Food and Drug Administration
Center for Drug Evaluation and Research
ACS Conference Room, Room 1066, 5630 Fishers Ln. Rockville, MD

Summary Minutes of the
Pediatrics Subcommittee of the Anti-Infective Drugs Advisory Committee
February 3 - 4, 2004

AntiInfective Drugs Advisory Committee Members Present

Mary Glode, M.D. Steven Ebert, Pharm. D.

Consultants

Patricia Chesney, M.D.	Victor Santana, M.D.	Norman Fost, M.D.
David Danford, M.D.	Robert Fink, M.D.	Richard Gorman, M.D., FAAP
Mark Hudak, M.D.	Susan Fuchs, M.D.	Tal Geva, M.D.
Judith O'Fallon, Ph.D.	Craig Sable, M.D.	Vasken Dilsizian, M.D.
Marilyn Siegel, M.D.	Phillip Moore, M.D.	Mark Fogel, M.D.
	Ralph D'Agostino, Ph.D.	

HHS Guest	**Guest Speaker**	**Industry Representative**
Mario Stylianou, Ph.D.	John Ring, M.D.	Samuel Maldonado, M.D.

FDA Participants

Dianne Murphy, M.D.	Julie Beitz, M.D.	Shirley Murphy, M.D.
Susan Cummins, M.D.	Sally Loewke, M.D.	ShaAvhree Buckman, M.D.
	Solomon Iyasu, M.D.	Hari Sachs, M.D.

These summary minutes for the February 3 & 4, 2004 meeting of the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee were approved on February 17, 2004.

I certify that I attended the February 3 & 4, 2004 meeting of the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee, and that these minutes accurately reflect what transpired.

_____//S//_____
Thomas H. Perez, M.P.H., R.Ph.
Executive Secretary

_____//S//_____
Patricia Chesney, M.D.
Chair

The Pediatric Subcommittee of the AntiInfective Drugs Advisory Committee, of the Food and Drug Administration, Center for Drug Evaluation and Research met February 3 & 4, 2004 at the Advisors and Consultant's Conference facility located at 5630 Fishers Ln. Rockville, MD

On February 3, 2004 at 9:15 p.m. the agency reported to the subcommittee on Adverse Event Reporting as mandated in Section 17 of the Best Pharmaceuticals for Children Act. The products reported on during this portion of the meeting included, Paxil (paroxetine), Celexa (citalopram), Pravachol (pravastatin), and Navelbine (vinorelbine). Following this, and continuing at 8:00 a.m. on February 4, the subcommittee discussed the use of imaging drugs in conjunction with cardiac imaging procedures in the pediatric population.

The Subcommittee and invited guests received a briefing document from the FDA in preparation for this meeting.

There were approximately 50 persons present at the meeting on February 3 & 4, 2004. The meeting was called to order at 9:10 a.m. on February 3 by the Chair, Joan Chesney, M.D. The Subcommittee members and discussants introduced themselves. Thomas H. Perez, Executive Secretary of the Pediatric Subcommittee of the AntiInfective Drugs Advisory Committee read the Meeting Statement. A welcome and opening comments were provided by Rosemary Roberts, M.D., Deputy Office Director, Office of Counterterrorism and Pediatric Drug Development.

Presentations began at 9:15 a.m. and proceeded as follows.

Adverse Event Reports per Section 17 of BPCA	Solomon Iyasu, M.D., Lead Medical Officer Division of Pediatric Drug Development

There were no Open Public Hearing participants for the adverse events report session.

At 10:35 after a brief break the session on the Use of Imaging Drugs began with the following presentations.

Pediatric Regulatory Update	Susan Cummins, M.D., Lead Medical Officer Division of Pediatric Drug Development
FDA Perspective	Sally Loewke, M.D., Acting Director Div. of Medical Imaging & Radiopharmaceutical Drug Products
American Academy of Pediatrics Perspective	John Ring, M.D. University of Tennessee Health Science Center
Cardiologist Perspective	Tal Geva, M.D., Children's Hospital Boston

At 12:25 the subcommittee began a question and answer period of the prior presentations. After a 20 minute lunch break the subcommittee reconvened with the following presentation at 1:20 p.m.

Contrast Enhanced *Cardiac Magnetic Resonance Imaging*	Mark Fogel, M.D., The Children's Hospital of Philadelphia
Contrast Enhanced *Cardiac Computed Tomography*	Marilyn Siegel, M.D. Washington University School of Medicine
Contrast Enhanced *Invasive Cardiac Imaging*	Phillip Moore, M.D., UCSF Children's Hospital

After a 20 minute break the subcommittee reconvened at 3:00 p.m. with the following presentations.

Contrast Enhanced Cardiac Ultrasound	Craig Sable, M.D., Children's National Medical Center
Radiopharmaceuticals in Nuclear Cardiac Imaging	Vasken Dilsizian, M.D., Univ. of Maryland School of Medicine

At 3:45 the subcommittee began a question and answer period of the afternoon's presentations. The Open Public Hearing began at 4:50 with the following 4 individuals addressing statements to the committee.

Michael Gelfand, M.D., Society of Nuclear Medicine
Peter Gardiner, M.D., Medical Director, Medical Affairs, Bristol Meyers Squibb
Manuel Cerqueira, M.D., American Society of Nuclear Cardiology
Jack Rychik, M.D., American Society of Echocardiography

At 5:30 p.m. the meeting was adjourned for the day, and reconvened at 8:05 a.m. the following day February 4 by the Chair, Joan Chesney, M.D. Sally Loewke, M.D., Acting Director, Division of Medical Imaging & Radiopharmaceutical Drug Products reviewed and clarified issues discussed the prior day. David Danford, M.D., provided the subcommittee with a recap to the prior day's proceeding. The meeting continued with discussion of the questions to the Committee.

Drs. Julie Bietz, Susan Cummins, and Sally Loewke thanked the committee for their efforts and guidance. Joan Chesney, M.D., chair, adjourned the meeting at 11:30 a.m.

The discussion will be made available through the meeting transcripts and placed on the web in approximately three weeks. Transcripts may be accessed at: www.fda.gov/ohrms/dockets/ac/acmenu.htm.

Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee

Questions for February 4, 2004

1. Given the differences in cardiac disease processes that occur in adults and children, in what cases (if any) can adult data from approved imaging drugs be extrapolated to pediatric patients in whom cardiac imaging is needed? If so, in what cardiac disease states?
   Members of the panel expressed that in general it is not wise to extrapolate because of differences existing relative to the maturity, functionality and disease in pediatrics. However, each modality is different and therefore how practical it is to extrapolate will vary. In the adolescent patient it may be appropriate.

If further studies in pediatric patients are needed, please further define the gaps in our knowledge regarding imaging agents to be evaluated for cardiac imaging applications by discussing the following questions.

2. Please discuss each of the following questions for cardiac computed tomography (CT).

   What is the most relevant question for CT?
   Safety, dose, and flow. What is the minimum dose that will provide the desired diagnostic image. What is the flow rate that will provide the desired diagnostic image

   a) What imaging agents need further study?
   The agents are proven. There is a need for dose and flow rate studies

   b) What populations should be studied?
   Populations should be studied by age, particularly the younger patients that have vascular, valvular, complex heart disease, and or septal defects.

   c) What disease states should be studied?
   Same as b)

   d) What endpoints should be used?
   Clinical outcomes that will lead to further studies or termination of studies.

   e) How should a trial be designed?
   Trials in animals should study dose and flow rates and look at enhancements and diagnostics. Repeat the study in adults to determine a starting dose.

   f) How should the standard for comparison be defined? Is there a gold-standard?
   Cardiac Catherization or Echocardiography.

3. Please discuss each of the following questions for cardiac magnetic resonance imaging (MRI).

   What is the most relevant question for MRI?
   For anatomy the efficacy and safety relative to the dose, and perfusion and viability in CHD.

a) What imaging agents need further study?
Gadolinium

b) What populations should be studied?
People that are at most risk i.e. cardiac scarring. Extracardiac in neonates, toddlers and children.

c) What disease states should be studied?
Extracardiac abnormalities.

d) What endpoints should be used?
For anatomy, surgery. For perfusion, nuclear medicine.

e) How should a trial be designed?
Non-contrast, followed by contrast with double dose of gadolinium as an adjunct, or studies with ½, 1, or 1 ½ gadolinium dose to obtain information on dose response.

f) How should the standard for comparison be defined? Is there a gold-standard?
Nuclear scan and summation of all available information i.e. CT, autopsy.

4. Please discuss each of the following questions for cardiac ultra sound (US).

What is the most relevant question for ultra sound?
Improvement in left ventrical opacification in patients difficult to image including those with complex heart disease.

a) What imaging agents need further study?
Difinity and Optisom

b) What populations should be studied?
Patients with complex heart repairs and heart transplants. All ages down to 1 year.

c) What disease states should be studied?
Patiens with repaired congenital heart defects and at risk for coronary heart disease i.e. Kawasaki, heart transplant and CHD .

d) What endpoints should be used?
MRI or nuclear medicine. Also use historical controls starting with older patients.

e) How should a trial be designed?
Start with patients having a poor prognosis. Study with two arms, one arm at rest and the other arm with stress.

f) How should the standard for comparison be defined? Is there a gold-standard?
Pre and post evaluation and comparison of the patient.

5. Please discuss each of the following questions for cardiac nuclear imaging.

What is the most relevant question for nuclear imaging?
Physiologic studies of perfusion in ischemia and perfusion viability.

a) What imaging agents need further study?
Thallium-201, Technetium tracers, and PET tracers.

b) What populations should be studied?
Microcirculation in pediatrics, neonates and premature infants.

c) What disease states should be studied?
Perfusion ischemia and viability anomalies.

d) What endpoints should be used?
Endpoints are physiologic and outcomes are symptom related. Anatomy as a gross basis, and how the patient feel is a surrogate endpoint.

e) How should a trial be designed?

f) How should the standard for comparison be defined? Is there a gold-standard?
Patients improvement and recovery.

6. Please discuss each of the following questions for cardiac angiography.

What is the most relevant question for angiography?
Pediatric studies should be part of the focus for new agents being developed.

a) What imaging agents need further study?
All agents to determine smallest dose for each technique.

b) What populations should be studied?
Infants and premature infants.

c) What disease states should be studied?

d) What endpoints should be used?

e) How should a trial be designed?

f) How should the standard for comparison be defined? Is there a gold-standard?
Angiography is the gold standard for adult ischemic heart disease.

7. Please discuss the relevance of new developments in the field of adult cardiac imaging that may have potential application to the pediatric population? Can we anticipate the need for future drug development for pediatric cardiac imaging?
Manganese, and iron oxide agents for liver imaging.
Contrast echo would be of value in the obese.
Non-contrast MR would be of value for left ventricular mass and volume.
Contrast MR would be of value for perfusion.