

MINUTES OF THE  
**PEDIATRIC ADVISORY COMMITTEE**

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

**Thursday, November 29<sup>th</sup>, 2007**

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

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**Members Present (voting) for November 29<sup>th</sup>, 2007**

Marsha Rappley, M.D. (*Chair*)

Dennis Bier, M.D.

Amy Celento

Avital Cnaan, Ph.D., M.S.

Michael Fant, 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**

Karen Feibus, M.D.

Sandra Kweder, M.D.

Lisa Mathis, M.D.

Dianne Murphy, M.D.

Robert Nelson, M.D.

**Voting Consultants**

Sharon Dooley, M.D.

Geraldine Fitzgerald

Thomas Hale, M.D.

Ruth Lawrence, M.D.

Anthony Scialli, M.D.

**Non-Voting Consultants**

Richard L. Gorman, M.D. (*Acting Pediatric Health Organization Representative*)

## **Presentations**

### Introduction

CDR Lisa Mathis, M.D., Associate Director, Pediatric and Maternal Health Staff, Office of New Drugs, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA)

### Background on Draft Guidance for Clinical Lactation Studies

Karen B. Feibus, M.D., Medical Team Leader, Maternal Health Team, Office of New Drugs, CDER, FDA  
Charles Bonapace, PharmD, Office of Clinical Pharmacology, CDER, FDA

### Breastfeeding Physiology, Benefits and Research

Ruth Lawrence, M.D., Neonatologist, Professor of Pediatrics, Obstetrics, & Gynecology, University of Rochester Medical Center, Director, Newborn Nursery, Golisano Children's Hospital

### Physiology and Pharmacology of Drugs in Breast Milk

Thomas W. Hale, Ph.D., R.Ph., Clinical Pharmacologist and Professor, Texas Tech University School of Medicine

### Ethical Issues in Conducting Clinical Lactation Studies

Robert Nelson, M.D., Ph.D., Pediatric Ethicist, Office of Pediatric Therapeutics, Office of the Commissioner, FDA

## **Summary of FDA Questions, Committee Discussions, and Recommendations**

Question 1- Would data from clinical lactation studies be useful to practitioners and pregnant and breastfeeding patients when making risk/benefit decisions regarding medicine use during breastfeeding?

### Committee Discussion –

- Committee members agreed that clinical lactation studies would be useful to practitioners and pregnant and breastfeeding patients when making risk/benefit decisions regarding medicine use during breastfeeding.

### Committee Recommendations –

- Committee members recommended studying medicine use of FDA regulated products, including food ingredients and dietary supplement during clinical lactation studies.

Question 2- FDA is seeking guidance from the Advisory Committee regarding timing of study enrollment for mother/infant pairs. Is it important for breastfeeding to be well established before enrolling mother/infant pairs in clinical lactation studies? Is there a minimum number of weeks postpartum before which mother/infant pairs should not be enrolled? Please consider both infant feeding issues and maternal physiology and pharmacokinetics issues.

### Committee Discussion –

- Committee members discussed studying the use of pharmaceuticals in the post-partum period;
- Committee members noted the following factors as important to consider when defining a clinical lactation study population and when to enroll mother/infant pairs: health and gestational age of the infant, whether the nursing mothers is experienced with breastfeeding, and whether the mother anticipates returning to work and either pumping or weaning at that time; and
- Some committee members recommended studying transfer of drug into breast milk among mothers pumping milk for a preterm infant.

Committee Recommendations –

- Committee members recommended clinical lactation studies would be useful to practitioners and pregnant and breastfeeding patients when making risk/benefit decisions regarding pharmaceutical use during all stages of lactation.

Question 3-Should clinical lactation studies only enroll mother/infant pairs who are exclusively breastfeeding? If yes, explain why. If no, describe study scenarios where enrollment of mother/infant pairs who are not exclusively breastfeeding would be useful.

Committee Discussion –

- Some committee members believed that studying exclusively feeding mother/infant pairs is ideal but that studying not exclusively breastfeeding pairs is acceptable;
- Other committee members believed that mother/infant pairs who are exclusively breastfeeding should be compared to and mother/infant pairs who are not exclusively breastfeeding; and
- Committee members advised that enrollment be based upon the drug therapy of interest.

Committee Recommendations –

- Committee members recommended the use and comparison of mother/infant pairs who are exclusively breastfeeding and mother/infant pairs who are not exclusively breastfeeding.

Question 4-Given that estimated infant daily dose can be calculated from drug concentrations in breast milk, are there situations where a maternal milk/plasma ratio would offer additional clinically useful information?

Committee Discussion –

- Committee members believed the maternal milk/plasma (M/P) ratio provides additional information, but that while it would be nice to have, it is not essential; and
- Committee members identified some potential situations where M/P ratio could be clinically useful: when levels of drug in breast milk are highly variable; when genetic variations exist and contribute to maternal pharmacokinetic differences; when different dosing regimens are used or recommended; when investigators want to evaluate how the presence of drug alters other breast milk characteristics.

Committee Recommendations –

- Committee members recommended collecting maternal (M/P) ratios when clinically feasible given that the additional information can be useful; and
- Committee members recommended a circumstance- and drug-dependent approach when choosing whether a milk-only or milk-plasma study should be performed as the initial clinical lactation study.

Question 5-Based on drug characteristics or existing clinical concerns, are there situations when a mother/infant pair study with infant plasma sampling should be recommended? Are there situations when a mother-infant pair study should be conducted without a prior milk-only or milk/plasma study? Please describe.

Committee Recommendations –

- Committee members recommended that the choice to perform a mother/infant pair study should be dependent upon clinical outcomes and what is known about the drug.

Question 6-Are there any situations where it is appropriate to enroll healthy volunteers in clinical lactation studies? Please consider: single versus multiple dose studies, ongoing breastfeeding versus weaning, and continued nursing during drug administration versus pumping and discarding milk. If no, explain why. If yes, describe the acceptable situations.

Committee Discussion –

- Committee members agreed it is appropriate to enroll healthy volunteers in clinical lactation study situations when the baby is not exposed to drug (pump and discard milk temporarily after dosing) or in situations that mothers identify as acceptable minimal risk, such as studying a commonly used over-the-counter (OTC) medicine or dietary supplement;
- Committee members noted opportunities to enroll health volunteers who breastfeed infants while not placing undue risk upon infants. Some members defined this threshold differently; and
- Committee members agreed that healthy volunteers are probably not appropriate for drugs with known serious side effects.

Committee Recommendations –

- Committee members agreed it is appropriate to enroll healthy volunteers in clinical lactation studies, with the requirement that healthy volunteers were suited for enrollment and infants were not exposed to undue risk.

Question 7-When in the drug regulatory process should clinical lactation studies be requested and done?

Committee Discussion –

- Committee members believed that clinical lactation studies should be performed for specific drugs only after safety and effectiveness have been demonstrated in Phase 3 clinical trials. Committee members believed that the dose and safety profile should be previously established;
- Clinical lactation studies should be conducted earlier in the drug development process only in isolated situations when a lactating woman has a disorder that requires treatment with the drug in question;
- Post-marketing studies and post-marketing commitments were discussed as well as opportunities to utilize survey data and research networks to gather additional information;
- Committee members noted that labeling for infants and children should not be a prerequisite for conducting clinical lactation studies; and
- The new authorities for requiring post-marketing safety studies granted by the Food and Drug Administration Amendments Act of 2007 (FDAAA) were discussed.

Committee Recommendations –

- Committee members recommended clinical lactation studies be conducted following Phase 3 clinical trials either as a post-marketing commitment or potentially prior to filing a New Drug Application in certain situations when data to be gained is important to lactating women.

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The meeting adjourned at approximately 3:30 p.m.

*Please see transcript for details*

I certify that I attended the November 29<sup>th</sup>, 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.  
Executive Secretary

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Marsha Rappley, M.D.  
Chair