Food and Drug Administration

Office of the Commissioner

Office of Pediatric Therapeutics and Office of Science and Health Coordination

SUMMARY MINUTES OF THE
PEDIATRIC ADVISORY COMMITTEE

February 14-15, 2005
5630 Fishers Lane, Rm 1066
Rockville, MD

Monday, February 14th, 2005

The meeting was convened at 2:00 p.m.

Members Present (voting)
Joan Chesney, M.D. (Chair)
Dennis Bier, M.D.
Angela Diaz, M.D., M.P.H.
Deborah Dokken, M.P.A. (Patient Family Representative)
Michael Fant, M.D., Ph.D.
Mary Glode, M.D.
John Moore, M.D., M.P.H.
Thomas Newman, M.D., M.P.H.
Judith O'Fallon, Ph.D.
Vistor Santana, M.D.

FDA Participants
Dianne Murphy, M.D.
Solomon Iyasu, M.D., M.P.H.
Rosemary Roberts, M.D.

Executive Secretary
Jan Johannessen, Ph.D.

Pediatric Advisory Committee Pediatric Health Organization Representative (non-voting)
Richard Gorman, M.D.

Pediatric Advisory Committee Industry Representative (non-voting)
Elizabeth Garofalo, M.D.

Open Public Hearing Speakers
(none)

FDA Presentations:

Welcome and Introductory Remarks	Dianne Murphy, M.D.
Adverse Event Reporting for Benazepril	Lawrence Grylack, M.D.
Adverse Event Reporting for Esmolol	Lawrence Grylack, M.D.
Adverse Event Reporting for Orlistat	Hari Cheryl Sachs, M.D.
Adverse Event Reporting for Glyburide/Metformin	Hari Cheryl Sachs, M.D.
Adverse Event Reporting for Atovaquone/Proguanil	Alan M. Shapiro, M.D., Ph.D.
Adverse Event Reporting for Nelfinavir	Alan M. Shapiro, M.D., Ph.D.
BPCA-mandated Review and Reporting of Adverse Events for Drugs Granted Exclusivity: Committee Feedback and Options for Improvement	Solomon Iyasu, M.D., M.P.H.

Sponsor Presentations:
(none)

Comments from the Committee on Specific Safety Presentations:

Benazepril
The Committee recommended unanimously by a show of hands that FDA continue to monitor Benazepril closely in the pediatric population and update the committee on adverse events in another year.

Esmolol
The Committee by a show of hands (15 =yes, 2=no), recommended that the FDA continue to monitor the safety of esmolol in the pediatric population, and update the committee on its safety in another year.

Orlistat
The committee agreed with the FDA recommendation to continue to monitor Orlistat for 1 year, particularly for the risk of cholelithiasis.

Glyburide/Metformin, Atovaquone/Proguanil and Nelfinavir
The Committee unanimously agreed with the FDA recommendation to revert to routine monitoring of the safety of these drugs.

Questions to the Committee

Question 1*: OPT proposes to submit an abbreviated written summary report to the PAC for drugs where the 1-year safety review does not raise a safety concern i.e. there were no post-marketing reports submitted or the reported pediatric events did not provide any concern of a possible safety risk. The entire written summary will not be presented at a public PAC meeting. However, a slide summarizing the products reviewed and our recommendation to the PAC will be presented. The PAC will still retain the opportunity to comment upon our recommendation at a public hearing. Do you concur with this approach?*

The committee received some clarification from Dr. Iyasu on their role under BPCA, learning that the committee is only required to review the safety data collected in the time since a drug was granted pediatric exclusivity. Dr. Iyasu noted that the Committee has routinely been provided with more extensive safety and use information, some derived from the clinical trails supporting the IND, to provide a more complete background for the Committee members.

The committee assented to the suggestion of receiving written reports from the FDA on those drugs for which few or no adverse events have been reported and which are not of concern to the FDA. There were, however, several stipulations from the committee, as well as suggestions for improving the process.

- The committee would like to continue to receive the full range of data on all drugs, as they have been getting to date (e.g., no abbreviated reports for drugs which are not of concern to FDA)
- All briefing materials and communications to the committee regarding drugs for which there is no safety concern will continue to be posted in their entirety on the FDA committee website.
- In the written reports to the Committee on drugs for which the FDA has no special pediatric safety concern, the FDA should provide its rationale for why it feels a detailed presentation to the committee is not needed.
- One member suggested that the FDA should include a table in their reports, showing a comparison of adverse events in children vs adults
- One member suggested that the FDA restrict their detailed reporting on adverse events to serious adverse events (e.g hospitalizations and deaths)

Please see transcript for details

Question 2: *OPT proposes to provide a public presentation of the mandated safety review at the PAC meeting for drugs where the 1-year safety review raised a possible pediatric safety signal i.e. increase in the frequency or severity of expected adverse events relative to adults or background rate; occurrence of unexpected or new serious pediatric events; reports of events that are unique to pediatric patients. When possible, in addition to the adverse event reporting and our usual review, the*

presentation will include an assessment of incidence rates, biological plausibility and review of the literature. Do you concur with this approach?

The committee did agree with the FDA's approach (no votes taken), noting that additional information will aid the committee in making informed recommendations.

Please see transcript for details

Question 3: *The limitations of spontaneous post-marketing adverse event reporting system are well known to you. Please discuss and prioritize potential programs, assuming additional resources were available, to supplement and/or overcome the limitations of spontaneous reporting system for assessing and monitoring safety of marketed drug products in the pediatric populations. Some examples of potential programs include:*

a. Population-based active surveillance
b. Analysis of claims databases (e.g. United Health Group, Harvard Pilgrim, TenCare)
c. Exposure and/or outcome/disease registries and creation of linkages with AERS

Long-term pediatric safety studies to assess drug adverse events including assessment of growth and development; discuss if and how prioritization of products for additional long-term studies might be approached.

Members of the committee commented on the shortcomings of the Medwatch system and the AERS data. It was expressed that the passive, voluntary reporting system leads to vastly under-reported adverse events. From practical experience with this system, there was agreement amongst physicians that the reporting mechanism is cumbersome and time consuming. It was noted that physicians are reluctant to file reports because of the time required for writing lengthy narratives and the time taken from clinical duties to answer follow-up phone calls. It was felt that if the system were made simpler and the reporting requirements less time consuming, that compliance would increase significantly. Several suggestions for achieving this objective were made:

- Instead of following up with phone interviews, the FDA should email report filers with their questions, so that they can be responded to as time permits.
- Create a system that has more specific and consistent descriptors
- Streamline the AERS – will get better compliance

Regarding the options in question 3, bullets a.-c., there were several suggestions from committee members:

- Any of the options are better than what is available now through AERS. FDA should pursue those options which are most achievable with obtainable resources
- An active surveillance system is desirable, as are claims databases
- FDA should explore collaborations with other pediatric organizations that collect data on children (e.g. NICHD, CDC).
- If passive surveillance system currently can't be made better (e.g. better compliance), then legislative remedies may be required.
- The committee recommended that AERS database should be streamlined and that this recommendation be forwarded to ODS

The meeting adjourned at approximately 6:15 p.m.

Please see transcript for details

Tuesday, February 15, 2005

The meeting commenced at 8:00 a.m.

Members Present (voting)
Joan Chesney, M.D. (Chair)
Dennis Bier, M.D.
Angela Diaz, M.D., M.P.H.
Deborah Dokken, M.P.A. (Patient Family Representative)
Michael Fant, M.D., Ph.D.
Mary Glode, M.D.
John Moore, M.D., M.P.H.
Thomas Newman, M.D., M.P.H.
Judith O'Fallon, Ph.D.
Victor Santana, M.D.

FDA Participants
Dianne Murphy, M.D.
Jonathan Wilkin, M.D.
Anne Trontell, M.D.
Lisa Mathis, M.D.
Susan Cimmins, M.D.

Executive Secretary
Jan Johannessen, Ph.D.

Pediatric Advisory Committee Consultants (voting)
Elizabeth Andrews, M.P.H., Ph.D. (CDER SGE)
Ruth Day, Ph.D. (CDER SGE, member of DSRMAC)
Roselyn Epps, M.D. (CDER SGE)
Norman Fost, M.D., M.P.H. (CBER SGE)
Paula Knudsen (CDER SGE, Consumer Representative to DODAC)
Donald Mattison, M.D. (NIH)
Robert Stern, M.D. (CDER SGE)

Pediatric Advisory Committee Pediatric Health Organization Representative
Richard Gorman, M.D. (non-voting)

Pediatric Advisory Committee Industry Representative
Elizabeth Garofalo, M.D. (non-voting)

Open Public Hearing Speakers

- Daniel Yarosh, Ph.D., AGI Dermatics, Freeport, NY
- Robert Silverman, M.D., American Academy of Dermatology Association
- LaDonna Williams, Inflammatory Skin Disease Institute

- Ruthann Newton, Inflammatory Skin Disease Institute
- James Hendricks, National Eczema Association
- Eva Guinan, M.D., Dana-Farber Cancer Institute

In addition, comments were received and are posted from several who could not attend:

- Dr. Vincent Beltrani, American College of Allergy, Asthma and Immunology
- Dr. Tsunetoshi Shimazu, Shimazu Clinic, Japan
- Rokuro Hama M.D., Japan Institute of Pharmacovigilance

FDA Presentations

Overview and Charge to the Committee	Dianne Murphy, M.D.
Assessing Cancer Risk and Assuring Safe Use of Topical Immunosuppressants: Recent History	Susan Cummins, M.D., M.P.H.
Epstein-Barr Virus Infection and Cancer	Jeffrey I. Cohen, M.D.
FDA Perspective- Topical Immunosuppressants	Bindi Nikhar, M.D.
Systemic Human Exposure of Pimecrolimus and Tacrolimus Following Topical Application	Tapash Ghosh, Ph.D.
Topical Immunosuppressants (Calcineurin Inhibitors) – Animal Toxicology	Barbara Hill, Ph.D.
Post-Marketing Cases of Tumors Reported With the Topical Immunosuppressants (Calcineurin Inhibitors)	Marilyn Pitts, Pharm.D.
Risk Minimization Action Plans	Anne Trontell, M.D., M.P.H.
Product Labeling and Drug Promotion	Melissa Moncavage, M.P.H.
Summary of the Issues and the Evidence	Jonathan Wilkin, M.D.

Presentations from Sponsors

Presentation by Novartis Pharmaceuticals Corporation	Mathias Hukkelhoven, Ph.D.
Elidel (pimecrolimus) Cream 1% Safety Update	Thomas Hultsch, M.D.
Atopic Dermatitis: Disease Impact and Therapy	Lawrence F. Eichenfield, M.D.
Presentation by Fujisawa Healthcare, Incorporated	Amy Paller, M.D.
	M. Joy Rico, M.D.

Questions to the Committee

Question 1: <u>Messages about Risk</u>

A. Based on the presentations today and the background materials provided, do you find that additional information about the potential carcinogenicity of these products in humans should be communicated to physicians, patients and consumers?
B. If no, explain why not.

If yes, what messages about these products should be communicated? Examples might include:

- *There is a potential increased risk of cancer in humans, based on animal studies (including non-human primates);*
- *Reports of humans developing tumors at the site of application;*
- *Increased potential risk of cancer with increase in the dose or duration of exposure;*
- *Use of the product only as second line therapy because of this potential risk;*
- *The product should not be used in children younger than 2 years of age;*
- *The product should not be used in immunosuppressed patients or those with an increased risk for cancer.*

For Question 1, there was agreement from all but one of the committee that additional information should be provided. No formal vote was taken.

For question 1, several comments were made by committee members, the consensus was that the message should include the following points:

- The potential increased risk of cancer from treatment with the topical calcineurin inhibitors (TCIs) is based on animal data
- There is inadequate human data at this time to ascertain the cancer risk from the topical use of calcineurin inhibitors
- The products should be used as second-line therapy
- The products should not be used in patients under the age of 2 (though there was some discussion that room should be left for those special situations in which it was warranted).
- Sun exposure to treated areas should be minimized
- The safety of these products in immunosuppressed patients has not been fully evaluated
- Use should be limited to the affected area and only used intermittently

No vote was taken on a final list of messages to include.

Please see transcript for details

Question 2: <u>Warnings</u>

Under 21 CFR 201.57(e) special problems, particularly those that may lead to death or serious injury may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning is usually based on clinical data but serious animal toxicity may also be the basis of a boxed warning.

Does the Committee believe that a boxed warning is appropriate for the topical immunosuppressant calcineurin inhibitors? Please explain your answer, whether yes or no.

The committee voted on this question, but not on the specific items to include in the boxed warning. Reference was made to the messages to be conveyed captured under question 1B.

Yes= 15 No=1 Abstain=1

Please see transcript for details

Question 3<u>: Mechanisms for Risk Communication</u>

Does the Committee recommend any of these, or any other approaches, to communicating and minimizing risk for these products?

Prescriber Targeted:
- *Dear Health Care Provider letter*
- *Professional Organization Letter and electronic alerts*
- *Continuing medical education courses (for whom, and by whom?)*

Patient Targeted:
- *Patient Package Insert*
- *Patient Medication Guide (MedGuide)*
- *FDA Public Health Advisory and Information Page*

Other:
- *Government sponsored symposia*
- *Other*

One vote was taken on this question – on whether to recommend issuing a Patient Medication Guide (MedGuide) for these products.

Yes=10 No=4 Abstain=3

Other suggestions the committee members recommended were:
- Dear Health Care Provider Letter – strongly supported by the committee

- Patient Package Insert – recommendation was to improve the patient readability, to include repetition within the message.
- Include information on the FDA website.

One member recommended linking the messages with the intended outcomes listed in question 5. (e.g. "should not be used in children under 2" could be linked to monitoring of % of prescriptions to those under 2).

Please see transcript for details

Question 4: <u>Risk Minimization</u>

In addition to communicating information about risk, there are a number of ways to help ensure that products are used appropriately.

A. Does the committee recommend that in addition to communicating risk information, additional mechanisms be employed to minimize risk to individual patients or to the population at large? If yes, what should the goal of such mechanisms be (e.g. additional education, restricting distribution, increasing frequency of patient assessment)?

B. Examples of approaches that have been used for other products are listed below. Does the Committee recommend any of these approaches, or other approaches, for these products at this time? If yes, state how the intervention would address the goal(s) cited previously

- *Specialized training for prescribers*
- *Limiting use to prescribers with specified expertise or training*
- *Limiting the amount that can be dispensed to a patient in a given time period*
- *Other?*

Question 4A. The committee recommended a graduated approach and wished to provide an opportunity for the new labeling and other communication activities to have an impact before recommending additional approaches. The committee voted on this question.

Yes=1 No=16

One member that voted yes, suggested that one possible remedy to overuse is to limit the size of the individual prescription.

Please see transcript for details

Question 5: <u>Monitoring Outcomes</u>

Based on the goals for any of the recommended approaches in your answers to the questions above, consider how FDA should measure the success or failure of those approaches.

A. What would be reasonable performance measures and sources of data? Examples might include reports to MedWatch, active surveillance, additional clinical trials, drug utilization data, managed care databases, physician or consumer surveys, etc.
B. How long or over what period of time should FDA assess the interventions?

The committee discussed two types of follow-up activities; (1) activities that would enhance the quality of the human data collected by the sponsor's registry studies and (2) follow-up activities that would enable the FDA to monitor the effectiveness of the risk communication information disseminated to practitioners, patients and the public.

(1) Committee members suggested that the quality of data generated by the registry studies being planned by the sponsors would be enhanced if the data could be linked to existing cancer registries. This would enable a better comparison of cancer incidence within the product registry studies with background cancer rates in similar populations. Two databases were mentions, COG (Children's Oncology Group) and State Cancer registries. The committee advised the sponsors to contact these entities and attempt to develop linkages
(2) Regarding monitoring the effectiveness of risk communication in discouraging inappropriate use of the products, several suggestions were made by committee members:
    - In a laboratory setting, survey people on their perceptions of risk associated with product use using the current label information and with the revised labeling
    - Evaluate prescriber perceptions of risk related to the products
    - Monitor IMS data on prescriptions sorted by age, by prior steroid use and by other possible risk factors

The committee was asked how a decrease in off-label prescriptions might be effectively measured and what might be a target outcome. Using a absolute number of prescriptions was deemed not useful, as the total prescriptions may well increase significantly, based on recent sales trends. However, some members of the committee felt it was important to see a decline in the rate of increase of sales as it appears much of this is being driven by off-label use. Also, it was recommended that the FDA might monitor prescription data to look for a decrease in the percentage of total prescriptions being written for children under 2 as a reasonable outcome. (e.g. members expressed an interest in seeing a decrease in the proportion of prescriptions for children under 2).

The meeting was adjourned at approximately 5:20 p.m.

Please see transcript for details

I certify that I attended the February 14-15, 2005 meeting of the Pediatric Advisory Committee and that these minutes accurately reflect what transpired.

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Jan N. Johannessen, Ph.D.
Executive Secretary

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P. Joan Chesney, M.D.
Chair