

**MEMORANDUM      DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** September 26, 2005

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HFD-130

**SUBJECT:** October 25 & 26, 2005 Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC)

**TO:** Members, PDAC

**Tuesday, Oct 25<sup>th</sup>: Long-Term Efficacy for Psychiatric Drugs**

Most psychiatric illnesses are chronic, and all psychiatric illnesses for which psychiatric drugs have approved indications in the US are chronic. Nevertheless, FDA has, in the past, not required long-term efficacy data for an initial approved indication for any of these illnesses. In fact, most initial drug approvals for psychiatric indications have been based on studies of relatively short duration. FDA has generally asked for longer-term efficacy studies as a post-approval commitment. Although these studies have, in a majority of cases, ultimately been conducted, they have often not been completed for a number of years after the initial approval. Since most treatment guidelines for chronic psychiatric illnesses recommend continuing patients for 4 to 6 months or longer after response during short-term treatment, clinicians have generally not had a sufficient evidence base to support what is the standard of practice for drug treatment of psychiatric illnesses.

An additional problem has been the design of the longer-term trials that have been conducted. It is generally not considered acceptable to conduct long-term placebo-controlled trials with symptomatic patients for most psychiatric disorders. The alternative design that has been considered acceptable for most such disorders is the so-called “relapse prevention” design, otherwise known as the “randomized withdrawal study”. This study design typically involves initial treatment on an open basis of symptomatic patients for some defined period of time. Those patients who meet criteria for being responders and who remain stable for some defined period of time are then randomized to either continue on medication or switch to placebo. The endpoint in such a trial is generally either time to relapse or some measure of relapse, e.g., relapse rate at the nominal endpoint of the trial. Relapse in this setting is generally considered to be return of the symptoms of the illness being treated. The majority of such trials done for registration purposes have had relatively brief open run-in phases for stabilization, e.g, 6 to 12 weeks. With such brief run-in periods, patients are actually in a responder status for only a few weeks prior to

randomization. The double-blind, randomized phase of these trials is the phase during which patients are observed for relapse. This phase generally lasts for 6 to 12 months, and has to be long enough for patients to have an opportunity to relapse.

In recent years, FDA has begun to look more critically at these trials, particularly with regard to how to interpret the results of such a study. The purpose of these trials presumably is to provide information about longer-term efficacy, and in the literature they have generally been characterized in terms of the duration of the randomized phase during which patients are observed for relapse. The problem with this approach is that, very often, the majority of relapse events occur early in this phase so that only a minority of patients remain during the later months of such a study. An alternative approach, and one that we have adopted in recent years, is to think of these trials from the standpoint of the question of greatest interest to a clinician. If an acutely ill patient responds while being treated with a drug, the assumption is that the response is due at least in part to the drug, and the clinician is faced with the decision of how long to continue the drug in order to maintain the response. Thus, the relevant clinical question is, 'What is the probability of relapse after stopping treatment in a patient who has responded during treatment of an acute episode of the illness?' This question can be reasonably asked at various intervals, e.g., after 3 months of responder status, after 6 months, 1 year, 2 years, etc. We think that the randomized withdrawal study addresses this question by determining if there is a benefit for continuing drug compared to a switch to placebo in patients who have been in a responder status on drug for some defined period of time. However, if the average time in a responder status is only a few weeks, the study would not seem particularly useful because, for most chronic psychiatric illnesses, a clinician would not discontinue treatment in a responding patient after only a few weeks. In fact, it might be considered ethically questionable to stop a psychiatric drug in a patient who has been in a responder status for only a few weeks. We think that the question of continuing benefit becomes more clinically relevant and the study design more ethically acceptable as the period of time in a responder status is extended. For this reason, we have, in recent years, strongly encouraged sponsors to consider longer open run-in periods for these randomized withdrawal studies.

We are, of course, aware of the distinction that is often made between relapse and recurrence and between continuation and maintenance treatment. The term relapse generally refers to the return of symptoms of the same episode of illness that was treated acutely following discontinuation of the drug, and continuation of that drug following response is referred to as continuation therapy. The term recurrence generally refers to the return of a different episode of the same illness that was treated acutely following discontinuation of the drug in a patient who has been in a responder status for an extended period of time, and continuation of that drug beyond some arbitrary extended period of time is referred to as maintenance therapy. For depression, the arbitrary interval for distinguishing between continuation and maintenance treatment is 6 months. This interval is based on the average duration of a major depressive episode. Of course, for any given patient, it is impossible to know if the re-emergence of the illness is a relapse of the same episode or the recurrence of a new episode. We would argue that, from the patient's and the clinician's perspective, it doesn't make any difference. Thus, from a regulatory standpoint, we have not made this distinction, and we have referred to any continuation of treatment beyond response as maintenance treatment and to any emergence of the treated illness as a relapse.

Over the past 6 months, we have been taking the position that, for chronic psychiatric illnesses, it is necessary to have both acute and longer-term efficacy data to support even an initial efficacy claim for a drug. Further, we have indicated that patients need to be in a responder status for at least 6 months prior to randomization in a randomized withdrawal trial. This proposed policy has been met with considerable resistance and questions, and for this reason, we thought it would be useful to bring this general issue to the committee for discussion.

We have developed a list of questions that we would like the committee to address during the discussion phase of the meeting. For purposes of simplifying the discussion, we will focus the initial questions (Questions 1 through 8) on Major Depressive Disorder (MDD), and then return later to expand the questions to any chronic psychiatric disorder. [Note: We are asking for a vote on certain of these questions, while for others, discussion and comments would suffice.]

1. Is it a reasonable expectation that a sponsor would have accumulated data for both acute and longer-term efficacy trials at the time of filing of an application for a drug for the treatment of MDD? [**Vote requested**]
2. If the answer to question 1 is yes, is it a reasonable expectation that the sponsor must have demonstrated both acute and longer-term efficacy for MDD? [**Vote requested**]

For those voting No on this question, 2 additional questions [Note: When asking for longer-term trials as a phase 4 commitment at the time of approval of an acute claim, it has been our standard to request a single longer-term trial. In the one situation where a sponsor submitted an application based only on longer-term data, we required 2 positive longer-term trials to support the claim.]:

- a. If the acute studies support an acute claim, but the longer-term trial fails to demonstrate an effect, could the drug be approved for short-term use, with a mention of the negative longer-term findings in the label? [Note: We do not, at present, require the mention of negative findings for a negative longer-term trial in labeling.] [**Vote requested**]
- b. If the longer-term studies support a maintenance claim, but the acute trials fail to demonstrate an effect, could the drug be approved for maintenance treatment, with a mention of the negative acute findings in the label? [Note: We have, in fact, already approved a drug for maintenance treatment in the absence of acute efficacy, i.e., Lamictal for bipolar maintenance, however, without mention of the negative acute findings in the label.] [**Vote requested**]

[Background for Question #3: At the point in time when a new regulatory requirement is introduced, it is inevitable that development programs will be in various stages, ranging from just getting started in humans to almost having completed phase 3. We feel that the phase of development should be taken into consideration in the implementation of the new policy, because the consequences of implementing such a policy late in development could be viewed as detrimental to the public health if the impact of a last minute policy shift is the delay in introduction of a promising drug, or even the termination of a program. One timepoint we had considered as a compromise position was to ask companies who are still in phase 2, or earlier, to adopt this change. It should also be noted that even this proposed solution has some complexity, because it is not always straight-forward establishing whether or not a sponsor has completed phase 2.]

3. If the answer to question 1 is yes, at what point in a development program for a drug for MDD should this new requirement for longer-term data at the time of filing of an application be implemented? **[Discussion requested]**

[The questions will now shift to the issue of optimal design for a longer-term efficacy trial. These questions are important regardless of whether or not there is a requirement for longer-term efficacy data at the time of filing of an initial application. As described in the introductory comments, the typical longer-term efficacy trial for psychiatric indications involves open label treatment for acutely ill patients until they reach a responder status and remain in that status for some period of time. At some point, responding patients are randomized to either continue on active drug or switch to placebo, and patients are then observed for relapse. We have a number of questions about the details of such a trial, the first focusing on the duration of time that a patient is in a responder status prior to randomization. As noted, we have suggested 6 months as a duration that is clinically relevant and consistent with treatment guidelines regarding the recommended duration of therapy after response to acute treatment for many chronic psychiatric conditions, including MDD.]

4. What is the minimum period of time that patients with MDD should remain in a responder status before being randomized in a randomized withdrawal study? An extension to this question is whether or not this duration should be different depending on whether this is a monotherapy or an add-on maintenance trial? **[Discussion requested]**

[A related question is how should “response” be defined. Typically, patients are required to meet some criterion score on a rating instrument and remain at or below that level before they can be randomized. Similarly, they are often considered to have changed from their responder status if they need a dose adjustment of their assigned medication. An alternative that has been suggested by some sponsors and experts in this field is to permit some minor excursions around this criterion value and still consider such a patient a responder. Similarly, it has been suggested that some minor dose adjustments may be acceptable without considering such changes sufficient to declare that a patient is no longer a responder. For example, if the criterion is for patients to have a CGI-S  $\leq 2$ , an accepted excursion on no more than 2 visits during some extended period of time might be a value of 3 for the CGI-S. The argument is that, over time, patients often have minor and temporary fluctuations in their rating scores, or may need minor dose adjustments, that do not necessarily reflect a true deterioration from their responder status. Permitting such excursions or dosage adjustments might facilitate longer run-in periods.]

5. Would it be reasonable to accept minor and temporary excursions above criterion scores for “responder” status for MDD patients in an open run-in phase, or minor dosage adjustments, and still consider such patients to have remained in a “responder” status? **[Discussion requested]**

[A related question is how should “relapse” be defined. Typically, patients are required to meet some criterion score on a rating instrument and remain at or below that level during the randomized phase, or if not, they are considered to have relapsed. Similarly, they are

often considered to have relapsed if they need a dose adjustment of their assigned medication. This is done primarily to provide for early rescue of patients who are not doing well. However, if these definitions are applied too rigidly, patients who are having normal variations in scale scores, or minor variations in their status that require minor dosage adjustments, are identified as having relapsed when they have not. An alternative that has been suggested by some sponsors and experts in this field is to permit some minor excursions around this criterion value, including some minor dose adjustments, without considering such changes sufficient to consider such a patient as having relapsed. The argument is that, over time, patients often have minor and temporary fluctuations in their rating scores and may even need slight dose adjustments that do not necessarily reflect a true deterioration from their responder status. It is argued that permitting such excursions might facilitate the conduct of these trials.]

6. Would it be reasonable to accept minor and temporary excursions above criterion scores for MDD patients in the randomized phase, and even slight dose adjustments, without considering such patients to have relapsed? **[Discussion requested]**

[One design question that has emerged in our discussions with sponsors regarding longer-term efficacy trials is what patients can be considered stable responders and randomized for observation for relapse. As noted, typically these would be patients who had been stabilized in an open run-in phase. Another source of stable responders would be patients who achieved a responder status during a double-blind acute study. Some of these would be patients who had responded on drug, and were then continued in open continuation phases on active drug; these would also seem to be reasonable candidates. However, there would also be patients who had “responded” while assigned to placebo in the double-blind phase and were then switched to active drug in an open continuation phase [Note: Their status during the double-blind phase would not be known until the blind is broken.]

7. Should placebo responders during a double-blind phase of an acute trial, who are switched to active drug during a continuation phase, be considered for randomization in a randomized withdrawal trial, i.e., should they be considered similar to (or different from) patients who responded on active drug and were then continued on active drug for longer-term stabilization? **[Discussion requested]**

[Typically in randomized withdrawal studies, responding patients who are randomized to drug treatment receive the same dose of drug they were receiving when they were considered optimally controlled. However, it is possible that the dose that optimally maintains a patient after responding is different than the dose needed to achieve optimal response. An alternative approach would be a dose response trial in which patients are randomized to fixed doses of the drug or placebo. A fixed dose study would, of course, need to be larger, and thus, would take longer and be more costly.]

8. Should sponsors be encouraged (or even required) to utilize fixed dose randomized withdrawal studies rather than randomizing MDD patients to their optimal dose during the run-in phase? **[Discussion requested]**

[We will now broaden the discussion beyond MDD. We ask the committee to consider questions 1 through 7 with regard to any of the psychiatric disorders which may be the focus of drug development programs, including any of the affective or anxiety disorders, any psychotic disorders, ADHD, etc.]

9. Would the answers to any of the questions change in considering other chronic psychiatric disorders? **[Discussion requested: Note—It isn't necessary or possible to discuss every chronic psychiatric disorder at this one-day meeting. Rather, we are trying to get a sense of whether or not, if you agree with a requirement for longer-term data, that requirement should be applied generally to all chronic psychiatric disorders. If not, what are the exceptions to the rule? In addition, should the course of long-term illness (e.g., chronic with discrete episodes, cyclical, or persistent symptoms) determine the specific design of the longer-term trial needed to show longer-term efficacy?]**

[Although the randomized withdrawal design is the usual design for a longer-term efficacy trial, we have seen alternative designs on occasion. (1) In a development program for Effexor XR in GAD, the sponsor proposed and conducted a 6-month placebo-controlled trial. This trial was successful and is the basis for a labeling claim for longer-term efficacy in GAD for this drug. (2) In a development program for Abilify in schizophrenia, the longer-term trial involved patients who still had substantial psychotic symptoms on a drug other than Abilify, yet could be considered stable even if not optimally controlled. They were randomized to either switch to Abilify or switch to placebo, followed by observation for relapse. (3) In a development program for Risperdal in schizophrenia, the longer-term trial involved patients who were randomized to either Risperdal or haloperidol, and the study demonstrated a superiority of Risperdal over haloperidol in time to relapse in that trial, and was the basis for a longer-term efficacy claim for Risperdal.

An even more substantial departure from the typical randomized withdrawal design has been suggested by some experts, i.e., the use of active control rather than placebo. The argument is that, for certain disorders, the relapse rate on drug and on placebo is so predictable that one can interpret a finding of no difference between 2 active drugs (one an active standard with demonstrated longer-term efficacy and one a new drug being tested) as evidence of longer-term efficacy for the newer drug. [Note: This would require testing of a formal noninferiority hypothesis.] The argument is that effective drugs always have lower relapse rates in this setting and placebo always has a higher relapse rate. [Note: This argument has been made in particular for schizophrenia.]

10. Are there alternative designs that should be considered for establishing longer-term efficacy [Note: We are happy to consider discussion of the suggestion of active-controlled comparisons in longer-term trials for schizophrenia, however, until more data are accumulated and presented, we are not likely to consider this issue ripe for resolution.]?

[Once there is agreement on the design of longer-term efficacy trials, it is important to address the issues of interpretation of the outcome of such a study and the characterization of the findings from such a study in product labeling. A critical question is what can one infer about longer term benefits on the basis of a positive study of the design being

suggested. As noted earlier in this memo, we have focused on the open run-in period as critical in interpreting such a study. Information about longer-term efficacy from such a trial is generally located in 3 different sections of labeling: (1) Clinical Trials, under Clinical Pharmacology; (2) Indications and Use; and (3) Dosage and Administration. To illustrate what is the division's current approach to including this kind of information in labeling, we have included here language from these sections of labeling for the drug Zyprexa:

## **Clinical Pharmacology/Clinical Trials**

### Bipolar Disorder

(3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of bipolar disorder who had responded during an initial open-label treatment phase for about two weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of olanzapine at their same dose (n=225) or to placebo (n=136), for observation of relapse. Approximately 50% of the patients had discontinued from the olanzapine group by day 59 and 50% of the placebo group had discontinued by day 23 of double-blind treatment. Response during the open-label phase was defined by having a decrease of the Y-MRS total score to  $\leq 12$  and HAM-D 21 to  $\leq 8$ . Relapse during the double-blind phase was defined as an increase of the Y-MRS or HAM-D 21 total score to  $\geq 15$ , or being hospitalized for either mania or depression. In the randomized phase, patients receiving continued olanzapine experienced a significantly longer time to relapse.

## **Indications and Usage**

### Bipolar Disorder

Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with oral ZYPREXA after achieving a responder status for an average duration of two weeks was demonstrated in a controlled trial (see Clinical Efficacy Data under CLINICAL PHARMACOLOGY). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

## **Dosage and Administration**

### Bipolar Disorder

Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with oral ZYPREXA at a dose of 5 to 20 mg/day, after achieving a responder status for an average duration of two weeks, was demonstrated in a controlled trial (see Clinical Efficacy Data under CLINICAL PHARMACOLOGY). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

11. Is this language a reasonable interpretation and translation of the data from the longer-term trial that supported the longer-term claim for Zyprexa in bipolar disorder, or is there a better way of presenting this information in labeling? **[Discussion requested]**

12. If there are data supporting a longer-term claim for adults for a drug for a chronic psychiatric indication, is there a need to obtain longer-term data for a pediatric indication for this same disorder, or would it be sufficient to obtain acute data for the pediatric population and extrapolate from adult data for the longer-term claim? **[Discussion requested]**

Feel free to modify these questions, or add others that you think are relevant.

cc:  
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**DOC:** PDAC Oct2005 Memo 01.doc