MINUTES OF THE
**PEDIATRIC ADVISORY COMMITTEE**

Hilton Washington DC North/Gaithersburg, Grand Ballroom
620 Perry Parkway, Gaithersburg, Maryland

**Tuesday, November 27th, 2007**

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

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**Members Present (voting) for November 27th, 2007**
Marsha Rappley, M.D. *(Chair)*
Dennis Bier, M.D.
Amy Celento
Avital Cnaan, Ph.D., M.S.
Robert Daum, M.D.
Michael Fant, M.D.
Melissa Maria Hudson, M.D.
Keith Kocis, M.D., M.S.
Thomas Newman, M.D., M.P.H.
Geoffrey Rosenthal, M.D.
Elaine Vining
Robert Ward, M.D.

**Pediatric Advisory Committee Industry Representative**
Elizabeth A. Garofalo, M.D.

**Executive Secretary**
Carlos Peña, Ph.D., M.S.

**FDA Participants**
Linda Lewis, M.D.
Kirk Chan-Trak, M.D.
Ann McMahon, M.D.
Dianne Murphy, M.D.
Adrienne Rothstein, PharmD

**Voting Consultants**
Caroline Hall, M.D.
Peter Havens, M.D.
David Kimberlin, M.D.

**Non-Voting Consultants**
Richard L. Gorman, M.D. (*Acting Pediatric Health Organization Representative*)

**Open Public Hearing Speakers**
A public letter to the FDA from Rokuro Hama, M.D., was read into the meeting transcript.

**Presentations**
Pediatric Advisory Committee: Agenda Overview
Dianne Murphy, M.D., FAAP, Director, Office of Pediatric Therapeutics, OC
Influenza-Related Mortality and Encephalopathy among Children in the US (via telephone)
David Shay, MD, MPH, Influenza Division, Centers for Disease Control and Prevention
Influenza Surveillance, Influenza Encephalopathy and Therapy for Influenza in Japan
Nobuhiko Okabe, MD, PhD, Director, Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Tokyo, Japan
Tamiflu Safety Update - 2007
Linda Lewis, MD, Medical Officer, Division of Antiviral Products, Office of New Drugs, CDER, FDA
Postmarketing Safety Update for Influenza Antivirals
Adrienne Rothstein, PharmD, Division of Drug Risk Evaluation, Office of Surveillance and Epidemiology, CDER, FDA
Tamiflu "Wrap-up" and Five Questions for the Committee
Linda Lewis, MD, Medical Officer, Division of Antiviral Products, Office of New Drugs, CDER, FDA

**Sponsor Presentations**
Tamiflu (oseltamivir) – Sponsor Presentation, Roche
Relenza (zanamivir) – Sponsor Presentation, GlaxoSmithKline

**Summary of FDA Questions, Committee Discussions, and Recommendations**
Question 1-Based on the totality of data presented today on neuropsychiatric/behavioral (NP) events and the possible relationship to oseltamivir, does the current labeling for oseltamivir adequately address the safety concerns regarding NP events? If not, what other steps should be taken to ensure safe use of oseltamivir in the U.S. (e.g. labeling, risk communication and/or prescriber/patient education)? Please explain.
Committee Discussion –

- In general, Committee members commented upon the substantive analysis and data that have been provided to address the issue. They also expressed an increasing level of comfort in the evidence that NP events may be more likely a manifestation of influenza than of drug or the interaction of drug and disease, although uncertainty still exists.

Committee Vote –

- Six (6) Committee members recommended no change to the labeling. Eight (8) Committee members recommended changes to the labeling.

Committee Recommendations –

- Update labeling to describe NP symptoms which may occur due to the disease influenza, irrespective of drug therapy;
- Update labeling to convey uncertainty in causality of NP symptoms;
- Update labeling to note abrupt appearance of symptoms;
- Indicate that "injurious behavior" included fatal outcomes; and
- Present data on rarity of events.

Question 2-Based on the totality of the data presented today on NP events and the possible relationship to zanamivir, does the current labeling for zanamivir adequately address the safety concerns regarding NP events? If not, what other steps should be taken to ensure the safe use of zanamivir in the U.S. (e.g. labeling, risk communication and/or prescriber/patient education)? Please explain.
Committee Vote –

- Eleven (11) Committee members recommended an update to the labeling, similar to the updates for Tamiflu. One (1) Committee member recommended no change to the current labeling. One (1) Committee member abstained.

Committee Recommendations –

- Eleven (11) Committee members recommended an update to the labeling, including the appropriateness of any information on NP events related to influenza;
- Committee members expressed concern that labeling updates not drive use from newer products to older, less safe products.

Question 3-Based on the totality of the data presented today on NP events and the possible relationship to the M2 inhibitors amantadine and rimantadine, does the current labeling for amantadine and rimantadine adequately address the safety concerns regarding NP events? If not, what other steps should be taken to ensure the safe use of amantadine and rimantadine in the U.S. (e.g. labeling, risk communication and/or prescriber/patient education)? Please explain.
Committee Recommendations –

- Committee is satisfied that the current labeling for amantadine and rimantadine adequately address the safety concerns regarding NP events, however, Committee members expressed concern that labeling for the influenza therapies not drive use from newer products to older products.

Committee Vote –

- All Committee members concurred.

Question 4-Do you have any suggestions for other studies or analyses that are feasible and might clarify this safety issue?
Committee Recommendations –

- Retrospective studies are unlikely to be useful;
- Continue case control of NP events, genotyping, and in depth evaluation of adverse events;
- Recommend natural history studies on influenza;
- Prospective studies are recommended;
- Recommend prophylactic use studies; and
- Recommend Sponsor/Health Care Organizations' adverse event definitions correlate with FDA adverse event definitions.

Question 5-Presently we meet on a monthly basis during the influenza season to review adverse event reports for the 4 influenza products. We plan to continue the current monitoring schedule. At this time, an update for future PACs is not planned. However, if important safety concerns emerge, we will report back to the committee. Does the committee agree?
Committee Recommendations –

- The Committee recommended should important safety concerns emerge, the FDA report back to the Committee.

Committee Vote –

- All Committee members concurred.

The meeting adjourned at approximately 5:30 p.m.

*Please see transcript for details*

I certify that I attended the November 27th, 2007 meeting of the Pediatric Advisory Committee and that these minutes accurately reflect what transpired.

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| Carlos Peña, Ph.D., M.S. | Marsha Rappley, M.D. |
| Executive Secretary | Chair |