

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION**

DATE: June 24, 2005

FROM: Dianne Murphy, MD
Director
Office of Pediatric Therapeutics
Office of the Commissioner

SUBJECT: Overview of the June 29-30, 2005 Meeting of the Pediatric Advisory Committee (PAC)

TO: Members of the Pediatric Advisory Committee

Thank you for participating in the upcoming Pediatric Advisory Committee meetings on June 29-30, 2005. Attached you will find some background information and an overview of the agenda for the two days.

The Pediatric Advisory Committee (PAC) will meet on June 29th to discuss the recommendations of the Pediatric Ethics Subcommittee meeting of June 28th 2005, and to discuss adverse event reports for drugs granted pediatric exclusivity as mandated by Section 17 of the Best Pharmaceuticals for Children Act (BPCA). It will continue the discussion of adverse event reports on June 30th 2005.

On June 29th from 12:30-2:00 PM, the PAC will begin with a brief outline of the Subpart D referral process that led to the Pediatric Ethics Subcommittee meeting on June 28th 2005. Following this introduction, the Chair of the Pediatric Ethics Subcommittee will summarize the June 28th meeting and the conclusions and recommendations of the Subcommittee. The PAC will discuss the conclusions and recommendations of the subcommittee and provide recommendations to the FDA Commissioner and the HHS Secretary, based on the report of the Pediatric Ethics subcommittee. This section of the agenda is discussed in more detail below.

On June 29th from 2:15-4:30 PM, Medical Officers within the Center of Drug Evaluation and Research's Division of Pediatric Drug Development (DPDD) will report on adverse events for the first year of marketing following the granting of exclusivity under 505A of the Federal Food, Drug, and Cosmetic Act for the following 7 drugs: ORTHO-TRI-CYCLEN[®] (ethinyl estradiol;norgestimate), DETROL LA[®] (tolterodine), CIPRO[®] (ciprofloxacin), ZEMPLAR[®] (paricalcitol), ZOMIG[®] (zolmitriptan), TRUSOPT[®] (dorzolamide), and ARAVA[®] (leflunomide).

On June 30th from 8AM-4:30 PM, the focus of the meeting will be on the adverse events for the first year of marketing following granting of exclusivity for CONCERTA[®]

(methylphenidate). The Committee will hear about adverse event reports for this product and other methylphenidate products, several background presentations by FDA staff, and an invited external expert. These presentations will be followed by the open public hearing.

As per the discussion between the PAC and FDA at the February 14-15, 2005 meeting, a new presentation approach will be used to allow the PAC to focus on those drugs that may have safety issues warranting greater discussion. For these drugs, there will be a more extensive oral presentation from the DPDD Medical Officer as well as other presentations from the FDA if needed. For those drugs with less concerning or no adverse event reports during the one-year post-exclusivity period and for which the FDA has determined that there are no new safety concerns, FDA will provide a brief verbal summary to the PAC, but the full range of written reviews are included in your package.

The background package for the adverse event review portion of the June 29-30 meeting includes the following documents under separate tabs for each drug in addition to this cover memo:

- 1-year Post-Pediatric Exclusivity Post-marketing Adverse Event Reviews for all 8 drugs granted exclusivity
- 1-year Post-Pediatric Exclusivity Drug Use Reviews for all 8 drugs granted exclusivity
- The Clinical and Pharmacology/Toxicology reviews of trials conducted for pediatric exclusivity for these 8 drugs
- Product labeling for all 8 drugs to be presented during the adverse event reporting portion of the meeting (please note that there is an indication in the margin of each label that identifies the pediatric sections of the product label)
- Draft of the slide presentations of the adverse event reviews for the 8 products.
- Selected published background articles relevant to the methylphenidate discussion on June 30th

In addition to the above materials, the background package for the adverse events portion of the meeting will include:

- a copy of section 17 of the Best Pharmaceuticals for Children Act along with a description of the role of the PAC in post-exclusivity adverse event review
- summary description of the pediatric market exclusivity incentive program

Additional Background on the June 28th 2005 Meeting of the Pediatric Ethics Subcommittee

Both FDA and HHS regulations provide a process for an IRB to refer to FDA and/or HHS under § 50.54/§ 46.407 any protocols which the IRB does not believe meets the requirements of § 50.51/ 46.404, § 50.52/46.405 or § 50.53/46.406, and presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Under the Subpart D regulations, a clinical investigation/research may proceed if the Commissioner and/or Secretary find, after consultation with a panel of experts in pertinent

disciplines (for example: science, medicine, education, ethics, law) and following an opportunity for public comment that certain conditions are met.

The Office for Human Research Protection (OHRP) and the FDA have been working to develop a unified and comprehensive process for Subpart D referrals under 21 CFR 50.54 and 45 CFR 46.407. We have agreed to utilize FDA's Pediatric Ethics Subcommittee and experts designated by OHRP to handle these referrals. The Pediatric Ethics Subcommittee will then present its deliberations to the full PAC, which will then provide a recommendation to the Commissioner of the FDA and the Secretary of HHS.

On June 28th 2005 the Pediatric Ethics Subcommittee will meet to address a referral from the Washington University Medical Center Human Studies Committee of the protocol, "*Precursor Preference in Surfactant Synthesis of Newborns.*" The recommendations of the subcommittee regarding this protocol will be presented to the PAC on June 29th 2005 by the Pediatric Ethics Subcommittee meeting chair. The PAC will discuss the advice of the Pediatric ethics Subcommittee, then make a recommendation to the Commissioner, based on its assessment of the information provided. To enhance your understanding of the recommendations that will be presented to you, you have been provided the same background materials that the Pediatric Ethics Subcommittee will be reviewing prior to its meeting and to prepare to reach its decision. A copy of the Subpart D regulations is included in these background materials.

The FDA relies on the knowledge, judgment, experience, and wisdom of scientists and practitioners who participate as advisors and consultants. We thank you for your time and effort, and we look forward to seeing you and hearing from you on June 29-30.