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 The
sponsor plans to use this agent as a
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 —— 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 Dr. Pil	aro
reviewed the product, proposed use and clinical hold issues as stated in the doc provided. The hold issues were based on clinical trial issues exclusively. There product issues. There was insufficient preclinical information. The IND was Hold 12/5/97. Additional information in response to the Hold letter was receive and is being evaluated at this time. There was a pre-IND meeting with the spot included discussion and analysis of deficiencies in the clinical design. The IND without addressing the issues. The preclinical data does not address the dosag scheme, and safety. The results from the mouse model were of great concern mice dying at the medium and high dosing schemes. The sponsor repeated the study with more appropriate design and dosage, but the design remained inade spite of requests, the sponsor has provided no histology, no clinical observation final report from the laboratory that did the safety testing.	e were no put on ved 1/20/98 nsor which was filed ge, dosing a, with all animal equate. In

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.