M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 16, 2004

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Overview for September 13 & 14, 2004 Meeting of Psychopharmacological Drugs Advisory Committee (PDAC) and Pediatric Drugs Advisory Committee (Peds AC)

TO: Members of PDAC and Peds AC

On September 13th and 14th, the PDAC and Peds AC will meet to consider the occurrence of suicidality in the course of treatment of pediatric patients with various antidepressants. This September meeting is followup to a meeting on this same topic held on February 2, 2004. At the February meeting, the committees were presented with preliminary data on suicidality occurring in clinical trials involving pediatric patients being treated with various antidepressants. The major focus of that meeting was on FDA's plans for a more definitive evaluation and analysis of these data. The two key aspects of FDA's plans for evaluation of these data were the following: (1) the classification of suicidality events captured under the broad category of "possibly suicide-related" into more specific and meaningful categories by experts in pediatric suicidality; and, (2) an analysis of patient-level data from these trials that would permit adjustment for potential confounders. The committees generally endorsed FDA's proposed plan for further evaluation of these data. This additional work has now been completed, and the committees will be presented the results of these analyses.

The committees recommended at the February meeting that, while we were completing our analyses of the pediatric suicidality data, FDA should strengthen the labeling for these products. In particular, there was concern that some patients being treated with these drugs may not be closely monitored for suicidality. There was a consensus of the committees that, whether or not any of these drugs could be shown more definitively to have a role in the induction of suicidality, it would be important to remind clinicians treating patients with any of these drugs to be alert to the emergence of suicidality and to various other symptoms that might represent precursors to suicidality. FDA issued a Public Health Advisory on March 22, 2004, announcing an initiative to ask companies to add Warning statements to address this concern. This new Warning language has been accepted by the sponsors for all of these products.

The new language warns clinicians to observe closely patients who are being treated with antidepressants, for clinical worsening and suicidality, especially at the beginning of a course of therapy, or at times of dose changes. Clinicians are advised to consider changing the therapeutic regimen in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. The new language notes that a causal role for antidepressants in inducing such behaviors has not been established. The new warning applies both to adults and children, and is not limited to patients being treated for major depression, but rather, applies to patients being treated with antedepressants for any condition, psychiatric or nonpsychiatric. Clinicians are also advised to observe for the emergence of other symptoms that have been reported in association with antidepressant treatment due to the concern, but not yet proof, for a possible causal link between such symptoms and worsening depression or suicidality. These symptoms include: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania. The new language also advises families and caregivers of these patients to be alert to the emergence of these symptoms, and to report such symptoms to the health care providers. Finally, the new language alerts clinicians to be particular careful in using these medications in patients with bipolar depression or a family history of bipolar disorder.

The primary focus of our presentations at this meeting will be to provide you with (1) a detailed description of our approach to evaluating and analyzing the pediatric suicidality data, and (2) the results of this work. However, we have also included presentations on related studies, in particular, several pertinent epidemiological studies and TADS (Treatment of Adolescents with Depression Study). Thus, you will hear presentations by both FDA staff and experts in pediatric suicidality from the academic community outside of FDA.

?? Dr. Diane Wysowski from the Office of Drug Safety will summarize and comment on findings from several published epidemiological studies that are pertinent to the concerns about suicidality in association with antidepressant drug treatment.

?? Dr. John March from Duke University will briefly summarize results from the NIMH-sponsored TADS (Treatment of Adolescents with Depression Study), with an emphasis on findings pertinent to suicidality.

?? Dr. Greg Dubitsky from the Division of Neuropharmacological Drug Products will provide an overview of the 23 pediatric antidepressant trials that have been the focus of our review, in order to give you important background information about the structure and conduct of these trials, and about the populations studied.

?? Dr. Kelly Posner, from Columbia University, will describe their approach to the blinded classification of suicidality events and their experience in accomplishing this task.

?? Dr. Solomon Iyasu from the Office of Counter Terrorism and Pediatrics will provide comments on FDA's independent appraisal of the Columbia approach to classification of suicidality data.

?? Dr. Tarek Hammad, from the Safety Group in the Division of Neuropharmacological Drug Products, will present the results of our analysis of the suicidality data, using the events classified by the experts assembled by Columbia University.

?? Dr. Andrew Mosholder from the Office of Drug Safety will provide comments based on a comparison of the findings from his initial analysis of pediatric suicidality data that was completed before the results of the Columbia classification of cases was available, with analyses conducted by Dr. Hammad since the classifications were completed.

?? You will also hear presentations by several sponsors of antidepressant products who have requested an opportunity to comment on the suicidality data for their products.

There will be an open public session on the afternoon of September 13th, to provide an opportunity for others in the community to make statements pertinent to this concern about a possible causal association between antidepressant drug treatment and emergent suicidality in pediatric patients.

The morning of September 14th has been reserved for your deliberations on this topic.

The background package for this meeting will include the following documents in addition to this cover memo:

?? A January 5, 2004 memo written by me in preparation for the February 2. 2004 Advisory Committee meeting. This memo provides a more complete discussion of various events leading up to that earlier meeting and the basis for DNDP's analysis of the suicidality data. It also includes a summary of efficacy findings from the 15 studies in pediatric major depressive disorder (pp. 5-6 and Appendix 1).

?? Summary minutes from the February 2, 2004 Advisory Committee Meeting.

?? Several published epidemiological studies that are pertinent to the concerns about suicidality in association with antidepressant drug treatment.

?? A recent paper (August 18, 2004) from JAMA providing the results of the Treatment for Adolescents with Depression Study (TADS), along with an editorial commenting on the findings from this trial.

?? A review by Dr. Greg Dubitsky from DNDP, providing details about the structure and conduct of these trials, and about the populations studied.

?? A review by Dr. Solomon Iyasu from OCTAP, describing the methods and results of OCTAP's independent appraisal of the Columbia classification effort. His review includes as appendices several documents from the Columbia University suicidality group describing their approach to the blinded classification of suicidality events.

?? A review by Dr. Tarek Hammad from DNDP, providing the detailed results of the analysis of the pediatric suicidality data.

?? A review by Dr. Andrew Mosholder from ODS, providing the results of his analysis of the original pediatric suicidality data completed before the results of the classification of cases was available, along with an update on that review to provide a comparison of the findings of that initial analysis, with analyses conducted on the basis of the definitively classified cases.

?? Public Health Advisorys on suicidality and antidepressant medications issued by FDA on June 19, 2003, October 27, 2003, and March 22, 2004, and related documents.

?? Product labeling for 7 antidepressants that have implemented the labeling changes announced in the March 22, 2004 Public Health Advisory

?? Briefing packages from several companies

Additional background information on this general topic of antidepressants and suicidality, including documents generated in relation to the February 2nd advisory committee meeting and those developed in association with FDA's March 22nd Public Health Advisory can be found at the following link: http://www.fda.gov/cder/drug/antidepressants/default.htm. A transcript for the February, 2004 meeting can be found at this link as well.

I would like to draw your attention to some particular issues of interest as you review the package and prepare to answer the questions we will present to you. The data continue to show differences between individual drugs, drug classes, and even across studies within individual drugs, even when the focus is limited to those trials done in patients with major depressive disorder. We have explored a number of possible explanations for such differences, but none has provided a satisfactory answer. Thus, while there remains a "signal" of risk for suicidality for some drugs in some trials, it is important to note that the data are not "black and white" in providing a clear and definitive answer to the question of a link between the drugs and pediatric suicidality. Consequently, we are very interested in hearing comments from committee members on how these data should be interpreted and how these data should be translated into information to guide physicians, patients, and families in the use of these drugs. Now that we have completed our analysis of these data, we would like to move forward to update the labeling of these products to reflect the results from these analyses, and we seek your specific guidance on how best to accomplish this task.

The following are draft questions and topics for discussion at the meeting. These questions and discussion topics may be revised before the meeting.

?? Please comment on our approach to classification of the possible cases of suicidality (suicidal thinking and/or behaviors) and our analyses of the resulting data from the 23 pediatric trials involving 9 antidepressant drugs.

?? Do the suicidality data from these trials support the conclusion that any or all of these drugs increase the risk of suicidality in pediatric patients?

?? If the answer to the previous question is yes, to which of these 9 drugs does this increased risk of suicidality apply? Please discuss, for example, whether the increased risk applies to all antidepressants, only certain classes of antidepressants, or only certain antidepressants.

?? If there is a class suicidality risk, or a suicidality risk that is limited to certain drugs in this class, how should this information be reflected in the labeling of each of the products? What, if any, additional regulatory actions should the Agency take?

?? Please discuss what additional research is needed to further delineate the risks and benefits of these drugs in pediatric patients with psychiatric illness.

The FDA relies on the knowledge, judgement, experience and wisdom of scientists and practitioners like you to help determine how to move forward and address newly emerging issues related to drug development. We thank you for your time and effort, and we look forward to seeing and hearing from you on September 13th and 14th .

cc:
HFD-120/TLaughren/RKatz/JRacoosin/PDavid
HFD-960/DMurphy/SMurphy/SCummins
HFD-030/PSeligman/ATrontel/MAvignan
HFD-040/RTemple
HFD-020/JJenkins

DOC: PDAC_Sept2004_Memo_Laughren_04.doc