Summary Minutes of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee
December 6, 2006:

The summary minutes for the December 6, 2006 meeting of the Pediatric Oncology Subcomittee of the Oncologic Drugs Advisory Committee were approved on January 5, 2006.

I certify that I attended the December 6, 2006 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

/S/	/S/
Johanna Clifford, M.Sc., RN Executive Secretary, ODAC	Michael Link, M.D., Acting Chair Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee

The Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee was held on December 6, 2006 in the ACS Conference Room, Room 1066, 5630 Fishers Lane, Rockville, MD 20857. There were approximately 50 people were in attendance. The meeting was chaired by Michael Link, M.D.

The subcommittee met to consider endpoints for trials intended to suppport the approval of new drugs to treat pediatric brain tumors.

Attendance:
Oncologic Drugs Advisory Committee Members Present (voting):
Michael Link, M.D. (Acting Chair); Pamela Haylock, RN

Pediatric Oncology Subcommittee Consultants (voting):
Daniel Armstrong, Ph.D., Susan Blaney, M.D., James Boyett, Ph.D., Kenneth Cohen, M.D., Stewart Goldman, M.D., Craig Lustig (Patient Representative), Mark Kieran, M.D., Larry Kun, M.D., Christina Meyers, Ph.D., Roger Packer, M.D., Ian Pollack, M.D., Charles P. Reynolds., M.D., Malcolm Smith, M.D., Loice Swisher, M.D. (patient representative), Kathy Warren, M.D.

Industry Representative (non-voting):
Unable to attend at the last moment

FDA Participants:
Richard Pazdur, M.D., Karen Weiss, M.D., Ramzi Dagher, M.D., Rajeshwari Shridhara, Ph.D., Joseph Gootenberg, M.D.

Open Public Hearing Participants:
Susan Weiner, M.D.

The agenda proceeded as follows:

Opening Remarks	**Karen Weiss, M.D., Deputy Director** Office of Oncology Products (OOP), CDER, FDA
Non-Inferiority Trial Design	**Rajeshwari Sridhara, Ph.D., Statistical Team** Leader for Oncology Drugs, Division of Biometrics V, Office of Biostatistics, CDER, FDA
Summary of January 2006 Workshop on Clinical Trial End Points in Primary Brain Tumors	**Larry Kun, M.D** Chair, Dept of Radiological Sciences St. Jude Children's Research Hospital
Biology of Pediatric Brain Tumors and the Heterogeneity of this Disease	**Mark Kieran, M.D., Ph.D.** Dept. of Pediatric Oncology, Dana Farber Cancer Institute Assistant Professor of Pediatrics, Harvard Medical School
Children's Oncology Group Experience with Pediatric Brain Tumor Clinical Trials	**Ian Pollack, M.D. F.A.C.S., F.A.A.P.** Walter Dandy Professor of Neurosurgery Chief, Pediatric Neurosurgery Children's Hospital of Pittsburgh

Neurocognitive Sequelae of Pediatric Brain Tumors	**Daniel Armstrong, Ph.D.** Professor & Associate Chair, Dept of Pediatrics Director, Mailman Center for Child Development Associate Chief of Staff, Holtz Children's Hosp at Univ of Miami/Jackson Memorial Medical Center

Break

Questions to the Presenters

Open Public Hearing

Lunch

Questions to the Pediatric Oncology Subcommittee and Discussion

Adjourn

MEETING QUESTIONS

I. Brain tumors in children comprise a heterogeneous group of tumors whose biology, clinical manifestations, treatment and outcome differ from one another and from brain tumors in adults. Treatment decisions are in part based on risk-assignment models (*i.e.* low, intermediate and high-risk). For example, patients with low-risk characteristics receive therapy aimed at maintaining excellent survival while decreasing toxicity. Risk models may also be useful for regulatory purposes – e.g., in determining optimal endpoints and other study design features for new agents with the ultimate goal of market approval for the treatment of pediatric patients with brain tumors.

A. Please discuss the value and/or pitfalls of categorizing pediatric brain tumors based on *risk strata,* as a first step to defining appropriate outcomes for use in regulatory decisions.

B. If it is appropriate to develop categories, please suggest: (a) categories and (b) criteria for such categories. The criteria could include, for example, histopathology characteristics and grade alone or in conjunction with other demographic and disease factors.

The panel addressed a number of issues related to the heterogeneity of brain tumors in children and the fact that location has an important role. Broadly, high risk tumors can include Brain Stem Gliomas, High Grade Gliomas, AT tumors, Infantile tumors vs low grade gliomas; even within the low grade group, there exists patients who experience a lot of associated morbidity. They discussed various trial designs and algorithms related to disease states and specific treatments. The panel commented on various trial designs and mechanisms, the limitations associated with these trials, risk reduction trials, effect on sample size, generalized cytotoxic therapies vs. targeted therapies. They commented that these tumors cannot be classified solely on risk, but on biology as well. They suggested "high risk" patients are those for whom the doctors/patients are willing to place on novel therapies; only in the 'good risk' are risk reduction strategies appropriate.

(please see transcript for additional details)

II. FDA considers a variety of outcomes as informative for assessing efficacy for regulatory purposes. Examples of efficacy endpoints include overall survival, progression free survival, overall response rate and duration. For each of the risk strata (or specific tumor types) identified in your response to Q 1 please discuss study endpoints that represent a meaningful clinical benefit or a surrogate endpoint reasonably likely to predict clinical benefit. In your discussion consider:

- In what settings (population and design) is overall survival the appropriate endpoint for registration purposes?
- In what settings (population and design) can other endpoints (e.g., progression-free survival (PFS), overall response rate (ORR)) be considered?
- For PFS or ORR, what methodologies should be used to define the endpoint and to minimize potential bias?

The panel suggested that progression free survival for: medulloblastoma, low grade and high grade glioma and midline enhancing tumors such as hypothalamic tumors as PFS is most likely to translate into overall survival. For those brain tumors associated with a poor outcome (e.g, brain stem glioma), the panel felt that overall survival was the most appropriate endpoint. There was some discussion about the need for early markers of disease progression. Depending on tumor location, the committee felt it appropriate to consider radiographic plus other symptomatic measures in the definition of progression free survival, such as visual impairment in tumors of the optic chiasm. The committee discussed the various limitations with applying specific endpoints to all pediatric brain tumors suggesting that various disease states would require different outcomes and that particular consideration should be given to quality of life measures and neurotoxicities.

(See transcript for additional details)

III. Neurological outcomes are important measures of response to as well as toxicity of treatment. Neurologic toxicity may manifest early and/or late in the course of treatment or follow-up, and ways to assess these outcomes, and their impact on the patient, will vary based on age of the patient, the functional status of the patient, validity and reproducibility of the assessment tools, etc. Please discuss:

- Acute effects (i.e. neuron-cognitive, memory loss)
- Late effects (cognitive – school performance, endocrine – thyroid, growth)
- Age and developmental status appropriate tools to identify/minimize effects of chemotherapy, radiation and surgical therapies on the developing brain and predictive models/markers for toxicity.

The committee suggested that for acute toxicity, the same assessment tools can be used, whole for late toxicity, different tools and multiple assessments are needed to take into account the developing brain. The panel noted that identifying specific markers to define neurotoxicity is difficult, but that the need for early markers for late effects and the need to define these markers earlier in the disease is paramount. They further discussed the need to define damage to the host by defining host vulnerability; specifically suggesting the use of surrogates such changes in white matter or changes in cerebrospinal fluid as well as neuropsychiatric testing and metabolic ratios. There was some discussion about how to incorporate neuron-psychiatric testing into all trials in a way that will not be overly burdensome.

IV. New agents could be licensed on the basis that they demonstrate a reduction in toxicity without a decrement in efficacy (e.g., a drug designed to obviate the need for or to minimize doses of radiation). Such a claim usually necessitates evaluation in the context of a randomized, controlled non-inferiority study. However, such studies are particularly challenging when there is uncertainty regarding the active control effect size and when there are limited numbers of patients with the disease. Given the constraints of non-inferiority studies, please discuss in what clinical settings a non-inferiority study should be conducted in pediatric patients with brain tumors.

The committee felt overwhelmingly that a non-inferiority trial is generally not feasible given the limited patient numbers. For a few tumor types such as medulloblastoma where the prognosis is good, active controlled studies have been performed that show a better toxicity profile while maintaining an acceptable PFS. For most of the tumor types, there is a critical need to identify effective drugs. Overall, the committee preferred a superiority trial over with documented evidence of survival and increase quality of life.

The meeting adjourned at approximately 4:00 p.m.