Food and Drug Administration
Center for Drug Evaluation and Research
ACS Building, 5630 Fishers Lane, Rockville, MD

Summary Minutes of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee March 4, 2003

Members Present

Jody Pelusi, R.N., Ph.D.
Gregory Reaman, M.D.

Consultants

Victor Santana, M.D.	Alice Ettinger, R.N.	Jerry Finklestein, M.D.
Patrick C Reynolds, M.D.	James Boyett, M.D.	Nancy Keene (patient rep.)
Henry Friedman, M.D., Ph.D.	Susan Cohn, M.D.	

Guests (Non-Voting)

Malcolm Smith, M.D.	Francesco Pignatti, M.D.	Katherine Cheng, M.D.
Anne Mathieu-Boue, M.D.	Gilles Vassal, M.D.	Harald Schweim, M.D.
Mark Bernstein, M.D.		

Industry Guest Attendees

Anne Hagey, M.D., Abbott
Alan Melemed, M.D., Lilly

FDA Participants

Richard Pazdur, M.D.	Joseph Gootenberg, M.D.	Steven Hirschfeld, M.D.

These summary minutes for the March 4, 2003 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee were approved on March 12, 2003.

I certify that I attended the March 4, 2003 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee, and that these minutes accurately reflect what transpired.

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

Victor Santana, M.D., Chair
Chair

The Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee, of the Food and Drug Administration, Center for Drug Evaluation and Research met March 4, 2003 at the FDA's Advisors and Consultant Staff conference facility at 5630 Fishers Lane, Rockville, MD

The Committee discussed pediatric labeling of oncology products.

The Committee received a briefing document from the FDA in preparation for this meeting.

There were approximately 40 persons in the audience. The meeting was called to order at 8:30 a.m. by the Chair, Victor Santana, M.D. The Committee 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. Welcome, and opening remarks were provided by Steven Hirschfeld, M.D., Ph.D., Division of Oncology Drug Products.

The scheduled presentations began at 8:45 a.m. and proceeded as follows.

History of Pediatric Labeling		Steven Hirschfeld, M.D., Ph.D.
Case Studies of	Case 1 By -	Anne Zajicek, Pharm.D., M.D.
Pediatric Submissions	Case 2 By -	Ramzi Dagher, M.D.
for Oncology Products	Case 3 By -	Steven Hirschfeld, M.D., Ph.D.
	Case 4 By -	Susan Honig, M.D.
	Case 5 By -	Alla Shapiro, M.D.

The presentations were followed at 9:45 by questions to the presenters and a break at 10:45.

The Open Public Hearing was held at 11:00 with one presenter, Edward J. Allera, J.D., Buchanan & Ingersoll.

At 11:10 the Subcommittee began its discussion of the questions. During its deliberations, Jerry Finklestein, M.D. provided a journal article (published ahead of print on February 7, 2003 as 10.1200/JCO.2003.11.138), from the Journal of Clinical Oncology. The publication titled "Regulatory Approvals of Pediatric Oncology Drugs: Previous Experience and New Initiatives" authored by Steven Hirschfeld, Peter T.C. Ho, Malcolm Smith, and Richard Pazdur is set to print in Vol. 21, No 6, March 15, 2003".

At 12:15 p.m. the Subcommittee paused for Lunch, and reconvened at 12:50.

The Subcommittee adjourned at 2:10 p.m.

Questions to the Committee

Federal government initiatives are aimed at developing therapeutics for pediatric patients and including product information in the approved package insert or product label. Although the majority of children with cancer in the United States are treated on protocols from National Cancer Institute supported study groups, the majority of products used in children with cancer are used without dosing and safety information in the package insert. Given that the U.S. Congress has indicated in the Best Pharmaceuticals for Children Act of 2002 that pediatric use information should be included in product labels as one of the mechanisms to publicly disseminate that information, consider each of the following situations.

If adequate and well controlled trials in children that independently establish safety and efficacy are submitted to the FDA as a New Drug Application (NDA) or Biological Licensing Application (BLA) or as a supplement to an NDA or BLA, then product labeling would follow standard procedures. The situations that follow describe circumstances when information other than adequate and adequate and well controlled trials sufficient to independently establish safety and efficacy are submitted.

The first questions pertain to the situation where a product is approved (safety and efficacy established) for an adult indication and the same disease or condition exists in a pediatric population.

Previously the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee, at a meeting in November 2001, recommended that to extend efficacy from an adult indication to a pediatric population (use extrapolation), pediatric dosing studies and a demonstration of clinical proof of concept should be performed.

1. If a product is approved for an adult disease or condition that also exists in children and extrapolation is used, consider what information you would consider necessary and appropriate to be in the product label.

   Factors may include:
   - Dosing
   - Safety information
   - Proof of concept data regarding clinical effect in children
   - Separation of pediatric and adult safety data if differences exist

The Committee members indicated that all information available should be included. Beyond the factors listed in the question the committee mentioned the following other important information that it would like to see included; pharmacokinetics, pharmacodynamic endpoints, dosing schedules (as much precise information to guide dosing in children), unacceptable toxic dose, dose limiting toxicity, and bioequivalence.

2. If pediatric dosing and safety information are available but clinical proof of concept has not been established, consider whether dosing and safety information be included in the product label. This circumstance could arise if studies were done in children with diseases other than the one that is being considered for an indication yet extrapolation is being considered on the basis of other evidence.

A statement of dosing and safety may be included with comment on the limitations of the data.

The next question pertains to the situation where there is not a linkage between an adult indication and data from pediatric studies.

3. If pediatric dosing information and proof of concept data exist for a pediatric disease or condition that does not exist in adults, what information, if any, should be included in the product label.

   An example may be that a product is approved for second line colorectal cancer in adults and pediatric data are available for dosing and pharmacokinetics plus a single arm phase II study showing a modest response rate in 20 pediatric patients with refractory or relapsed neuroblastoma (There is no existing product with this profile).

   Factors may include:
   - dosing
   - safety information
   - clinical response data

The Committee agreed that primarily dosing and safety information should be included. The information should be qualified with a statement that efficacy has not been established in the approved indication.

The following question pertains to the situation where there is no evidence of clinical benefit in a pediatric oncology population and there are data of a lack of activity

4. If dosing, safety, and lack of activity information are available from studies that enrolled children with cancer, consider what information, if any, be included in the product label. Factors may include:

   - a statement restricted to stating that no meaningful clinical activity has been observed
   - the number and diagnoses of the patients in the studies
   - dosing information

The Committee agreed that primarily dosing and safety information should be included, and a statement that no clinical activity was observed relative to a specific study or inquiry with confidence intervals or other qualifying information as appropriate.

The following question pertains to the situation where no efficacy or safety data are available in pediatric patients.

5. When no efficacy or safety data are available in pediatric patients consider if a statement that safety and efficacy have not been tested in children be included in the product label

A statement may be appropriate if the date is referred to and qualifying information is included. Refer to the meeting transcript for the committee's discussion of this question.