



MEMORANDUM

Office of Pediatric Therapeutics
Office of the Commissioner
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From: Robert M. Nelson, M.D., Ph.D.
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Through: Dianne Murphy, M.D., Director
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To: Members of the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee

Re: **June 9-10, 2008 Meeting of the Pediatric Ethics Subcommittee**

The meeting of the Pediatric Ethics Subcommittee (PES) of the Pediatric Advisory Committee on June 9-10 will be the first time that the PES will discuss the ethics of pediatric clinical trials outside of the context of a 21 CFR 50.54 referral. The focus of the meeting is the application of 21 CFR 50.52 (greater than minimal risk, prospect of direct benefit) to FDA-regulated clinical trials. We appreciate your willingness to participate in this important event, and look forward to the discussion.

Three hypothetical cases will serve to illustrate different aspects of 21 CFR 50.52, and are meant as a starting point for the subcommittee to engage with the ethical issues, with the goal of stimulating a diverse and broad discussion of these issues. Rather than provide specific advice about each case, the questions have been framed for discussion so that the focus is on the general applicability of the ethical principles found in 21 CFR 50.52 to FDA-regulated clinical trials. At the end of the meeting, time is provided for the subcommittee to step back from the specific cases and to reflect in general on the ethical issues that have been discussed.

The meeting is structured to offer sufficient time for the subcommittee to explore the range of ethical issues raised by the application of 21 CFR 50.52 to the hypothetical cases, and in general. Following introductions, there will be a presentation of a general overview of 21 CFR 50, Subpart D, highlighting the ethical principle of scientific necessity and the practical application of that principle in the use of extrapolation. The subcommittee will then consider the first of three hypothetical case presentations, a clinical trial of an investigational HIV vaccine in adolescents. Following an open public hearing, we will then discuss our second hypothetical case, a clinical trial of an inhaled corticosteroid in children with mild persistent asthma. Prior to the case presentation and discussion, a brief overview will be provided of several concepts that the subcommittee may find useful as background for the case discussion, specifically assay sensitivity and choice of control group, equipoise, use of placebos, and component analysis. On the second day, the committee will discuss the ethical issues raised by early phase research in pediatric conditions that may lack an adult analog for prior clinical testing. After an open public hearing, there will be a brief presentation on ethical issues raised when the prospect of direct benefit may be based on animal studies. The hypothetical case that will illustrate these issues is

a clinical trial of human neurostem cells for neonatal hypoxic ischemic injury. Finally, time is set aside for reflection on the general applicability of the concepts and issues that have been identified during the course of the discussion.

The briefing packet for the meeting contains the slides for each presentation, the narrative description of the hypothetical cases and the slides that will be used to present that case. At the end of each case description you will find the question(s) that will be used to stimulate discussion, and a list of the background literature specific to each case. Your briefing packet contains a copy of each of these documents.

We have tried to provide you with background literature that will inform you about the science involved in each case, along with selected articles on pertinent policy. All the case-specific background literature has been selected for a purpose, and is best read in their entirety with the possible exception of reference three for the hypothetical case on inhaled corticosteroids. This recent NAEPP summary report is provided so that the subcommittee has a good understanding of the current diagnostic and treatment recommendations for asthma. Useful figures are provided on pages 40-42 which can serve as a summary of these recommendations. Three general background documents are provided. Two of the documents address the topics of choice of control group in clinical trials and the clinical investigation of medicinal products in the pediatric population. These guidance documents are a result of the International Conference on Harmonisation process. The third document is the Interim Final Rule published by the Food and Drug Administration in April 2001 and adopting 21 CFR 50, Subpart D, as FDA regulations.

Again, we thank you for your willingness to participate in this important and historic meeting. We are looking forward with great anticipation to the discussion.