I certify that I attended the March 17, 2004 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Johanna Clifford, MS, RN Victor Santana, M.D.

All external requests for the meeting transcripts should be submitted to the CDER Freedom of Information office.

Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. There were no sponsors in attendance at this meeting. The meeting was called to order by Victor Santana M.D. (Committee chair); the conflict of interest statement was read into the record by Johanna Clifford (Executive Secretary). There were approximately 50 persons in attendance. There were no scheduled speakers in either session for the Open Public Hearing.

Attendance:
Oncologic Drugs Advisory Committee Members Present (Voting):
Donna Przepiorka, M.D., Ph.D. (ODAC Chair), Pamela J. Haylock, RN (ODAC Consumer Representative) and Antonio Grillo-Lopez, M.D. (Acting Industry Representative, non-voting)

Pediatric Oncology Subcommittee Consultants (Voting):
Victor Santana, M.D. (Subcommittee Chair), Peter Adamson, M.D., Alice Ettinger, M.S., RN, Peter Houghton, M.D., Eric Kodish, M.D. (via telephone), C. Patrick Reynolds, M.D., Susan Weiner, Ph.D., Ruth Hoffman (Patient representative).

Government Employee Participants (Voting):
Barry Anderson, M.D., Ph.D., Lee J. Helman, M.D., Malcolm Smith, M.D. Ph.D.

FDA Participants
Richard Pazdur, M.D., Patricia Keegan, M.D., Susan Ellenberg, M.D., Grant Williams, M.D., Steven Hirschfeld, M.D., Ph.D., Patricia Dinndorf, M.D., Ramzi Dagher, M.D.

March 17, 2004:
The subcommittee met to discuss safety monitoring in clinical studies enrolling children with cancer in the a.m. session and the use of non-clinical data to complement clinical data for pediatric oncology in the p.m. session

Introduction	Richard Pazdur, M.D. Director, Oncology Drug Products, FDA
Introduction of Issues and Agenda	Steven Hirschfeld, M.D., Ph.D. Oncology Group Leader, Office of Cellular and GeneTherapy Center for Biologics Evaluation and Research, FDA
Protecting Children in Cancer	Eric Kodish, M.D.

Research: What Really Matters	Director, Rainbow Center for Pediatric Ethics
Legal Responsibilities for HHS Supported Studies	Michael Carome, M.D. Associate Director for Regulatory Affairs Office for Human Research Protection, HHS
Legal Responsibilities for Studies with FDA Regulated Products	Steven Hirschfeld, M.D., Ph.D. Oncology Group Leader, Office of Cellular and Gene Therapy Center for Biologics Evaluation and Research, FDA
Break	
Enrollment and Monitoring Procedures for NCI Funded Studies	Barry Anderson, M.D., Ph.D. Cancer Treatment Evaluation Program National Cancer Institute National Institutes of Health
Monitoring Procedures in a Private Children's Hospital	Victor Santana, M.D., Head Division Director, Solid Tumor Malignancies St. Jude Children's Hospital
Committee Discussion	
Lunch	
What are Microarrays and How Can They Help Us with Clinical Studies In Pediatric Oncology	Paul Meltzer, Acting Chief Cancer Genetics Branch National Human Genome Research Institute National Institutes of Health
Advantages and Limitations of Cell Culture Models in Pediatric Drug Developments	Peter Adamson, M.D. Chief, Division of Clinical Pharmacology & Therapeutics Children's Hospital of Philadelphia
Committee Discussion	
Break	
Human Cell-Animal Xenografts: The Current Status, Potential and Limits of Informing Us about Clinical Studies	Peter Houghton, Ph.D. Member and Chair, Department of Molecular Pharmacology St. Jude Children's Research Hospital
An Integrated and Comparative Approach to Preclinical/Clinical Drug Development	Chand Khanna, DVM, Ph.D, DACVIM Head, Comparative Oncology Program & Head, Tumor and Metastasis Biology Section National Cancer Institute National Institutes of Health
What Can Be Learned About Safety?	Kenneth Hastings, Ph.D. Center for Drug Evaluation and Research, FDA
Committee Discussion	
Assessing Anti-tumor Activity in	Malcolm Smith, M.D., Ph.D., Section Head

Questions for Discussion

Adjourn

Questions to the Committee: A.M. Session

The tolerance for risk in cancer therapeutics is different than for most other medical therapies. It is also recognized that children are a particularly vulnerable population and regulations and procedures have been implemented to provide protection to children participating in clinical research. The following questions relate to the setting of children with cancer participating in clinical trials.

Principles:

1. What are the principles that should be addressed in safety monitoring of clinical studies that enroll children with cancer? If the principles are adequately stated in existing documents, statues, or regulations, please identify the relevant documents and sections.

The principles stated in the Belmont Report of respect and beneficence and the guidance provided in International Conference of Harmonization Documents E6 and E11are relevant for pediatric oncology studies. Studies should be performed by experts in the field, maintaining confidentiality, open communication, and transparency. In addition it is necessary to preserve integrity and address any potential conflict of interest. Safety monitoring should be timely to be meaningful and study results should be disseminated.

Practice:

2. Recognizing that particular populations, disease settings, and products may have specific requirements, what general parameters should be monitored for safety in all clinical studies?

The parameters for monitoring are context dependent and may vary based upon the different study phases of product development (Phase I, II, III, etc) and the type of disease. In all cases, the standard of care for the disease should be taken as a minimum threshold with any particular agent. Specific toxicities guiding further monitoring. Information from relevant non-clinical models and adult Phase I studies may be informative, especially for early phase pediatric studies. Eligibility criteria and waivers for assent should be monitored. Pediatric specific concerns that should be monitored are effects on growth, neurocognitive development and other late effects. Late effect monitoring has not been systematically undertaken by the pharmaceutical industry, so if it is to occur it is dependent upon cooperative group resources.

3. Based on the response to the previous question, how often should the parameters be monitored?

The committee maintained that there is currently no need for a prescriptive plan and that frequency is phase dependent and agent specific. Earlier phase studies should have frequent monitoring guided by any previous clinical experience and non-clinical data. Later phase studies monitoring should be guided by the general standard of care for the disease or condition.

4. Based on the response to question 2, who should do the monitoring? Is it adequate to have the personnel involved in the study be responsible for safety monitoring?

The committee recommended a flexible approach with the personnel involved in performing safety monitoring independent upon the phase of the study. There was consensus that phase I studies, which are primarily dose-finding and toxicity assessments are best served by close monitoring by the research team, whereas later phase studies should have additional layers of data safety monitoring independent of the investigator The general principle is to avoid conflicting roles for an individual. Individual investigator studies at single institutions should seek outside monitoring, even it if is another member of the same institution. In all cases safety monitoring should be based on a prospective plan ideally defined in the protocol document and monitoring of the consent/assent/eligibility process should be independent of the investigators. It was noted that the pharmaceutical industry generally does not have external review of early phase studies.

What circumstances would benefit from a Data Monitoring Committee (Data Safety Review Board) oversight?

The committee agreed that the following circumstances consistent with National Cancer Institute policy should have the oversight of a Data Monitoring Committee:

a. *Phase III Studies*
b. *Multi-institutional trials*
c. *High-risk therapy*
d. *Complex treatment regimens*
e. *Vulnerable population*
f. *Phase II upfront "window" trials in previously untreated patients*
g. *Gene transfer studies*

The composition of a Data Monitoring Committee should be prospectively stated in a charter and should include non health care professionals.

5. Are there additional recommendations for safety monitoring?

There is an absence of normative data for toxicity and adverse events across clinical studies and a need to collect and analyze such data.

Institutions lack resources to properly process the volume of safety reports and in addition safety reports are being routed to many parties including investigators, IRBs, regulatory authorities, data monitoring committees, and others. There is a lack of coordination among the recipients and often a lack of context, where the cumulative numerator of the event and denominator of the relevant patient population is not known. To effectively monitor studies, coordination and data sharing are essential. In addition a filtering mechanism was discussed whereby only the serious and unexpected events would have expedited reporting In addition a filtering mechanism that would either flag pediatric cases or eliminate possibly uninformative cases based on age, diagnosis, or other criteria was discussed.

Questions to the Committee: P.M. Session

Because of the limited number of pediatric oncology patients and because of problems unique to pediatric drug development, it may not always be feasible to evaluate all aspects of efficacy and safety in clinical studies. In some settings, extrapolation of results from non-clinical studies may be appropriate.

1. What types of questions are of potential clinical relevance but are not feasible or acceptable to answer in a clinical study could be addressed by non-clinical studies?

Examples may include the need for repeated tissue sampling, assessment of long term effects of treatment, effects on reproduction, access to critical anatomic structures, exposure to toxic reagents, evaluation of non-monitorable or irreversible toxicities, identification of biomarkers for clinical monitoring.

In addition to the proposed list, which was noted to be useful and weighted toward host effects, additional uses for non-clinical data would be validation of combination therapies, target validation, and establishing criteria for patient selection.

Given the need to correlate findings from most non-clinical models with clinical outcomes, the committee recommended that studies would be informative if done in parallel with clinical studies Exploratory non-clinical studies should not delay clinical development.

2. What type of evidence and data would be recommended in each of the following domains to allow extrapolation from non-clinical data and be informative for a clinical condition?

a. Pharmacology and pharmacokinetics
b. Safety
c. Efficacy
d. Behavior
e. Long term effects
f. Developmental aspects
g. Other domains?

The committee noted that currently most non-clinical model systems do not have systematic data correlation with clinical outcomes. In addition, the data may be biased. It is therefore important to examine models in a systematic manner. An additional domain proposed to the suggested list is pharmacodynamics.

Examples where correlations do exist are in the use of xenograft models for pharmacology and pharmacokinetics where the same parameter using the same technique is used in the clinical and non-clinical setting. Further approaches that may be used by non-clinical models to inform clinical findings are using validated surrogates for a molecular target, the use of prior clinical knowledge to test a non-clinical model, prospective parallel testing studies using standard Phase II clinical endpoints such as response rate, and the use of biological correlates that address disease or drug mechanism. The value of negative predication was discussed as a mechanism to minimize exposure of patients to inactive agents. Additional uses of non-clinical models discussed were hypothesis testing of mechanisms of action and providing explanations for clinical findings-especially negative findings. It was noted that non-clinical model validation can be context dependent subject to the disease, stage, and patient population. It is unlikely that any model will be universally predictive.

The National Cancer Institute is beginning a 5 year program to formally examine the validity of various non-clinical models in pediatric cancers for predicting clinical response,

3. Are there additional recommendations for the effective use of non-clinical data? For example, will open literature reports be generally acceptable? Is documentation of compliance with Good Laboratory Practice (GLP) necessary to evaluate animal data? Should non-clinical data be submitted as an independent report with a presentation of primary data sufficient for verification and review?

The subcommittee discussed issues surrounding the documentation and submission of animal data. The subcommittee acknowledged that full compliance with GLP may be difficult in an academic setting.