DEPARTMENT OF HEALTH & HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Rockville MD 20857

Date: November 24, 2004

From: Sara F. Goldkind, M.D., M.A.
Bioethicist, Office of Pediatric Therapeutics, Office of the Commissioner, FDA

To: Lester Crawford, DVM, Ph.D.
Acting Commissioner, FDA

Through: Murray Lumpkin, M.D.
Acting Deputy Commissioner, Office of International Activities and Strategic Initiatives, FDA

Dianne Murphy, M.D.
Director, Office of Pediatric Therapeutics, Office of the Commissioner, FDA

Subject: Pediatric Advisory Committee Recommendations regarding Commissioner's finding under Food and Drug Administration regulations at 21 CFR 50.54 relevant to the research protocol entitled "Effects of a Single Dose of Dextroamphetamine in Attention Deficit Hyperactivity Disorder: A Functional Magnetic Resonance Study," referred jointly to the FDA under 21 CFR 50.54 and the Department of Health and Human Services under 45 CFR 46.407.

Pertinent Attachments:

1. Summary of the Pediatric Advisory Committee, Pediatric Ethics Subcommittee deliberations of September 10, 2004, drafted by Robert Nelson, M.D., Ph.D., chair
2. Letter from Joan Chesney, M.D., chair of the Pediatric Advisory Committee, September 20, 2004
3. Roster of the Pediatric Ethics Subcommittee members and expert invited guests
4. Roster of the Pediatric Advisory Committee members
5. Subpart D *Additional Safeguards for Children in Clinical Investigations* categorizations and Federal Register Information
6. Summary of Public comments

Issue: Whether the above-referenced proposed clinical investigation involving FDA regulated products is approvable under FDA's human subject protection regulations at 21 CFR Part 50, Subpart D. This protocol was referred by the National Institute of Mental Health Institutional Review Board.

Overview of Study Design and Goals:
The principal investigator proposes to administer a single 10 mg dose of dextroamphetamine in conjunction with functional magnetic resonance imaging (fMRI) in healthy children and children

previously diagnosed with ADHD, all between 9 and 18 years of age. The children would undergo neuropsychiatric testing and a diagnostic MRI before being given the dextroamphetamine.

According to the protocol, the goal of the study is to better understand the pathophysiology of ADHD while focusing on three specific aims:

1. To study brain activation patterns during response inhibition tasks in children with and without ADHD
2. To simultaneously examine the central and behavioral effects of a single-dose of amphetamine versus placebo in the two groups
3. To examine (using monozygotic and dizygotic twins) brain activation patterns in relation to both clinical state and to the degree of genetic relatedness. This part of the protocol would only be initiated if a distinction is demonstrated between children with and without ADHD.

BACKGROUND

The National Institute of Mental Health (NIMH) proposes to fund and conduct a study entitled, "Effects of a Single Dose of Dextroamphetamine in Attention Deficit Hyperactivity Disorder: A Functional Magnetic Resonance Study." All studies conducted or supported by the Department of Health and Human Services (HHS) that are not otherwise exempt and that propose to involve children as subjects require Institutional Review Board (IRB) review and approval in accordance with the provisions of HHS regulations at 45 CFR Part 46, Subpart D. Under FDA's Interim Final Rule effective April 30, 2001 (21 CFR Part 50, Subpart D), FDA adopted similar regulations requiring IRB review to provide additional safeguards for children enrolled in clinical investigations regulated by FDA. Since the proposed study would be conducted and supported by HHS, and would involve a clinical investigation regulated by FDA, the study is subject to both HHS and FDA regulations.

After reviewing the protocol, the NIMH IRB determined that the study could not be approved under 45 CFR 46. 404, 46.405, or 46.406, but that, as required under 45 CFR 46.407, the study presented a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. Accordingly, the NIMH IRB referred the proposed investigation to HHS on 4/23/04. HHS referred the protocol to FDA for FDA to determine whether the study was FDA regulated. On 6/14/04, FDA informed NIMH IRB by letter that the proposed study was also subject to 21 CFR 50 Subpart D because both the dextroamphetamine and the MRI are FDA-regulated products.

Pursuant to HHS regulations at 45 CFR 46.407 and FDA regulations at 21 CFR 50.54, if an IRB reviewing a protocol conducted or supported by HHS for a clinical investigation involving products regulated by FDA does not believe that the proposed research or clinical investigation involving children as subjects meets the requirements of HHS regulations at 45 CFR 46.404, 46.405, or 46.406, and FDA regulations at 21 CFR 50.51, 50.52, or 50.53, respectively, the research or clinical investigation may proceed only if the following conditions are met:

(a) the IRB finds and documents that the research or clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) the Secretary (HHS) and the Commissioner (FDA), respectively after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment determine either:

(1) that the research or the clinical investigation in fact satisfies the conditions of 45 CFR 46.404, 46.405, or 46.406 under HHS regulations, and 21 CFR 50.51, 50.52, or 50.53 under FDA regulations, or

(2) that the following conditions are met:

(i) the research or clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) the research or clinical investigation will be conducted in accordance with sound ethical principles; and

(iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in 45 CFR 46.408 and 21 CFR 50.55.

Summary: On September 10, 2004, the Pediatric Ethics Subcommittee(PES) of the Pediatric Advisory Committee (PAC) held an open public meeting to discuss the protocol referral from the NIMH IRB. The PES was comprised of four ethicists, and pediatric expert consultants in the areas of ADHD, neurobehavioral development, education, psychology, and psychiatry. In addition there were two public representatives who were parents of children with ADHD and members of Children and Adults with Attention/Hyperactivity Disorder (CHADD). There was an opportunity for public comment both prior to the public meeting via comments to the FDA docket, and at the meeting itself in the form of an open public hearing.

The PES, after substantial discussion and the opportunity for public comment, **reached the following recommendations:**

1. **Approval Categories**
   a. The portion of the study involving children previously diagnosed with ADHD could be approved under 21 CFR 50.53 and 45 CFR 46.406 as a clinical investigation involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.
   b. The portion of the study involving children without ADHD could be approved under 21 CFR 50.54 and 45 CFR 46.407 as a clinical investigation not otherwise approvable but that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.
   c. The risk associated with a single dose of dextroamphetamine for a child between the ages of 9 and 18 years (both for subjects with and without ADHD) is more than minimal risk, but is limited to a minor increase over minimal risk.[1]

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[1] The transcripts of the PES deliberations also reflect discussion about the relative risk exposure of a single 10 milligram dose of dextroamphetamine. There was discussion of the fact that the proposed starting dose would actually be less of a stimulant than many children are exposed to at home on a daily basis, as a result of use of caffeinated soft drinks or iced tea. See http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4066T1.htm at pages 58-9.

d. The PES concurred with the IRB's findings that the proposed clinical investigation presents a reasonable opportunity to further the understanding of a serious problem affecting the health or welfare of children and that, even though there is no direct health benefit to the children included in the research, the protocol addresses a unique central response to stimulants in ADHD, utilizing a better research design than previously published studies.

2. Protocol Design Modifications

a. Required Modifications (Stipulations)

i. The descriptions of the interventions and procedures involved in the study must be clearly and completely stated, preferably in one section of the protocol.

ii. Given that the principal investigator informed the PES that each subject will undergo a diagnostic MRI as well as fMRI, this information must be included in the protocol.

iii. Given that the principal investigator stated that, in order to limit unwarranted exposures to interventions and procedures she plans to study the twin cohorts only if differences are noted between non-ADHD and ADHD subjects, this sequence of testing must be described in the protocol.

iv. The protocol must be clear and consistent regarding the dose of the drug to be administered. (The principal investigator stated that a single 10 millligram dose of dextroamphetamine will be used (not to exceed 0.25 mg/kg).

v. In order to minimize the risks of this drug, it should be administered in the morning such that its effects will have dissipated by the children's bedtime.

vi. The protocol must include additional information regarding the precautions that will be taken to minimize psychological risks associated with the fMRI testing (i.e., use of head cushion but no restraints, training sessions, screening measures to exclude fearful or claustrophobic children).

vii. Given that the principal investigator stated that pregnancy testing will be conducted, information on this must be added to the protocol. This information must specify whether this will be a blood or urine test, and describe the process by which this information will be discussed with the adolescent and/or parent(s), what information will be disclosed to the parent(s), and methods for protecting the child's confidentiality.

viii. The results of the neuropsychological testing should not be made available to parents, as the testing is not being performed for diagnostic or treatment purposes and thus could be misleading or misinterpreted by the parents. Information should be included to alert parents to the fact that their child

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Other discussion centered on the fact that the proposed single dose would be no more than the starting dose of a stimulant used in clinical practice. See http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4066T1.htm at pages 201-2.

may be excluded from taking the WISC-III for one year, given concerns about repeat performance affecting scores.

ix. Genetic testing performed pursuant to the protocol must be restricted to the determination of zygosity (i.e., genetic relatedness). Samples should be destroyed after the DNA analysis of the listed markers, and not stored for future testing. In addition, the data on the individual markers should be destroyed once zygosity has been determined.

b. Recommended (but not required) Modifications
   i. Given the variability in neurodevelopmental stages and responses to stimulants the PES strongly recommended narrowing the age range to either the younger (i.e., 9-12) or older (i.e., 13-18) groups.
   ii. To further reduce any confounding variables the PES encouraged the investigators to restrict the ADHD subjects either to those who have not been exposed to treatment with stimulants (i.e., treatment naïve) or to those who fall within a more uniform and lower range of stimulant exposure (i.e, 10-25 milligrams).
      1. Information regarding current and prior stimulant exposure (e.g., duration, dose) should be recorded and considered in the data analysis.

3. Required Modifications to the Parental Permission and Child Assent Process and Documents

a. The documents must describe what opportunities will be provided to the study participants to dissent, if they so desire.
b. The interventions and procedures for each visit must be clearly stated in chronological order, grouped by visit.
   i. The consent/assent documentation must include a clear statement that this study will not provide any direct benefit to the participants and any misleading language referring to any portions of the study as "treatment" must be deleted.
   ii. With regard to the study drug:
      1. The timing, dosing, and form of dosing of dextroamphetamine must be consistently described throughout the documents.
      2. The risks associated with the study drug should be described using categories of "frequent," "infrequent," and "rare," to improve understanding of potential adverse events.
      3. Any references regarding "falling within the range of {normal} experience" must be deleted, since normalcy is poorly defined.
      4. The consent/assent forms must address the issue of addiction risk (specifically the lack thereof) from taking one dose of dextroamphetamine within a research context, although there should also be an explanation of the fact that this drug is classified as a "drug of abuse."
   iii. The list of screening tests should include teacher contact for his/her assessment of the child's ADHD.
   iv. The information on pregnancy testing must address:
      1. Type

2. Process for discussion of positive results
3. Issue of protection of the child's confidentiality, including whether the information will be shared with the parent(s).

v. The information on the neuropsychiatric testing must include:
   1. The fact that the results will not be available to the parent(s).
   2. The fact that the child may not be allowed to participate in WISC-III testing for up to one year

vi. The information on genetic testing must include:
   1. The fact that the samples will be destroyed after they have served the purpose of determining zygosity
   2. The reassurance that the genetic testing being performed in this study on the twin cohorts is not likely to lead to insurance discrimination. [N.B. The Office of Pediatric Therapeutics agrees with the sentiments of this recommendation insofar as, as part of the informed consent process, it is aimed at reassuring the parents that the privacy of the genetic test results will be protected. The Office of Pediatric Therapeutics recommends that this issue be addressed by the NIMH IRB as part of the informed consent process.]

vii. The information on the fMRI must include a description of the sessions and training session, including the schedule for these sessions.

viii. The information on the diagnostic MRI should specify that:
   1. Each child will be given one as part of the study
   2. There is a possibility of abnormal findings (i.e., chance of a false positive or uncertain finding)
   3. There will or will not be follow-up of positive findings, and provide a discussion of any potential financial implications of this follow-up

ix. The information on payment for participation should be modified as follows:
   1. The amount of compensation described in the protocol is excessive.
   2. To specify who is being compensated and for what
      a. Parents may be compensated for expenses incurred in making their child available for the study
      b. Younger children can be compensated in the form of token appreciation given after study
      c. Adolescents can be compensated using an appropriate - hourly wage, plus expenses, resulting in a payment of approximately $100-110, dividing any payments evenly so that the adolescents who desire to withdraw form the study will be compensated for the time they were involved.

c. Under 21 CFR 50.55(e)(2) and 45 CFR 46.408(b) the permission of both parents is required for a child to participate in research under 21 CFR 50.53/45 CFR 46.406 and 21 CFR 50.54/45 CFR 46.407 unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has

legal responsibility for the care and custody of the child, (if consistent with sate law).

d. Delete or explain in lay language any technical terminology.
e. Explain that the alternative to enrollment in the study is not to participate at all

A summary of the above recommendations by the PES was presented to the PAC for discussion, on September 15, 2004.

After discussing the recommendations of the PES **the PAC endorsed those recommendations with two additions**:

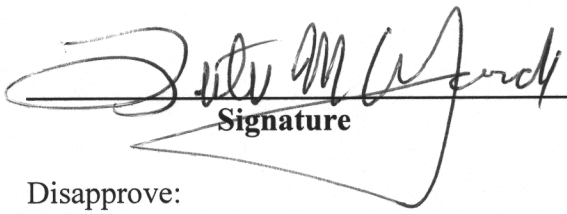
1. A recommended protocol modification that the subjects should be encouraged not to ingest products containing caffeine or other stimulants on the day of testing. Data about the use of such products prior to functional MRI scans should be collected and included in the analysis.
2. A required protocol modification that parents will be informed about the previous experience at NIH of the results of using "screening" diagnostic MRI scans, including the rate of positive findings of incidental or clinical importance.

With the exception of the recommendation regarding insurance discrimination (discussed above), the Office of Pediatric Therapeutics concurs with the Pediatric Advisory Committee's endorsement of the Pediatric Ethics Subcommittee's recommendations and concurs with the additional two recommendations by the Pediatric Advisory Committee (as summarized above). Therefore, the Office of Pediatric Therapeutics recommends that you find that the proposed protocol, "Effects of a Single Dose of Dextroamphetamine in Attention Deficit Hyperactivity Disorder: A Functional Magnetic Resonance Study," meets the requirements of 21 CFR 50.54(b) and may proceed as outlined above and with the stipulated modifications.

Please indicate by signing at the bottom of this memorandum whether you approve as outlined above, disapprove, or approve with additions/changes the referred proposed clinical investigation. A decision to approve (or approve with additions/changes) signifies that you have made the finding required under 21 CFR 50.54(b). After you make your decision, the Office of Pediatric Therapeutics will transmit a copy of this signed memorandum to HHS, via the Office of Human Research Protection, to provide to the Secretary to assist him in making his decision under 45 CFR 46.407.

DECISION

Approve as outlined above and with the stipulated modifications:



_____ Date DEC 16 2004

Signature

Disapprove:

_____ Date:

Signature

Approve with the following additions or changes:

_____ Date:

Signature