DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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October 11, 2000

Mark R. Neaman
President and Chief Executive Officer
Evanston Northwestern Healthcare Corporation
1301 Central Street
Evanston, Illinois 60201

Leopold Selker, Ph.D.
Senior Vice President for Research
Chief Administrative Officer
Evanston Northwestern Healthcare Research Institute
2650 Ridge Avenue
Evanston, Illinois 60201

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1396

Research Activities Conducted by the Clinical Pharmacology Unit

Dear Mr. Neaman and Dr. Selker:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed Dr. Selker's 21 January 1999 report responding to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects involving research activities conducted by the Clinical Pharmacology Unit at Evanston Hospital. OHRP apologizes for the delay in its response.

Findings and Concerns Regarding IRB Protocol # EH98-025 Entitled "Clinical Protocol for an Open Label Assessment of the Pharmacokinetics and Pharmacodynamics of Warfarin in the Presence of Steady-State Levels of SC-69124A IV in Healthy Adults"

Based upon its review of documents provided with Dr. Selker's report, OHRP makes the following determination regarding this research:

(1) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the Institutional Review Board (IRB) review and approve **all** proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP finds that the following protocol change was implemented without IRB approval:

The IRB-approved protocol stipulated that the dose of Warfarin to be administered to subjects would be based on a protime (PT) value obtained from a blood sample that was to be collected 15 minutes prior to the Warfarin dose. At the direction of Dr. Antoni Piergies, a study co-investigator, the timing of the blood sample collection was changed to two hours prior to Warfarin dose.

OHRP acknowledges your report that there were valid medical and scientific reasons the change in the timing of the blood collection. Nevertheless, such a change required IRB approval prior to implementation. Furthermore, if there was a need to eliminate apparent immediate hazards for some of the healthy adult volunteers because of the timing of blood drawing stipulated by the IRB-approved protocol, the appropriate course of action would have been for the investigators to discontinue administration of warfarin to subjects until the IRB reviewed and approved this protocol modification.

Required Action: By November 10, 2000, Evanston Northwestern Healthcare Corporation (ENHC) must submit a corrective action plan to ensure that the IRB reviews and approves all proposed changes in research protocols, during the period for which IRB approval has already been given, prior to initiation of such changes except when necessary to eliminate apparent immediate hazards to the subjects. The corrective action plan should include provisions for ensuring that all investigators are educated about this requirement on an on-going basis.

OHRP has the following additional concerns regarding this research:

(2) HHS regulations at 45 CFR 46.116 require that an investigator shall seek the legally effective informed consent of subjects only under circumstances that minimize the possibility of coercion or undue influence. This requirement to minimize the possibility of coercion or undue influence applies at the time of initial enrollment, as well as throughout the period of participation in the research activity. Furthermore, HHS regulations at 45 CFR 46.116(a)(8) stipulate that a subject may discontinue participation at anytime without penalty or loss of benefits to which the subject is otherwise entitled.

In reviewing the IRB-approved payment schedule for subject who participated in the research, OHRP notes following:

(a) Subjects were to be paid $2000 for completion of the study, including all follow-up and repeat tests.

(b) An initial payment of $1400 was to be made following a 16-day admission to the Clinical Pharmacology Unit (CPU). The remaining payment of $600 was to be made after completion of all follow-up tests.

(c) If the investigator withdrew a subject for the study due to study-related reasons, the subject was to receive a prorated payment to the point of withdrawal.

(d) If a subject choose to withdraw from the study before it was completed, the subject was to receive $5 per day of confinement in the CPU.

OHRP is concerned that the proposed payment schedule for subjects who withdraw from the study appears to be coercive and to penalize subjects for voluntarily withdrawing from the study at some point during the CPU stay, in contravention of the requirements of HHS regulations at 45 CFR 46.116 (this concern also applies to IRB protocol # EH97-124). Please respond. In formulating your response, please refer to the enclosed FDA information sheet regarding payment to research subjects. Furthermore, please provide OHRP with a list of all active studies being conducted by the CPU, including title, principal investigator name, IRB protocol number, study sponsor, and a description of the subject payment schedule, if any.

Questions and Concerns Regarding Alleged Research Involving Davercin

(3) In its December 10, 1998 letter, OHRP presented allegations that Dr. Piergies conducted human subject research on himself with the drug Davercin without obtaining IRB review and approval. Documents enclosed with OHRP's letter alleged that Dr. Piergies directed CPU research staff to draw serial blood samples at approximately 30-minute intervals and collect timed urine specimens following Dr. Piergies self-dosing with Davercin over a period of days to weeks between late December 1997 and early January 1998. The alleged purpose of these activities was to obtain pharmacokinetic data for Davercin.

Dr. Selker's report stated the following:

> "The investigator, Dr. Antoni Piergies, did not conduct unapproved research studies on himself with the drug Davercin. He has stated that while abroad in Europe in December of 1997 he became ill with an upper respiratory tract infection and was started on the Macrolide Davercin in Warsaw Poland. He continued medical treatment while returning to Chicago and since this drug is suspected to be hepatoxic, he had withdrawn several samples of blood as well as urine during the therapy with Davercin."

OHRP notes that clinical assessment of drug-induced hepatotoxicity typically would not involve serial blood drawing at 30 minute intervals or collection of timed urine specimens, whereas such procedures would be consistent with a pharmacokinetic study. Please respond. In your response please address the following:

(a) Please explain the nature of the "review of the activities of the investigator" that is referenced in Dr. Selker's report. Who conducted this review and from whom was information obtained during this review? Please provide copies of all documents relevant to this review.

(b) Please provide copies of all correspondence between Dr. Piergies and the IRB Chair regarding this matter.

Finding Regarding the Allegation that the IRB Fails to Routinely Review Clinical Investigator's Brochures When Reviewing Research Protocols Involving Investigational Drugs

(4) OHRP finds that Dr. Selker's report adequately responds to this allegation. In specific, OHRP acknowledges that Clinical Investigator's Brochures are routinely provided to the IRB and reviewed by primary and secondary reviewers.

Guidance Regarding Written IRB Policies and Procedures

(5) OHRP recommends that the IRB policies and procedures be expanded to include additional operational details for the procedures which the IRB follows for conducting its initial and continuing review of research. In particular, the written IRB policies and procedures should specify (a) the roles and responsibilities of the primary and secondary reviewers; and (b) the documents and materials that are provided to primary and secondary reviewers and all other IRB members prior to the IRB meetings for protocols undergoing initial or continuing review.

(6) Continuing IRB review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc95-01.htm). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

When conducting research under an expedited review procedure, the IRB Chair (or designated IRB member(s)) should receive and review all of the above referenced documentation.

(7) The IRB policies and procedures should be expanded to include a description of the procedures which the IRB follows for determining which projects need verification from sources other than the investigators that no material changes have occurred since the previous IRB review, as required by HHS regulations at 45 CFR 46.103(b)(4)(ii).

(8) IRBs must determine which protocols require continuing review more often than annually, as appropriate to the degree of risk [see 45 CFR 46.103(b)(4) and 46.109(e)]. OHRP recommends that the minutes of IRB meetings clearly reflect these determinations regarding risk and approval period (review interval) for each protocol that is approved.

(9) Where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which alters or waives the requirements for informed consent [see 45 CFR 46.116(d)]; (b) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP strongly recommends that all required findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding.

OHRP requests that you submit a follow-up written report responding to the above findings, questions, and concerns no later than November 10, 2000.

OHRP appreciates the commitment of your institution to the protection of human research subjects. Please contact me if you have any questions regarding this matter.

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

Enclosures: FDA Information Sheet, Payment to Research Subjects

cc: Mr. Robert Stanton, Director of Research, ENHC
Dr. Bernard Adelson, Chair, IRB, ENHC
Dr. Antoni A. Piergies, Director of Clinical Pharmacology Unit, ENHC
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Gregory Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. J. Thomas Puglisi, OHRP
Dr. Jeffrey M. Cohen, OHRP
Dr. Clifford C. Scharke, OHRP
Dr. Katherine Duncan, OHRP
Ms. Roslyn Edson, OHRP
Mr. Barry Bowman, OHRP

PAYMENT TO RESEARCH SUBJECTS

The Institutional Review Board (IRB) should determine that the risks to subjects are reasonable in relation to anticipated benefits [21 CFR 56.111(a)(2)] and that the consent document contains an adequate description of the study procedures [21 CFR 50.25(a)(1)] as well as the risks [21 CFR 50.25(a)(2)] and benefits [21 CFR 50.25(a)(3)]. It is not uncommon for subjects to be paid for their participation in research, especially in the early phases of investigational drug, biologic or device development. Payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive. Financial incentives are often used when health benefits to subjects are remote or non-existent. The amount and schedule of all payments should be presented to the IRB at the time of initial review. The IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence [21 CFR 50.20].

Any credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. Unless it creates undue inconvenience or a coercive practice, payment to subjects who withdraw from the study may be made at the time they would have completed the study (or completed a phase of the study) had they not withdrawn. For example, in a study lasting only a few days, an IRB may find it permissible to allow a single payment date at the end of the study, even to subjects who had withdrawn before that date.

While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable to FDA, providing that such incentive is not coercive. The IRB should determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn. All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document.

Also see FDA Information Sheets: "A Guide to Informed Consent Documents" and "Recruiting Study Subjects."