**CLINICAL HOLD OVERSIGHT COMMITTEE**
**February 10, 1998**

Committee Members Attending: David W. Feigal (Chair), Jerome Donlon, M. Carolyn Hardegree, Rebecca Devine, Jay Epstein, Jay Siegel, Kathryn C. Zoon

Presenters: Dr. Bernard Parker, Dr. Lydia Martynec, Dr. Fred Mills

Other Attendees: James Simmons, Don Peterson, William Egan, Patricia Keegan, Wendy Aaronson, Renita Johnson-Leva, Mary Meyer, Joseph Salewski, Glen Jones, Norman Baylor, Roger Eastep, Mark Brunswick, Karen Goldenthal, Richard Lewis, Steve Bauer, Anne Pilaro, Paul Richman

**Case 1:**

Dr. Parker reviewed the facts related to the IND as outlined in the documentation package. The product is a [redacted] The sponsor plans to use this agent as a [redacted] Dr. Parker addressed the design of the trial in light of the general standards for such trials and presented analysis of its inadequacies. He pointed out issues of radiotherapy, dosage, delay due to toxicities and/or immunosuppression which were not addressed by the sponsor. He expressed great concern over many aspects of the therapy which could endanger patients. Dr. Parker stated that there has been significant redesign of the trial via telephone conferences, with three remaining major issues. CBER asks that the sponsor (1) increase the interval phases to monitor for immediate and early-delayed toxicity; (2) decrease the dosage of the [redacted] when used with the chemotherapy; and (3) improve the informed consent documentation in indicating the options available. To date the sponsor has not provided structured or substantive response to the above issues. The supporting information provided does not address the issues and the dose regimen is not stringently defined. The sponsor continues to assert that they have no concerns regarding safety.

There was discussion by the Committee of the information provided by Dr. Parker. Dr. Goldenthal stated that the Office of the Commissioner has stated that informed consent issues cannot be used for Clinical Hold, but rather should be referred to the Office of Compliance.

- Dr. Zoon instructed that the CBER Office of Compliance investigate this sponsor's IRB procedures which clearly did not influence the informed consent in this case.

- Dr. Zoon will write an supporting E-mail to the review committee supporting the Clinical Hold action.

There was additional discussion as to the nature of the informed consent required to proceed with the trials as proposed. The sponsor is awaiting a response from CBER detailing steps required to remove the hold. The sponsor has not completely responded to the initial hold letter and state that they are awaiting information from the manufacturer on this component product.

The Clinical Hold action was upheld by the Committee.

**Case 2:**

This product is an [redacted] Dr. Pilaro reviewed the product, proposed use and clinical hold issues as stated in the documentation provided. The hold issues were based on clinical trial issues exclusively. There were no product issues. There was insufficient preclinical information. The IND was put on Hold 12/5/97. Additional information in response to the Hold letter was received 1/20/98 and is being evaluated at this time. There was a pre-IND meeting with the sponsor which included discussion and analysis of deficiencies in the clinical design. The IND was filed without addressing the issues. The preclinical data does not address the dosage, dosing scheme, and safety. The results from the mouse model were of great concern, with all mice dying at the medium and high dosing schemes. The sponsor repeated the animal study with more appropriate design and dosage, but the design remained inadequate. In spite of requests, the sponsor has provided no histology, no clinical observations and no final report from the laboratory that did the safety testing.

There was discussion of the information presented. Dr. Pilaro responded to questions from the committee regarding aspects of the treatment, the facility, previous interaction with the sponsor, etc. There was also discussion of the potential implications for safety if the clinical trial went ahead as proposed. There are also issues of reproduction and uncontrolled contagion resulting in a viral epidemic. Similarities to other public health issues were discussed. The discussion included raising to the sponsor whether killed virus could be used to avoid the potential problems of a live virus from another species.

The clinical hold was upheld by the Committee.