of informed consent. In his July 20, 1994 letter, Dr. Halikas stated:

> It is important to note that the first patient ... was given and signed an informed consent document as part of the routine admission process by hospital personnel. Having never before done an inpatient drug study, I then expected that this was the normal procedure at this research-oriented University hospital. In the normal course of events, I expected that each subsequent patient would also be offered an informed consent document as part of their routine admission process... Thereafter, my oversight of this process by the hospital personnel was not thorough enough.

Center Motion at Tab I, p. 2.

Dr. Halikas also stated:

> According to the University of Minnesota procedural 'Investigational Drug Studies Notebook,' no medications should have been released by the pharmacy, and no medications should have been dispensed by the nursing department, without the signed informed consent in the record. After the first patient, I erroneously relied on such hospital procedures being in place, and on the ability of the University Hospital as a research facility to handle this simple inpatient open-label study.

Id. at 4.

Dr. Halikas' statements that he assumed that other hospital procedures would fulfill what was his responsibility under 21 C.F.R. § 50.20, and that such reliance was "erroneous" is sufficient evidence in itself to support the Center's argument that no informed consent was obtained. Moreover, Dr. Halikas' attempts in his letters to equate evidence in the study subjects' records that they understood their "rights" because they occasionally refused to take the investigational new drug with evidence of legally effective informed consent demonstrates that Dr. Halikas did not obtain legally effective informed consent before he involved them in the [ ] IND study, as required by 21 C.F.R. § 50.20. For example, in his July 20, 1994 letter, Dr. Halikas states that:

> the [patient] records are replete with instances in which every one of the study

> subjects at one time or another refused [ ] This was the demonstration that these study subjects actually understood their rights. Further, the record makes clear that on no occasion was [ ] forced on any patients by any staff or hospital employee.

See Center Motion Tab J at p. 4..

Dr. Halikas goes on to state that he offered these records as evidence that he had fulfilled FDA's requirements for informed consent "[i]n item 9 of the Basic Principles enumerated in 21 CFR, Chapter 1, 312.120." *See* Center Motion Tab I at p. 6. These regulations, however, are not relevant to Dr. Halikas' study. The regulations in 21 C.F.R. § 312.120 contain the requirements for FDA's acceptance of foreign clinical studies not conducted under an IND. In particular, item 9 is found in 21 C.F.R. § 312.120(4), which is a statement from the "Declaration of Helinski" consisting of "Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects," and reads as follows:

> In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing. 21 C.F.R. § 312.120(c)(4).

Dr. Halikas, however, is charged with violating the requirements of 21 C.F.R. § 50.20, not 21 C.F.R. § 312.120. Thus, Dr. Halikas' statements that the records demonstrated compliance with 21 C.F.R. § 312.120 do not detract from the sufficiency of the Center's evidence that Dr. Halikas did not obtain legally informed consent from the first five Hmong study subjects.

Accordingly, viewing the evidence the Center has submitted in support of its motion as a whole, I find that the Center produced sufficient evidence to meet its initial burden on a motion for summary decision with regard to the charge that Dr. Halikas did not obtain legally effective

informed consent, as required by 21 C.F.R. § 50.20 and as defined by 21 C.F.R. § 50.25, from the first five Hmong study subjects. Further, I find that Dr. Halikas' Opposition to the Center's Motion did not create a genuine issue as to the facts supporting this charge.

In his Opposition, Dr. Halikas makes several arguments in support of his assertion that legally effective informed consent was obtained from all of the study subjects and therefore, that there is a genuine dispute as to whether legally effective informed consent was obtained. First, he asserts that it was the University of Minnesota Hospital's responsibility to ensure that each patient understands the nature of the treatment, the potential risks, potential benefits, alternative treatments and the patient's absolute right to discontinue treatment. *See* Halikas Opposition at 16. According to Dr. Halikas, during their hospital admission, each of the five study subjects read the bill of rights for hospital patients established by Minnesota State statute (MN ST s 144.651), or received an explanation of it (in the Hmong language) from an interpreter. *See* Halikas Opposition at 8 and 16. Dr. Halikas argues that, under Minnesota law, the hospital had the primary responsibility for adhering to the bill of rights, and that compliance with it would satisfy FDA's requirement for legally effective informed consent.[14]

Having reviewed the particular provisions of the Minnesota State statute bill of rights that Dr. Halikas cites, however, I cannot equate having patients read and understand these general provisions provided to all hospital patients on admission with ensuring that the Hmong study

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[14] Dr. Halikas specifically points to subdivisions 4 (requiring that study subjects be informed by the hospital of their rights in their own language upon admission); 6 (requiring that study subjects receive appropriate individualized care; 9 (requiring that each patient be informed by the hospital in his or her own language of the diagnosis, treatment, alternatives, risks, and prognosis); 10 (requiring that study subjects be given opportunity by the hospital to participate in planning their own treatment; and 12 (requiring that hospitals honor a patient's request to forego any medication or treatment). *See* Halikas Opposition at p. 8, n. 5.

subjects gave legally effective informed consent to participation in the [ ] Amendment 1 Study.[15] In fact, Subdivision 13, which Dr. Halikas did not cite, specifically requires that informed consent be obtained for "Experimental research."

> Written, informed consent must be obtained prior to a patient's or resident's participation in experimental research. Study subjects and residents have the right to refuse participation. Both consent and refusal shall be documented in the individual care record.

MN ST s 144.651, Subd. 13 (MN. ST. ANN. 1993)

Moreover, in the absence of any evidence that informed consent *was actually obtained*, the fact that Minnesota law also required informed consent does not create a genuine issue as to whether Dr. Halikas obtained informed consent pursuant to FDA requirements. Under FDA regulations, Dr. Halikas, and not the hospital, was responsible for ensuring that legally effective informed consent was obtained from the Hmong study subjects prior to their involvement in the [ ] study. *See* 21 C.F.R. § 50.20 ("no investigator may involve a human being as a subject in research covered by these regulations unless *the investigator* has obtained the legally effective informed consent of the subject ...." (emphasis added)). Indeed, as part of his IND application Dr. Halikas submitted to FDA a signed statement (FDA Form 1572 "Statement of Investigator") that stated as follows: "I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 C.F.R. Part 312." *See* Center Motion Tab F, IND No. [ ] FDA Form 1572 p. 2. 21 C.F.R. § 312.60 states that "[a]n investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered, except as provided in §§ 50.23

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[15] Indeed, it is clear from that fact that the patient enrolled under Amendment 3 signed *both* the Minnesota Patients' Bill of Rights as well as an informed consent form, that the Minnesota Patients' Bill of Rights alone was insufficient. *See* Opposition at 11.

or 50.24[16] of this chapter."

In a second, related argument, Dr. Halikas asserts that the study subjects signed a statement to the effect that they understood their rights under Minnesota's bill of rights for hospital patients. *See* Halikas Opposition at 16. As previously stated, however, the provisions of the bill of rights did not fulfill the requirements of 21 C.F.R. § 50.20. Therefore, the study subjects' understanding of their rights under the Minnesota bill of rights did not absolve Dr. Halikas of his responsibility to adhere to FDA's federal regulations to obtain legally effective informed consent before involving subjects in the [ ] Amendment 1 Study. It is, therefore, irrelevant that the study subjects may have signed statements that they understood their State statutory rights.

Dr. Halikas' third argument is that it was the hospital pharmacy's responsibility to assure that legally effective informed consent had been obtained from the [ ] study subjects before dispensing the [ ]. *See* Halikas Opposition at 10 and 30-31. For the reasons cited above, I find that, in the absence of any proffer that pharmacy staff did in fact obtain informed consent as required by FDA's regulations, Dr. Halikas' attempt to shift responsibility for obtaining consent to the hospital pharmacy staff does not serve to raise an issue of fact regarding his failure to obtain legally effective informed consent from the first five Hmong study subjects..

Dr. Halikas' fourth argument is that the study subject's patient records reflect that hospital staff, through translators, discussed with each study subject at the outset the proposed [ ] study and their absolute right to discontinue the experimental treatment. *See* Halikas Opposition at 16-17. Dr. Halikas argues that these records evidence that each study subject received legally

[16] Dr. Halikas does not assert that either of these exceptions applied in his study.

effective informed consent. In support of this argument, Dr. Halikas submitted copies of hospital records from one of the Hmong patients in the study. *See* Opposition to Summary Decision, Tab 2, pp. 99-100 and 114-119. In his response, Dr. Halikas asserts that these records document that the patient received and understood the patient's bill of rights upon admission to the hospital, and that a registered nurse explained, through an interpreter, the [ ] study. Several of these pages contain information that has been circled, apparently by Dr. Halikas, to highlight the portions that support his assertion.

I have reviewed these records and have concluded that they in no way establish a dispute as to whether informed consent was obtained from even this one subject. Plainly, they cannot establish such a dispute with respect to any of the other subjects. Instead, they show nothing more than that this one subject received doses of [ ] and was "instructed regarding new medication for withdrawal." *See* p. 99, 100 (documenting scheduled dose of [ ]); p. 114 (Daily Assessment Care Record bearing the statement: "*** interpreter***6/14 Declined purple group-rys Attended 3rd step community Was instructed regarding new medication for withdrawal***"); p. 115 (regarding comfort of patient); pp. 116-117 (containing nutritional and activity information); p. 118, 119 (Department of Psychiatry Daily Assessment Care Record bearing the entry: "6/15 Interpreter-informed [ ] was dc'd" and observing that the patient was uncomfortable and had vomited after receiving ([ ]).

In sum, none of these records constitute evidence that even this one patient gave his or her legally effective informed consent to participate in the [ ] Amendment I study. Furthermore, the records pertain to one patient and the Center has alleged that the first five Hmong patients never gave their legally effective informed consent to participate in the [ ] Amendment 1 Study. The

records cited by Dr. Halikas do not raise a genuine issue of fact regarding his failure to obtain legally effective informed consent from the first five Hmong study subjects.

Finally, Dr. Halikas argues that information about the [ ] treatment regime and each study subject's right to discontinue treatment "would have" been discussed during daily meetings of the study subjects's chemical dependency team (comprised of a staff academic psychiatrist, psychiatry residents, nurses, social workers, interpreter, and allied health professionals). *See* Halikas Opposition at 17, citing Facts at 11-13, paragraphs 17-19. Specifically, Dr. Halikas states that:

> Each day following admission, the study subjects participated in the daily team meetings....During those meetings, the resident physician in charge *would have* discussed the [ ] study and *would have* asked the study subjects if they in fact would prefer to continue receiving [ ]....In short, through a translator, these study subjects *would have* been repeatedly provided with all the information that appeared on the printed informed consent form before receiving any [ ], and continued to receive information about the study during daily meetings, even after some of them discontinued taking [ ].

See Halikas Opposition, at 13 (emphasis added).

Such supposition or conjecture is simply inadequate to overcome a motion for summary decision. Again, Dr. Halikas has offered no statements from a staff academic psychiatrist, psychiatry resident, nurse, social worker, interpreter, or allied health professional that he or she did in fact provide "all of the information that appeared on the printed informed consent form" to any of the first five Hmong study subjects. Nor does he ever contend that he obtained legally effective informed consent from any of these subjects.

Dr. Halikas' arguments that others were responsible for the violations, and that others would have fulfilled his responsibility, are simply not enough to avoid summary decision on this issue. Accordingly, I find that Dr. Halikas violated 21 C.F.R. § 50.20 by failing to obtain legally

effective informed consent from the first five Hmong study subjects in the [ ] Amendment 1 Study for which he was the principal investigator and grant summary decision on this violation to the Center.

In granting summary decision, I reject Dr. Halikas' argument that even if he violated 21 C.F.R. § 50.20, he is not subject to disqualification under 21 C.F.R. § 312.70 because he did not commit the violation repeatedly or deliberately. Dr. Halikas argues that I must find that there is no evidence in the record that he deliberately violated this regulation, and that to find repeated violations, I must find that he committed such violations in more than one study. I am unpersuaded. The undisputed evidence establishes not just an isolated violation, but a violation as to each of the first five Hmong subjects. Indeed, as set forth below, there were violations as to eight of the Hmong subjects.

FDA has long interpreted the term "repeatedly," as used in 21 C.F.R. § 312.70, to mean more than once.[17] Accordingly, I find as a matter of law that Dr. Halikas' failure to obtain legally informed consent from five Hmong study subjects to be repeated violations of 21 C.F.R. § 50.20.

I also find that Dr. Halikas' violations of 21 C.F.R. § 50.20 were deliberate. As cited by the Center in its Motion, the term "deliberate" has a specific meaning within the context of 21 C.F.R. § 312.70(b). As stated in the *Report of the Presiding Officer, In The Matter of John H.*

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[17] *See* e.g. Reports of the Presiding Officer: *In The Matter of Chaovanee Aroonsakul, M.D.* (1990), (findings adopted by the Commissioner, 1990); *In The Matter of Ronald R. Fuller, D.V.M.* (1987), (findings adopted by the Commissioner, 1988); *In The Matter of Stephen Steen, M.D.* at 25 (1982) ("I do not interpret the term, 'repeated,' to require proof of violations in two different studies"), (findings adopted by the Commissioner, 1984); *In The Matter of John H. Hopkinson III, M.D.* (1982), (findings adopted by the Commissioner, 1983); and *In The Matter of Michael C. Gelfand, M.D.* (1980), (findings adopted by the Commissioner, 1981).

Hopkinson III, M.D. (1982), at 10 (citing *Report of the Presiding Officer, In The Matter of Martin S. Mok, M.D.* (1982) at 5-6:

> In the context of 21 C.F.R. Part 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.

Applying this definition, I find that Dr. Halikas' violations of 21 C.F.R. § 50.20 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.

The record reflects that Dr. Halikas was well aware of the requirement to obtain informed consent from individuals before they are involved in clinical research. First, Dr. Halikas has been actively involved in clinical research for more than twenty years and his Curriculum Vitae lists twenty-one clinical studies for which he was the Principal Investigator. *See* Center's Motion at Tab E, pp. 5-7. Second, since 1986, Dr. Halikas was a member of the University of Minnesota's Committee on the Use of Human Subjects in Research, a committee required by FDA regulations, *See* 21 C.F.R. Part 56. One of that committee's principal duties is to approve the written informed consent forms to be used in clinical studies. *See* Center's Motion at Tab E, p. 14. Third, the record shows that Dr. Halikas knew before he started the [ ] Amendment 1 Study that the Hmong were a " 'vulnerable' population within the guidelines of the Human Subjects Committee at the University of Minnesota" who were "intimidated by all of western authority" and "would not understand the consent forms and study concept required in order to participate in a double-blind research protocol." *See* Letter from Halikas to FDA dated August 13, 1992, attached to the Center's Motion at Tab O; Halikas Opposition at 9-10.

In his Opposition, Dr. Halikas makes three arguments that his violations of 21 C.F.R. § 50.20 were not deliberate. First, he argues that such a determination is inappropriate for summary decision because it depends on the credibility of Dr. Halikas' testimony as to his state of mind at the time the violations occurred and such credibility can only be assessed at a hearing. Based on my review of the record, I find that such a credibility assessment is not required to resolve this issue. The evidence in the record as discussed above demonstrates that Dr. Halikas recklessly disregarded the rights of the first five Hmong study subjects to not participate in the [ ] IND clinical investigation without their informed consent to do so.

Dr. Halikas' second argument is that the Center failed to allege that Dr. Halikas acted deliberately, as that term is commonly used. Dr. Halikas argues that the common definition of the term is conduct that is the result of "careful thought and weighing of considerations,"quoting Black's Law Dictionary. *See* Halikas Opposition at 29. As a matter of law, I find the definition of the term as set forth in *Report of the Presiding Officer, In The Matter of John H. Hopkinson III, M.D.* (1982), at 10 (citing *Report of the Presiding Officer, In The Matter of Martin S. Mok, M.D.* (1982) at 5-6 applies here, and find that the Center did allege that Dr. Halikas acted deliberately, as that term is defined in *Hopkinson*.

Dr. Halikas' third argument is that, even if I were to find that deliberate conduct includes the reckless disregard of obvious and known risks, the factual record conclusively dispels any suggestion that Dr. Halikas displayed such disregard towards his patients' rights or safety. *See* Halikas Opposition at 30. Dr. Halikas argues that he was unaware that written informed consent had not been obtained from his study subjects and operated under the assumption that the Hospital or Pharmacy had obtained it; that his reliance on others was consistent with FDA's policy

that "investigators, institutions, and sponsors must share in this responsibility" citing 46 *Fed.Reg.* 8958, 8960 (Jan. 27, 1981)(preamble to FDA's IRB regulations); and that when he discovered the absence of informed consent, he immediately obtained it from the remaining Hmong subjects still on the study. *Id.* at 30-31.

Dr. Halikas goes on to argue that his reliance on others to fulfill his obligation to obtain informed consent is consistent with FDA's preamble to the IRB regulation he cites above. A closer reading of the preamble shows that the sentence cited by Dr. Halikas is preceded by one that states, "The Federal Government cannot bear alone the burden of protecting the rights and welfare of human subjects." 46 *Fed.Reg.* 8958, 8960 (Jan. 27, 1981). Based on my review of the preamble, I find that the sentence cited by Dr. Halikas merely refers to the scope of all of FDA's regulations that comprise its Bioresearch Monitoring Program and is clearly not inconsistent with the Center's argument. As the preamble states,

> The IRB regulation is one of five regulatory elements in FDA's bioresearch Monitoring Program. .. In addition to the [IRB regulations] the Bioresearch Monitoring Program includes proposed regulations to establish obligations of clinical investigators ... sponsors ... monitors ... and good laboratory practices regulations.

Id.

The regulation at issue here, 21 C.F.R. § 50.20, clearly assigned to Dr. Halikas the responsibility to obtain legally effective informed consent from his study subjects before he entered them into the study. He cannot avoid a finding that he deliberately violated this regulation by arguing that others were responsible for obtaining informed consent.

Lastly, Dr. Halikas argues that his swift correction of the violations with respect to the subjects remaining on the study is evidence that his original failure to comply with 21 C.F.R.

§ 50.20 was not deliberate. Dr. Halikas violated the informed consent regulation when the Hmong study subjects received their first dose of [ ]. His actions after the fact are irrelevant to whether, based upon his experience and prior statements, he exhibited a reckless disregard of the rights of the Hmong subjects when he failed to obtain their informed consent to be in the [ ] Amendment 1 Study.

Based on Dr. Halikas' extensive experience as a Principal Investigator, a member of the University's IRB for ten years, and his acknowledgment in his letter to FDA, before the [ ] Amendment 1 Study began, of his awareness of the particular vulnerability of the Hmong study subjects with whom he was dealing, I find as a matter of law 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.

<u>Charge 2.</u> Dr. Halikas violated 21 C.F.R. § 50.20 by failing to obtain timely informed consent from three other study subjects who received [ ]

CDER also moves for summary decision on a second charge under 21 C.F.R. § 50.20, arguing that there is no dispute that Dr. Halikas failed to obtain timely legally effective informed consent from three additional Hmong study subjects who did not sign informed consent forms until after they had already received [ ]. These three subjects were still in the study when Dr. Halikas discovered that written informed consent had not been obtained from any of the Hmong study subjects. *See* Center Motion at 16.

In his Opposition, Dr. Halikas makes the same arguments he made in response to Charge

1 above;[18] namely that, although written informed consent was not obtained prior to these three Hmong study subjects receiving [ ], the hospital was required to present to them upon admission the bill of rights required by state statute; that others "would have" obtained the informed consent; and that the portions of the one patient record discussed above evidenced that legally effective informed consent was obtained from all of the subjects. *See* Halikas Opposition at 11 - 13.

Dr. Halikas' response to Charge 2 is insufficient to withstand a summary judgment motion for the same reasons explained above under Charge 1. 21 C.F.R. § 50.20 required Dr. Halikas to obtain legally effective informed consent "before involving any human being in research...." The fact that these subjects signed informed consent forms after they had already received [ ] is irrelevant to this charge.

Accordingly, I grant summary decision as to Charge 2 on the basis that Dr. Halikas violated 21 C.F.R. § 50.20 by failing to obtain legally effective informed consent from an additional three Hmong study subjects in the [ ] Amendment 1 Study for which he was the principal investigator. Based upon the discussion under Charge 1 above, I also find as a matter of law that Dr. Halikas committed these violations repeatedly and deliberately.

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[18] In his Opposition, Dr. Halikas treated Charges 1 and 2 as the same violation and provided the same response for both.

Charge 3. **Dr. Halikas violated 21 C.F.R. § 50.20 by failing to provide informed consent forms in a language understandable to the study subjects or to provide a suitable interpreter.**

The Center argues that the written informed consent forms that the three Hmong study subjects signed after they began the [ ] Amendment 1 Study were inadequate because they were in English and the Hmong subjects could not read English. *See* Center Motion at 17. In support of its argument, the Center quotes Dr. Halikas in his February 17, 1994 letter to the Minnesota Committee on the Use of Human Subjects in Research, in which he stated:

> What we have all learned from this is that a signed, written consent form, not even understood by the interpreter, added nothing to these patients [sic] actual understanding of informed consent.

See Center Motion at Tab J, p. 4.

The Center also quotes Dr. Halikas in an August 13, 1992 letter to FDA's Office of Pilot Drug Evaluation, in which he stated:

> Amendment 1, which involves an opium addicted Hmong immigrant population, will not be followed by any double-blind studies. This is a 'vulnerable' population within the guidelines of the Human Subjects Committee at the University of Minnesota. Because of their lack of English comprehension and lack of acculturation, they would not understand the consent forms and study concept required in order to participate in a double-blind research protocol. They are, rather, intimidated by all of western authority.

See Center Motion at Tab O, p. 1.

In his Opposition, Dr. Halikas argues that the Center has misinterpreted his statements, and that he has never admitted that the written informed consent forms were insufficient to provide legally effective informed consent. He argues that the point of his statements was that the oral explanations given to the Hmong study subjects by others administering the [ ] Amendment 1 Study were enough to provide informed consent and were superior to the language of the written informed consent forms, and therefore, that the Hmong translation of the written

form added nothing to the subjects' understanding. *See* Halikas Opposition at 17-19.

Having already found under Charges 1 and 2 that Dr. Halikas repeatedly and deliberately violated 21 C.F.R. § 50.20 by failing to obtain legally effective informed consent from eight Hmong study subjects before they received [ ], it is irrelevant whether the informed consent forms given to the three Hmong study subjects were understandable to them, thus making it unnecessary for me to reach this issue.

<u>Charge 4.</u> Dr. Halikas violated 21 C.F.R. § 50.20 by failing to seek consent under circumstances that minimize or reduce the risk of coercion of the subjects.

In its Motion, the Center argues that Dr. Halikas created a potentially coercive environment when he failed to obtain legally effective informed consent from the Hmong study subjects before involving them in the [ ] Amendment 1 Study. The Center offers Dr. Halikas' own statement in his August 10, 1993 letter to the University of Minnesota Committee on the Use of Human Subjects in Research as supporting evidence:

> [R]esearch activity on [the [ ] study] was stopped on Thursday, August 5th because of irregularities in the implementation of the protocol which raised reasonable questions about the possibility of coercion in a vulnerable population with very poor levels of communication in English.

See Center Motion at Tab K.

In addition, the Center quotes Dr. Halikas from his November 10, 1994 letter to the FDA:

> [T]he question of possible coercion would certainly have been mitigated substantially had the consent form been written in the native Hmong language.

See Center Motion at Tab P.

Dr. Halikas argues in his Opposition that the Center's argument is premised on a conclusion that no informed consent was obtained, when in fact it was. He further argues that the

evidence cited above merely shows that he acknowledged that the absence of signed informed consent raised the possibility of coercion, but not that he admitted that there had been coercion.

I have already found, however, that Dr. Halikas did not obtain legally effective informed consent as required by 21 C.F.R. § 50.20 from any of the eight Hmong study subjects. Accordingly, there is no reason to even address a violation concerning the circumstances under which consent *was* sought.

Charge 5. Dr. Halikas violated 21 C.F.R. §§ 312.50 and 312.60 by failing to adhere to the study dosing limits.

21 C.F.R. § 312.50 requires that sponsors ensure that clinical investigations are conducted in accordance with the protocol contained in the IND on file with FDA. 21 C.F.R. § 312.60 requires clinical investigators to conduct clinical investigations in accordance with a signed investigator statement (Form FDA 1572), which commits the investigator to conduct the study in accordance with a relevant and current protocol, except when necessary to protect the safety, the rights or welfare of the study subjects. *See* Center Motion at Tab F.

The Center argues in its Motion that as a sponsor-investigator,[19] Dr. Halikas violated 21 C.F.R. §§ 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 thereby "subjected his patients to unacceptable, and completely unnecessary, risk." *See* Center's Motion at 21 and 24. The Center offers several of Dr. Halikas' own statements in support of this charge, including the following from his Final

[19] Dr. Halikas does not dispute the Center's characterization of him as a sponsor-investigator as defined by 21 C.F.R. § 312.3(b).

Report on the GHB Study, which he submitted to FDA on May 3, 1994:

> Protocol deviations occurred during the prior 12 months that were not previously reported to the FDA in a protocol amendment.... Beginning almost immediately with the first patient, it became apparent that a four times daily ("q.i.d.") schedule of medication administration such as enumerated in the protocol was less than adequate to meet the withdrawal needs of these patients. Rather, more frequent flexible titration was the appropriate regimen.... This enabled the staff to individualize treatment and give subsequent subjects [ ] as frequently as hourly on an as needed basis as they requested it.

See Letter from Halikas to FDA dated May 3, 1994 attached to Center's Motion at Tab G, pp. 6-7.

Dr. Halikas' first argument is that the Center has charged him with violating 21 C.F.R. § 312.50, which applies only to sponsors, not investigators, and that sponsors are not subject to disqualification under 21 C.F.R. § 312.70. *See* Halikas Opposition at 21. As an initial matter, I find that, based on the NOOH and the Center's Motion, there is no factual dispute that the Center charged Dr. Halikas with violating both 21 C.F.R.§§ 312.50, applicable to sponsors, *and* 312.60, applicable to investigators. *See* NOOH at p. 4 attached to Center's Motion at Tab C; Center's Motion at 21.

Accordingly, I find it unnecessary to address Dr. Halikas' argument that FDA lacks authority to disqualify a sponsor-investigator for actions taken by the individual in his capacity as a sponsor, and that FDA cannot apply its amended regulations expressly authorizing the disqualification of a sponsor-investigator retroactively to the date of the violations at issue here. *See* Halikas Opposition at 21.

I further find that, based on Dr. Halikas's statements cited above, there is no factual dispute that he deviated from the dosing regimen established in the protocol on file with FDA. *See* Letter from Halikas to FDA dated May 3, 1994, attached to Center's Motion at Tab G, p. 6-7. Protocol deviations can be particularly troubling because they may increase the potential for a

safety hazard.

Dr. Halikas' second argument is that, even if he did modify the dosing regime, he did so in his capacity as a sponsor and, thus, was only required to notify FDA if the increase in drug dosage or increase in duration of exposure of individual study subjects to the drug exceeded that in the protocol, citing 21 C.F.R. § 312.30(b)(I). *See* Halikas Opposition at 21. He bases this argument on the fact that 21 C.F.R. § 312.30(b)(I) only requires a sponsor to amend a protocol for a Phase I study if the change significantly affects the safety of the subjects, citing as an example "any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol." From this provision, Dr. Halikas extrapolates that lowering the dosing regimen established in the protocol is a change that a sponsor may make without violating 21 C.F.R. § 312.50.[20] Dr. Halikas argues that [ ] is metabolized in the body in a such a way that his changes to the dosing schedule actually resulted in lowering the doses his study subjects received, citing a publication attached as Exhibit 1 to his Opposition ("Ferrara article"). In its Memorandum in Reply, the Center argues at length that Dr. Halikas' argument is based on a mistaken interpretation of the Ferrara article. *See* Center Reply Memo at 4-6; *see also Id.* Declaration of Robert S. K. Young, M.D. attached at Tab 1.

Finding that Dr. Halikas was specifically charged in his capacity as an investigator and that he deviated from the study protocol is sufficient for me to conclude that he may have violated 21 C.F.R. § 312.60. However, under the particular facts of this case, I am not prepared to conclude that the Center has clearly established that the deviations were not necessary to protect the safety,

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[20] Indeed, under 21 C.F.R. § 312.23(a)(6)(I) "protocols for Phase I studies may be less detailed and more flexible than protocols for Phase 2 and 3 studies."

the rights, or the welfare of the study subjects. Nor am I, under the particular facts of this case, prepared to conclude that the Center has established that Dr. Halikas, as a clinical investigator, violated the strict requirement that he follow the Amendment 1 Study protocol when, depending on the nature and significance of the change to the protocol, Dr. Halikas, as a sponsor, may have had the latitude to permit the deviation. I believe it would be appropriate to determine the significance of the dosage changes Dr. Halikas made before deciding whether he violated 21 C.F.R. §§ 312.50 and 312.60 as charged.

On this record, given the differing interpretations of the Ferrera article by the parties, I cannot make this determination without further evidence, thus I deny the Center's Motion for summary decision on this charge.

CONCLUSION

After reviewing Charges 1 and 2 and the evidence presented by both parties, I find that Dr. Halikas failed to obtain legally informed consent from eight Hmong study subjects that he involved in the Amendment 1 Study in violation of 21 C.F.R. § 50.20. Dr. Halikas has raised no genuine and substantial issue of fact with regard to these charges, therefore, I grant summary decision to the Center on Charges 1 and 2. I further find, as a matter of law, that Dr. Halikas violated 21 C.F.R. § 50.20 repeatedly and deliberately. My findings as to Charges 1 and 2 make it unnecessary for me to reach Charges 3 and 4 (alleging violations of 21 C.F.R. § 50.20 for inadequate consent forms obtained after the study began and failure to minimize risk of coercion during informed consent, respectively) therefore, I have not addressed them. Based on the evidence thus far presented, I am unable to resolve on summary decision Charge 5, involving the alleged failure to follow the IND protocol, in violation of 21 C.F.R. §§ 312.50 and 312.60 and, therefore, deny the Center's motion for summary decision on this charge. Because my findings as to Charges 1 and 2 are sufficient to warrant a recommendation under 21 C.F.R. § 312.70 to disqualify Dr. Halikas, however, no further testimony need be taken regarding the fifth charge.

RECOMMENDATION

Clinical research is the cornerstone for decision making with regard to the safety and efficacy of new medical products. Members of the public must understand that some people participating in clinical research will receive a novel medical product without the benefit of complete knowledge of its effects and/or toxic potential. Also, members of the scientific community, notably physician investigators, must understand that the aim of clinical research is a commitment to the pursuit and the advancement of knowledge. Pivotal in the research ethic between the risk of the experiment and the benefit of scientific truth is informed consent and voluntary participation by the individual human research subject.

Because of a history of unorthodox treatment of human subjects in research experiments earlier this century, a number of authoritative documents such as the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report have come into existence. "The Nuremberg Code stands alone as the most eloquent and principled statement of the significance of human rights in the conduct of research involving human subjects."[21] Its first requirement that "[t]he voluntary consent of the human subject is absolutely essential." is the foundation of modern clinical research. The U.S. Code of Federal Regulations (21 CFR § 50.20) provides that "no investigator may involve a human subject in research covered by these regulations unless the investigator has obtained legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion." However, the mere existence of

[21]Faden *et al.* *JAMA*. 1996; 276: 1670.

these documents does not *ensure* "sufficient protection against exploitation and abuse of human subjects of research."[22]

Dr. Halikas enrolled a group of Hmong residents in a detoxification study of opium, using gamma hydroxybuterate. There is no evidence that Dr. Halikas received informed consent from eight of the nine individuals prior to his administration of the test drug. Although a seasoned member of the University of Minnesota's institutional review board, he did little to safeguard that this "vulnerable" population understood their rights regarding study participation. In short, Dr. Halikas committed one of the most egregious errors of clinical research. Repeated and deliberate failure to obtain informed consent should not be tolerated.

Based on my findings set forth above, I recommend that the Commissioner disqualify James Anastasio Halikas, M.D. from being eligible to receive investigational new drugs.

Linda Ann Sherman, MD

Linda Ann Sherman, M.D., M.P.A.
Presiding Officer

Date: 5/3/00

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[22]*Ibid.*