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September 5, 1995

Robert W. Day, M.D.
Director
Fred Hutchinson Cancer Research Center
1124 Columbia Street
Seattle, WA 98104

Subject: Conclusion of Evaluation of Compliance with Assurance M-1008 with Regard to the Complaint Filed by John M. Pesando, M.D., Ph.D.

Dear Dr. Day:

This is to inform you that the Office for Protection for Research Risks (OPRR) has completed its evaluation of the complaint filed by Dr. John M. Pesando (referred to here forward as the "complainant") against the Fred Hutchinson Cancer Research Center (referred to here forward as the "FHCRC"). I regret that the conclusion of this matter has taken as long as it has and trust that you realize that an extensive and careful review of this matter was essential.

Having carried out that extensive and careful review of all of the information filed by the complainant and by the FHCRC, and having reviewed the pertinent agency and FHCRC records, OPRR has determined that although there was room for improving procedures for informing the IRB of research outcomes during the course of IRB-approved research, there was no material failure to comply with the Department of Health and Human Services (HHS) Policy for the Protection of Human Subjects in regard to this matter. [The HHS Policy is codified at Title 45, United States Code of Federal Regulations, Part 46 (45 CFR Part 46) and is referred to here forward as the "regulations."]

Allegations of non-Compliance:

A letter from the complainant dated May 14, 1993, presented essentially the following allegations pertinent to compliance with the regulations:

- That clinical research activities involving locally prepared monoclonal antibodies (MAb) and bone marrow infusion which incurred "high therapy-induced mortality rates" were carried out by investigators who had a "conflict of interest" relative to the success or failure of the products used in the research.

- That the efforts of the FHCRC institutional review board (IRB) to carry out its review and approval responsibilities were obstructed, in that in its review of (allegedly, sloppily designed) protocols which used locally prepared MAb and bone marrow infusion, it had to contend with "...stiff opposition from the senior medical staff..."

- That when a "...clinical study involving MAb was causing very high mortality rates in patients who otherwise stood a good chance of a cure by [*presumably, non-MAb-treated*] bone marrow transplantation...the IRB learned of problems with this protocol through its own members, and not from the study's principal investigators..."

- That the IRB's requests to "...have clinical research protocols involving [*locally produced*] biological agents reviewed by independent outside examiners..." were "resisted" and not carried out.

- That the IRB lacked the "authority and guidelines" to carry out its responsibilities and had no "experience in regulatory matters."

- That patients continued to be enrolled in one protocol involving MAb and bone marrow infusion "...even after an alternative successful prophylaxis for graft-versus-host disease was published..."

Determinations in Regard to Allegations of non-Compliance:

With regard to alleged conflict of interest: The sole reference in the regulations to conflict of interest in the conduct of research involving human subjects applies to the exclusion of those with such a conflict from participating in IRB review (45 CFR §46.107(e)). FHCRC argues that the development of acceptable conflict of interest policies in research has been a difficult goal to achieve and that the policies in place at FHCRC were adopted subsequent to the formation of the relationships alleged to be a conflict and therefore criticized by the complainant. OPRR finds the arguments of both the complainant and FHCRC persuasive. However, since the regulations for which OPRR is responsible do not specifically address conflict of interest except in IRB review, OPRR must rely on the IRB's finding in this matter. The IRB, although urging outside review, accepted the additional review instituted by FHCRC (i.e., review by the Monoclonal Antibody Advisory Committee) and approved the research. OPRR will not second-guess the IRB's decision not to make its approval of MAb protocols contingent upon FHCRC's adoption of the IRB's recommendation for a review outside of FHCRC.

With regard to alleged obstruction of the IRB's efforts to carry out its review and approval responsibilities: The evidence will not support this allegation. The record demonstrates that lively debate of controverted issues went on between researchers and the IRB and there is no indication that the IRBs ultimate authority to withhold approval was denied, challenged or impliedly threatened. Therefore, OPRR concludes that although there may have been submission(s) of less than optimal (allegedly "sloppy") protocols for review, the IRB was not

reluctant to, and in fact did, require changes in protocols in order to obtain IRB approval. Similarly, the IRB's stipulation that it would not review and approve research which had not been signed by a statistician and approved by a committee designated to review the scientific merit, is indicative of the IRB's exercise of appropriate authority. And FHCRC's acceptance of this recommendation and ultimate implementation of it, to the satisfaction of the IRB, is indicative of support of the authority of the IRB and not an obstruction. The fact that the IRB accepted the establishment of an FHCRC review body (the Monoclonal Antibody Advisory Committee) in lieu of a non-FHCRC review body, will not be second-guessed by OPRR.

With regard to the alleged conduct of a study involving high mortality rates being carried out in patients for whom the outcome was known to be better outside of the activity and for which reporting of adverse outcomes came only indirectly to the IRB: The evidence presented leads to the conclusion that the protocol criticized was never carried out in the absence of IRB approval. OPRR will not attempt to establish, retrospectively, whether the risks of this research were reasonable in light of anticipated benefits. That is the function of the IRB, and the IRB approved this research. Further, there is no allegation that the IRB withdrew an approval or halted any project based upon information about adverse outcomes which had been previously withheld from it, or had not been intended to be provided to it, but came to the IRB circuitously. Nevertheless, it is not acceptable that the IRB be responsible for obtaining information about research outcomes which might influence its continued approval of ongoing research. Researchers and their institutions, in this case FHCRC, are responsible for communicating this information to the IRB. The regulations require that institutions ensure prompt reporting to IRBs of "...any unanticipated problems involving risks to subjects or others..." (45 CFR §46.103(b)(5)(i)). Mechanisms such as discussing these problems at a meeting to which an IRB administrator and one or more members of the IRB are invited do not meet this reporting requirement.

With regard to alleged resistance to the IRB's request for external scientific review of studies involving MAb and marrow infusion: As reflected in the OPRR determination above, the IRB sought to require this review and accepted FHCRC's decision to appoint the Monoclonal Antibody Advisory Committee in lieu of a non-FHCRC review body. There is no indication in the record that the IRB was in anyway inappropriately influenced in deciding that this was an acceptable alternative. It must be remembered that the IRB had the ultimate authority to approve or withhold approval of the study criticized. OPRR will not conclude that FHCRC should not have put forward an alternative mechanism to an outside review body, nor will it conclude that the IRB should not have found that alternative acceptable. Such negotiations are, as far as the record at hand indicates, acceptable.

With regard to alleged lacking on the part of the IRB of authority, guidelines, and regulatory experience to carry out its responsibilities: The record demonstrates that the IRB was then and continues to be properly qualified, adequately provided with guidance, and vested with the appropriate authority.

With regard to the alleged continued enrollment of subjects into a protocol involving MAb and bone marrow infusion after a successful alternative was published: This is comparable to one part of the third allegation and the determination is essentially the same. The evidence presented leads to the conclusion that the protocol criticized was never carried out in the absence of IRB approval and the arguments offered by FHCRC are on their face persuasive. However, OPRR will not attempt to establish, retrospectively, whether the risks of this research were reasonable in light of anticipated benefits. That is the function of the IRB, and the IRB approved this research.

Thank you for your response to these allegations and for your continued commitment to the protection of human subjects in research.

Sincerely,

J. Thomas Puglisi, Ph.D.
Chief, Compliance Oversight Branch
Division of Human Subject Protections
OPRR, OER, OD

cc: Dr. Gary B. Ellis, OPRR
Dr. Melody H. Lin, OPRR
Mr. F. William Dommel, OPRR