MINUTES OF THE
PEDIATRIC ADVISORY COMMITTEE

Bethesda Marriott Hotel 5151 Pooks Hill Road, Bethesda, Maryland 20814

Monday, March 22, 2010

The meeting was convened at approximately 8:00 a.m.

Members Present (Voting)
Geoffrey L. Rosenthal, M.D., Ph.D. *(Chair)*
Avital Cnaan, Ph.D., M.S.
Carl D'Angio, M.D.
Leon Dure, M.D.
Keith Kocis, M.D., M.S.
Kathleen Motil, M.D., Ph.D.
Daniel Notterman, M.D.
Alexander Rakowsky, M.D.
Elaine Vining B.A. (*Consumer Representative*)
Joseph Wright, M.D.

Members Present (Non-Voting)
Brahm Goldstein, M.D. (*Industry Representative*)

Temporary Voting Members (Voting Consultants)
Marilyn Eichner *(Patient Family Representative)*
Kathleen Neville, M.D. M.S.
Phillip LaRussa, M.D. (by phone)
Sharon Raimer, M.D.
Pablo Sanchez, M.D. (by phone)
Cindy Schwartz, M.D.

Executive Secretary
Doreen M. Kezer, MSN

U.S. Food and Drug Administration (FDA) Participants
Norman Baylor, Ph.D.
Yodit Belew, M.D.
Felicia Collins, M.D., MPH
Judith Cope, M.D., MPH
Anthony Durmowicz, M.D.
Virginia Elgin, M.D.
Linda Hu, M.D.

Wei Hua, M.D., MPH, M.S., M.H.S.
Namita Kothary, Pharm.D
Lois LaGrenade, M.D., MPH
Lisa Mathis, M.D.
Ann McMahon, M.D.
David Menschik, M.D., MPH
Dianne Murphy, M.D.
Robert M. Nelson, M.D., PhD
Andreas Pikis, M.D.
Susan Walker, M.D.
Rickey Wilson, M.D., JD
Robert Wise, M.D., MPH
Amy Woitach, D.O., M.S.
Jane Woo, M.D., MPH
Lucie Yang, M.D., Ph.D.

Non-voting Speaker
Logan Spector, Ph.D

Sponsor Presentations
Novartis
Astellas

Open Public Hearing Speakers
Sidney Wolfe, M.D.

Presentations
Welcome and Introductory Remarks
Geoffrey Rosenthal, M.D., PhD, Chair, Professor of Pediatrics, University of Maryland School of Medicine, Director of Children's Heart Program, and Executive Director of Critical Care Services, University of Maryland Medical Center, Hospital for Children
Doreen M. Kezer, MSN, Executive Secretary, Office of Science and Health Coordination, Office of the Commissioner (OC), FDA
Agenda Overview
Dianne Murphy, M.D., Director, Office of Pediatric Therapeutics (OPT), OC, FDA
Anthelois 40 sunscreen, Cardiolite (technetium Tc-99), Nasacort AQ (triamcinolone) Viramune (nevirapine) Abbreviated Presentations
Judith Cope, M.D. MPH, Medical Officer, OPT, OC, FDA
Introduction to CBER Vaccines
Robert Wise, M.D., MPH, Chief, Therapeutics and Blood Safety Branch, Office of Biostatistics and Epidemiology CBER, FDA
Daptacel (Diphtheria and Tetanus Toxoids and Accelular Pertussis Vaccine Absorbed Vaccine) Standard Review of Adverse Events
David Menschik, M.D., MPH, Medical Officer, Vaccine Safety Branch, CBER, FDA

Pentacel (diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus and haemophilus b conjugate (tetanus toxoid conjugate) vaccine)_ Standard Review of Adverse Events
Jane Woo, M.D., MPH, Medical Officer, Vaccine Safety Branch, CBER, FDA
Kinrix (diphtheria and tetanus toxoids and acellular pertussis adsorbed and inactivated poliovirus vaccine) Standard Review of Adverse Events
Jane Woo, M.D., MPH, Medical Officer, Vaccine Safety Branch, CBER, FDA
Valtrex (valacyclovir) Standard Review of Adverse Events
Felicia Collins, M.D., MPH, Medical Officer, Pediatric and Maternal Health Staff, Office of New Drugs, CDER, FDA
Zmax (azithromycin) Standard Review of Adverse Events
Virginia Elgin, M.D., Medical Officer, Pediatric and Maternal Health Staff, Office of New Drugs, CDER, FDA
Orlistat Update
Lisa Mathis, M.D., Director, Pediatric Maternal Health Staff, Office of New Drugs, CDER, FDA
Topical Calcineurin Inhibitors: Elidel and Protopic: Follow-up Presentation: Introduction and Background
Amy Woitach, DO, MS, Medical Officer, DDDP, CDER, FDA
Outside Speaker Presentation - Childhood Cancer Epidemiology in North America
Logan Specter, Ph.D., Epidemiology, University of Minnesota
Topical Calcineurin Inhibitors: Pediatric Registries
Lois LaGrenade, M.D., MPH, Medical Officer, Division of Epidemiology, CDER, FDA
Sponsor Presentations
Norvartis - Elidel (pimecrolimus)
Astellas - Protopic (tacrolimus)
Rotarix (rotavirus vaccine, live, oral) Standard Review of Adverse Events
Norman Baylor, Ph.D. FDA Press Release on Rotarix Vaccine
Wei Hua, M.D., MPH, Medical Officer, Analytical Epidemiology Branch, CBER, FDA
Adjourn
Geoffrey Rosenthal, M.D., Ph.D., Chair

Agenda Overview

Dianne Murphy M.D., Director of the Office of Pediatric Therapeutics, made the announcement that the Agenda was being changed. The Rotarix presentation was being moved to the afternoon session.

Abbreviated Presentations: Anthelois 40 sunscreen, Cardiolite (technetium Tc-99), Nasacort AQ (triamcinolone) : Dr. Judith Cope

Question to the Committee

- FDA will continue its standard ongoing safety monitoring for these products. Does the committee concur?

Committee Discussion

The Committee discussed the issue of use data for Cardiolite and inquired about the Nasacort AQ's risk benefit ratio.

Follow up to Nasacort AQ presentation: Question was answered later in morning when division representative could call-in via teleconference.

The committee raised questions about the total nasal symptom score and how reliable this endpoint might be in children. This is a 12-point score used in the pediatric studies evaluating pediatric efficacy with this drug. The study found a 1-point difference using this score, which was found to be statistically significant. The committee asked if this was a standard scale and if the scale had been validated. The Division explained that the score was used by surrogates (parents and caregivers) to evaluate nasal symptoms in children; this scale is customarily used in trials involving children for allergic and seasonal rhinitis products.

Committee Vote-(Separate votes were taken for each product)

- Thirteen (13) committee members unanimously agreed to continue ongoing safety monitoring for Anthelois 40.
- Thirteen (13) committee members unanimously agreed to continue ongoing safety monitoring for Cardiolite.
- Thirteen (13) committee members unanimously agreed to continue ongoing safety monitoring for Nasacort AQ.

Abbreviated Presentation: Viramune (Nevirapine): Dr. Judith Cope

Question to the Committee

- FDA will continue its standard ongoing safety monitoring for this product. Does the committee concur?

Committee Discussion

The Committee agreed that Viramune was a mature drug and that no labeling changes needed to be made.

Committee Vote

- Thirteen (13) committee members unanimously agreed to continue ongoing safety monitoring of these products.

Introduction to CBER Vaccines: Dr. Robert Wise

Committee Discussion

The Committee discussed the importance of the Vaccine Adverse Events Reporting System (VAERS) and asked for further information about collaboration with CDC to use the Vaccine Safety Datalink for evaluating vaccine safety questions. The Committee acknowledged that VAERS is important for signal detection

Standard Review of Adverse Events: Daptacel (Diphtheria and Tetanus Toxoids and Accelular Pertussis Vaccine Absorbed Vaccine): 2 vaccine experts join the discussion by telephone.

Committee Discussion
The Committee discussed the definition of major (serious) and minor adverse events and noted that in the clinical review provided, some information on efficacy was redacted. The Committee recognized that there were no safety-related label changes since approval of the 5th dose of Daptacel.

Committee Vote

- Fourteen (14) committee members agreed to routine monitoring of adverse event reports and drug use in pediatric patients.
- One (1) committee member opposed the strategy stating that vaccine monitoring should be expanded beyond the VAERS database.

Standard Review of Adverse Events: Pentacel (Diphtheris and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine

Question to the Committee

- Question 1- FDA recommends reviewing data from the postmarketing study. Does the Pediatric Advisory Committee concur?
- Question 2-FDA recommends continue surveillance, daily review of serious reports, and CDC/Vaccine Safety Datalink. Does the Pediatric Advisory Committee concur?

Committee Discussion
The Committee discussed the importance of reviewing the postmarketing data when it becomes available. The Committee also discussed the importance of closely examining the adverse events related to Urticaria and Intussusception. FDA discussed the importance of reviewing the VAERS reports and recognized that this was passive surveillance safety data with no defined denominator beyond doses sold. The reporting system has limitations in that the reports are not broken down by age, group or sex. FDA reported that the routine surveillance goes beyond VAERS. They have a standing process which involves regular meetings with the CDC to review data and develop approaches for potential problems.

Committee Vote

- Question 1- Fourteen (14) committee members agreed to review the data from the postmarking study, if it is not a negative study. One (1) member was not present for the vote.
- Question 2- Fourteen (14) committee members agreed to routine monitoring of adverse event reports in pediatric patients. One (1) member was not present for the vote.

Standard Review of Adverse Events: Kinrix (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine)

Question to the Committee

- FDA recommendations continued surveillance by reviewing data from study. Does the Pediatric Advisory Committee concur?

One panel member inquired about the reported death. FDA responded that there was not additional information provided. FDA reported that based on CBER's pharmacovigilance review and recommendations, the sponsor has established enhanced passive surveillance consisting of closely monitoring certain adverse events. However, no new signals have been identified.

Committee Vote

- Fourteen (14) committee members agreed to routine surveillance in pediatric patients. One (1) member was not present for the vote.

Standard Review of Adverse Events: Valtrex (valacyclovir)

Question to the Committee:

- FDA will continue its standard, ongoing safety monitoring for valacyclovir? Does the Pediatric Advisory Committee concur with this plan?

Committee Discussion

The committee asked if the efficacy data for children with chickenpox were extrapolated from adults. FDA stated that the efficacy data were extrapolated from three studies with oral acyclovir in pediatric patients with chickenpox. FDA reported that safety data from the pediatric exclusivity trials have been incorporated into the drug labeling, no new safety signal emerged during the safety review, and the Warning and Precautions section of the drug labeling has been clarified to specify that CNS adverse events have been reported in pediatric patients.

Committee Vote

FDA reported that safety data from the pediatric exclusivity trials have been incorporated into the drug labeling, no new safety signal emerged during the safety review, and the Warning and Precautions section of the drug labeling has been clarified to specify that CNS adverse events have been reported in pediatric patients, not just adults.

Committee Vote

- Thirteen (13) committee members unanimously members agreed to continue routine monitoring of adverse events in pediatric patients.

Standard Review of Adverse Events: Zmax (azithromycin)

Question to the Committee:

- FDA will continue its standard, ongoing safety monitoring for Zmax. Does the Pediatric Advisory Committee concur with this plan?

Committee Discussion

The Committee commented on the pyloric stenosis issue and suggested that FDA try to increase the sensitivity of the signal when monitoring Zmax. The committee asked if the other mycin drugs were labeled for pyloric stenosis. FDA stated that erythromycin is labeled for pyloric stenosis. FDA stated that no additional safety issues emerged during the safety review and it plans to conduct a thorough case review of hepatotoxicity cases for the class of macrolides in all age groups.

Committee Vote

- Thirteen (13) committee members unanimously agreed to continue routine monitoring of adverse events in pediatric patients.

Orlistat Update

Committee Discussion

The Committee discussed the importance public health issues that were identified in the safety review related to preexisting liver disease. Patients with liver disease should not use the product.

Open Public Statement Hearing:

Sidney M. Wolfe MD
Director, Health Research Group at Public Citizen
Requested that FDA more fully evaluate the risk/benefits of topical calcineurin inhibitors and further studies with these products were needed to define the risk. Dr. Wolfe also presented a recently published study for FDA to review. This study supported more actions be taken.

Topical Calcineurin Inhibitors: Elidel and Protopic-Pediatric Safety Update: Regulatory Background

Committee Discussion

Dr. Dianne Murphy gave a brief overview of previous 2005 committee activities for these two drugs. FDA reported to the Committee that extensive changes to both topical calcineruin products labels were made in 2006 related to cancer risk and currently the label and medication guide inform providers to the potential safety risks for topical calcineurin inhibitors. The prior committee was particularly interested in evaluating if there was a decrease in use in the under 2 year old population as it was not approved for that population and they have a larger surface body area and can absorb more product. The prior committee also wished to see if the product was being used more appropriately – not as first line and not for long durations but intermittently and for moderate and serious disease.

Outside Speaker Presentation - Childhood Cancer Epidemiology in North America: Logan Spector, Ph.D.

Dr. Spector provided background on childhood cancer epidemiology rates, highlighted increasing rates for melanoma in general and discussed what is presently known on cancer etiology regarding childhood cancers with a focus on lymphomas and melanomas.

Topical Calcineurin Inhibitors: Pediatric Registries

Questions to the Committee

- 1) - Does the Committee want to return to this topic after the FDA performs an updated literature review and when more registry data is available? (This question was added after there were a number of questions by the committee about the recent literature article presented by Sid Wolfe).
- 2) - Continue surveillance of spontaneous reports and continue to monitor for registry cases. Does the Committee concur?
- 3) - Do Protopic and Elidel labels and medication guides adequately reflect the risk for skin malignancies?
- 4) - Do Protopic and Elidel labels and medication guides adequately reflect the risk for all malignancies?

Committee Discussion

The Committee discussed the important pediatric public health issue of following to completion the 8,000 patients enrolled in the registry groups. Approximately 4,000 patients are enrolled at this time and will be followed for 10 years. The Committee asked FDA what they expect to accomplish at the end of the registries. FDA summarized by stating the reports of malignancies with topical calcineurin inhibitors use continue to be reviewed to see if they exceed a background rate expected in the pediatric population. The committee asked to be informed on what level of risk would be ruled out by this registry. The AERS reports largely reflect common pediatric malignancy except for the reports of melanoma cases in pediatrics. Childhood lymphomas and leukemias were also over represented in the AERS series compared to SEER data. There was a discussion by the pediatric dermatologist and Dr. Walker of FDA about the difficulty in making a diagnosis of true melanoma vs. a Spitz nevus in the pediatric population. These 2 variants of melanoma have very different courses and outcomes. One member pointed out, however, that even though the final diagnosis for a couple of the lesions was of the more benign Spitz classification, the children went on to receive rather aggressive therapy.

Use of the topical calcineurin inhibitors has declined sharply in the pediatric population. Some pediatric malignancies and infections were associated with off-label use. The Committee discussed the current labeling precautions; topical calcineurin inhibitors should be avoided on malignant or premalignant skin conditions. From a public health standpoint, the committee commented on the need to continue to closely follow these patients. The Committee recommended that FDA monitor the occurrence of cancer cases in pediatric patients using TCIs with careful review noting also cases of Spitz nevi. FDA should continue to work to further assess the risk/benefit for these products.

Committee Vote

- Question 1) – Ten (10) Committee members agreed to return to this topic when more information was available and FDA had completed a current literature review. Two (2) Committee members were absent for this vote.
- Question 2) - Ten (10) Committee members agreed with continued surveillance of spontaneous reports and continue to monitor for registry cases. Two (2) Committee members were absent for this vote.
- Question 3) - Four (4) Committee members agreed that Protopic and Elidel labels and medication guides adequately reflect risk for skin malignancies. Three (3) Committee members did not agree that the Protopic and Elidel labels and medication guides adequately reflected the risk for skin malignancies. Two (2) Committee members were absent for the vote. Three (3) Committee members abstained.
- Question 4) - Two (2) Committee members agreed that Protopic and Elidel labels and medication guides adequately reflect risk for all malignancies. Four (4) Committee members did not agree that the Protopic and Elidel labels and medication guides adequately reflected the risk for all malignancies. Three (3) Committee members were absent for the vote. Four (4) Committee members abstained.

Sponsor Presentations
Novartis Elidel (pimecrolimus) Judit Nyirady, M.D.

Astellas Protopic (tacrolimus) Joyce Rico, M.D. and Seth J. Orlow, M.D. PhD

Post-Approval Adverse Event Review-Rotarix
FDA Opening Comments
FDA has learned that DNA from porcine circovirus type 1 (PCV1) is present in Rotarix. There is no evidence at this time that this finding poses a safety risk. PCV1 is not known to cause illness in humans or other animals. While we are learning more about the situation, FDA is recommending that clinicians and public health professionals in the United States temporarily suspend the use of Rotarix.

Question to the Committee

- FDA recommends continued routine monitoring of AEs for Rotarix in VAERS, VSD near real-time surveillance, and the manufacturer's post-marketing studies. Does the Committee concur with this plan?

Committee Discussion
The Committee discussed intussusception and the populations in which this vaccine was studied.

Committee Vote

- Thirteen (13) Committee members recommended continued routine monitoring of AEs for Rotarix in VAERS, VSD near real-time surveillance, and the manufacturer's post-marketing studies. Three (3) members were absent for the vote.

Adjourn

- Next PAC meeting is June 21-22, 2010.

The meeting adjourned at approximately 5:10 p.m.

Please see transcript for details

I certify that I attended the March 22, 2010 meeting of the Pediatric Advisory Committee and that these minutes accurately reflect what transpired.

/s/

Doreen M. Kezer, MSN
Executive Secretary

/s/

Geoffrey Rosenthal, M.D., PhD.
Chair