Food and Drug Administration
Center for Drug Evaluation and Research
Holiday Inn, Kennedy Ballroom
8777 Georgia Ave., Silver Spring, MD

Summary Minutes of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee October 9, 2003

Members Present

Donna Przepirorka, M.D. Stephen George, Ph.D. (On Phone)

Consultants

Victor Santana, M.D.	C. Patrick Reynolds, M.D.	James Boyett, Ph.D.
Jerry Finklestein, M.D.	Ruth Hoffman (patient rep.)	Alice Ettinger, R.N.
Clinton Stewart, M.D.	Jeffrey Blumer, M.D.	Peter Adamson, M.D.

Guests

Walter Shaw, Ph.D.	Douglas Flanagan, Ph.D.	Malcolm Smith, M.D.
Anne Zajicek, M.D.	Don Mattison, M.D.	Louis Cooper, M.D.

FDA Participants

Richard Pazdur, M.D. Steven Hirschfeld, M.D.
Rosemary Roberts, M.D. Patricia Dinndorf, M.D. Rik Lostrito, Ph.D.

These summary minutes for the October 9, 2003 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee were approved on October 17, 2003.

I certify that I attended the October 9, 2003 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee, and that these minutes accurately reflect what transpired.

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Thomas H. Perez, M.P.H., R.Ph.
Executive Secretary

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Victor Santana, M.D.,
Chair

The Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee, of the Food and Drug Administration, Center for Drug Evaluation and Research met October 9, 2003 at the Holiday Inn, Kennedy Ballroom, 8777 Georgia Ave., Silver Spring, MD

During the morning session the Subcommittee considered off-patent oncology drugs for which pediatric studies are needed and discussed the availability of information concerning the safe and effective use of the drugs in the pediatric population; whether additional information is needed; and whether new pediatric studies concerning the drugs may produce health benefits in the pediatric population, as mandated by the Best Pharmaceuticals for Children Act (BPCA). During the afternoon session the Subcommittee discussed age-appropriate formulation changes to facilitate dosing of products used in the pediatric oncology setting.

The Committee had received a briefing document from the FDA.

There were approximately 18 persons in the audience. The meeting was called to order at 8:10 a.m. by the Chair, Victor Santana, M.D. The subcommittee members and discussants introduced themselves. Thomas H. Perez, Executive Secretary of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee read the Meeting Statement for the mornings session. A welcome was provided by Richard Pazdur, M.D., Director, Division of Oncology Drug Products.

The scheduled presentations began at 8:15 a.m. and proceeded as follows.

Labeling & Formulation: Challenges in Pediatric Therapeutics	Steven Hirschfeld, M.D, Ph.D., Medical Officer Division of Oncology Drug Products
BPCA: For Oncology Drugs	Louis I. Cooper, M.D., Medical Officer Division of Pediatric Drug Development
BPCA: Role of the NIH	Anne Zajicek, M.D., Pharm.D. National Institute of Child Health & Human Development
Off-patent Drugs for Young Children With Cancer – Gaps in Knowledge And Public Health Needs	Malcolm Smith, M.D., Ph.D. Cancer Therapy Evaluation Program, NCI
Population Pharmacokinetics in Childhood Cancer Drug Development	Peter C. Adamson, M.D., The Children's Hospital of Philadelphia

The subcommittee continued with a period of questions on the presentations, and paused for a brief Break at 10:15 a.m. The Subcommittee reconvened at 10:35. There were no participants present for the Open Public Hearing. A statement received from Gregory H. Reaman, M.D., Children's Oncology Group, was read into the record by the Chair. The Subcommittee continued with its discussion of the questions provided by FDA for the morning session.

The morning session was adjourned for lunch at 12:30 p.m.

At 1:15 p.m. the afternoon session of the meeting began. There were no participants for the Open Public Hearing, and the scheduled presentations for the afternoon followed

Lym-X-Sorb™ A Revolution in Oral Drug Delivery	Walter A. Shaw, Ph.D., Avanti Polar Lipids, Inc.
Best Pharmaceuticals for Children	Douglas R. Flanagan, Ph.D., University of Iowa

Best Formulation for Children

Drug Formulation in Pediatrics: If it tastes bad it must be good for you — Jeffrey Blumer, Ph.D., M.D., Case Western Reserve University

The subcommittee continued with a period of questions on the presentations, and at 3:10 p.m. began its discussion of the questions provided by FDA for the afternoon session.

The meeting was adjourned at 3:35 p.m.

The subcommittee discussed the following questions for which no votes were requested or taken.

Questions to Subcommittee

Morning Session

Off-patent oncology drugs for which pediatric studies are needed: availability of information concerning the safe and effective use of the drugs in the pediatric population; whether additional information is needed; and whether new pediatric studies concerning the drugs may produce health benefits in the pediatric population, as mandated by the Best Pharmaceuticals for Children Act (BPCA)

The BPCA of 2002 provides a mechanism to study off-patent medications in pediatric populations.

1. What factors should be considered in selecting off-patent drugs for study in children with cancer (these may include use in only a pediatric population, use in particular diseases, use in particular age groups, or toxicity questions of particular concern)?

   The Subcommittee consensus was that there is no one unique factor, but a matrix of factors that included the following: issues that address toxicity (acute and long term for patients being cured and end organ toxicity),frequency of use particularly use in younger age groups where the incidence of cancer is the highest, efficacy and safety profile-particularly if there is loss of efficacy or increased toxicity in a particular population, likelihood of drug-drug interactions, dosing issues in obese patients, and feasibility - availability of validated assays and relevant patient populations.

2. Are there any comments, on the proposed selections as discussed by the National Cancer Institute, on the drugs actinomycin-D and vincristine as priority choices, and others to follow?

   The Subcommittee endorsed the choices with an optional suggestion that both can be studied together in a reasonable study design and allow for an efficient use of limited resources. Other drugs were also mentioned as meriting priority (see answer to next question), but not necessarily at the expense of dactinomycin and vincristine.

3. Are there any other off-patent oncology drugs that should be studied in children with cancer that you would suggest? Please indicate the rationale.

   Cisplatin because of its short and long term toxicity, use in many tumor types and lack of detailed knowledge on individualizing the dose for maximum benefit and minimal toxicity.

6-thioguanine because of its unexpected hepatotoxicity.
Anthrocyclines because of the increased incidence of cardiotoxicity in the youngest patients children.
Alkylating agents cyclophosphamide and ifosfamide due to toxicity.
13-cisretinoic acid and other retinoids to better understand dosing and to avoid underdosing.
Corticosteroids due to the unpredictably of a wide range of toxicities.
Products used in supportive care such as anti-emetics and analgesics are also good candidates for study in cancer patients. The committee suggested that if products that are used in cancer patients were being considered in other settings, that including the oncology use would be desirable and beneficial.

Afternoon Session

Age-appropriate formulation changes to facilitate dosing of products used in the pediatric oncology setting

1. What factors would be considered essential in the development of a formulation for children with cancer? Please comment on any age-, disease-, or pharmaceutical-specific considerations.

   Factors that were discussed included the anticipated length of therapy, the usage, age and developmental stage of the patient, ability to use with food, palatability, volume or size of dose, development of a range of dose sizes for solid oral medications, ease of standardization, development of several alternatives to provide flexibility, stability and uniformity.

   Discussion on the applicability of pediatric formulations to other populations such as geriatric patients, handicapped patients, patients with chronic illness, post-surgical patients, patients requiring greater precision in dosing, and patients who wished to have alternatives recommended calling attention to manufacturers of the potential for greater use for a pediatric formulation.

2. What type of testing or clinical trial design would you recommend for establishing the efficacy and safety of a new formulation for an existing oncology drug that already has efficacy and safety demonstrated in the same population?

   Limited studies were recommended that would address bioequivalence and if needed, some proof of principle for efficacy. Similar response based on surrogate endpoints rather than complete demonstration of clinical benefit would likely be sufficient.

3. What type of testing or clinical trial design would you recommend for establishing the efficacy and safety of a new formulation for an existing oncology drug that already has efficacy and safety demonstrated in a different population?

   A separate efficacy study in the new population was recommended.