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**GENERAL CORRESPONDENCE**  
**Docket Number 00N-0088**

Food and Drug Administration  
Center for Drug Evaluation and Research  
Dockets Management Branch  
Room 1061  
5630 Fishers Lane  
Rockville, MD 20852

**Re: Position Paper for Psychopharmacological Drugs Advisory Committee  
Meeting on the Various Psychiatric and Behavioral Disturbances Associated with  
Dementia - March 9, 2000**

We are enclosing our written response to the Division of Neuropharmacological Drug Products position paper issued as **Docket 00N-0088** to support the upcoming March 9, 2000 Psychopharmacological Drugs Advisory Committee (PDAC) meeting. We are also following the procedures outlined in the Federal Register Notice of this PDAC meeting in order to make an oral presentation at the meeting.

Please call Dr. H. John Roth at (317) 433-3523 or me at (317) 277-3799 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.  
Director  
U. S. Regulatory Affairs

Enclosure

cc: Dr. Sandra Titus, Executive Secretary, PDAC

00N-0088

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# **Eli Lilly & Co. Position Paper**

## **Psychopharmacological Drugs Advisory Committee Meeting on the Various Psychiatric and Behavioral Disturbances Associated with Dementia March 9, 2000**

### **Introduction**

Eli Lilly & Co. is responding to the position paper issued by the Division of Neuropharmacological Drug Products (DNDP), FDA, entitled "DNDP Issues Paper for March 9, 2000 Meeting of the Psychopharmacological Drugs Advisory Committee (PDAC) on the Various Psychiatric and Behavioral Disturbances Associated with Dementia".

Eli Lilly & Co. is in full agreement with the DNDP regarding the importance of drug development for patients with Alzheimer's disease and other dementias, and is committed to the development of new pharmacological treatments to benefit these patients. Given the growing numbers of individuals with dementias and the substantial degree of unmet need that exists because of inadequacies of currently available pharmacological treatments, we call for a spirit of urgency in establishing clear guidelines for drug approval in this area. In addition, we believe there are promising agents available now in the pre-approval phase of drug development that may positively impact on the quality of life of these patients. It is imperative that the development of new treatments proceeds in a timely manner to meet the medical and economic burdens incurred by patients, their families, and society in general. Thus, we applaud the organizers of the March 9<sup>th</sup> PDAC meeting as we consider this an important opportunity to discuss and reach consensus on acceptable approaches for clinical evaluation of potential new treatments for patients with dementia. The development of these treatment options hinges on the ability of the medical and regulatory communities to successfully reach consensus on appropriate treatment targets (i.e., indications) and clinical approaches to evaluate new treatments.

Just as a clear regulatory path for registration has been defined for treatments of the cognitive deficits associated with Alzheimer's disease, it is critically important to establish similar clarity for the registration of treatments of the other manifestations of Alzheimer's disease. It is our position that current knowledge in the field is sufficient to pursue the clinical development of pharmacological treatments for some of the psychiatric and behavioral disturbances associated with Alzheimer's disease. This paper will focus on two examples: the psychosis and the agitation associated with Alzheimer's disease.

### **Psychosis Associated with Alzheimer's Disease**

The psychosis of Alzheimer's disease is a relatively specific clinical entity that is readily recognized by clinicians, operationally definable, and identifies a reasonably distinct

patient population. Accordingly, we believe that psychosis associated with Alzheimer's disease should constitute a distinct label indication. The psychosis of Alzheimer's disease, while bearing some overlap with the psychosis of other diseases such as schizophrenia, has clinical features that are relatively specific to the underlying disorder. Visual hallucinations are more common than auditory hallucination in dementia whereas the reverse is true for schizophrenia. It is common for persecutory and paranoid delusion to occur in both dementia and schizophrenia. However, schizophrenia is associated with very bizarre and Schneiderian first rank delusions and hallucinations which are uncommon in Alzheimer's disease. Conceptual disorganization and other types of formal thought disorder are common psychotic symptoms in schizophrenia, but their ascertainment in demented patients can be confounded by pronounced cognitive impairment.

The psychosis of Alzheimer's disease, namely delusions and hallucinations, are common clinical entities that are familiar to most clinicians who care for patients with dementia. Clinical training emphasizes the ascertainment and differential diagnosis of delusions and hallucinations. In addition, there are a number of rating instruments with established reliability and validity for assessing psychotic symptoms in Alzheimer's disease patients, which further supports the perspective that the psychosis of Alzheimer's disease is readily definable. These include the Neuropsychiatric Inventory (NPI) and the Behavioral Pathology in Alzheimer's Disease (Behave-AD) rating instruments.

A growing body of evidence indicates that Alzheimer's disease patients with psychosis versus those without psychosis have clinical and neuropathological differences, thus strongly suggesting that Alzheimer's disease with psychosis may be a distinct patient subgroup. For example, many studies show that Alzheimer's disease patients with psychosis have greater frontal lobe impairment, more rapid cognitive decline, and greater neurodegenerative cortical changes than Alzheimer's disease patients without psychosis.

One approach to establish specificity is to determine the pathophysiological uniqueness of the psychosis in these disease states. However, it is not particularly relevant in this instance since the understanding of the pathophysiology (ie, etiology, mediating neurochemical processes) of psychosis in schizophrenia, dementia and other diseases, (eg, bipolar, depression), is in its infancy and currently unclear. There is strong support for dopamine dysfunction as a mediating system in schizophrenia, but also compelling evidence for glutamatergic, GABAergic, cholinergic and serotonergic dysfunction and interactions among these neurochemical systems to cause psychosis. Thus, there may be several different pathways to produce psychosis. Moreover, there is evidence supporting the notion that individual psychotic symptoms may involve distinct brain regions and neurochemical systems.

Another approach to examine the specificity of the psychosis of Alzheimer's disease is response to antipsychotic drug treatment. These medications are routinely used to treat psychosis in schizophrenia for very long durations, whereas these agents tend to be employed for shorter treatment intervals and at significantly lower doses in demented patients. However, a direct dose response comparison between age-matched

schizophrenia and Alzheimer's disease cohorts is not available to more clearly determine if dose, side effects, and effect size are similar between these groups.

We support the notion that appropriate diagnostic categorization is needed in registration clinical trials' methodology as opposed to relying solely on cross-sectional symptom ratings scales for study inclusion. The Diagnostic and Statistical Manual (DSM)-IV currently offers a diagnostic approach for psychosis associated with Alzheimer's disease: the *Diagnostic criteria for Dementia of the Alzheimer's Type* coupled with the *Diagnostic criteria for Psychotic Disorder due to a General Medical Condition (Alzheimer's disease)*. Using this DSM approach, a categorical clinical judgement is made that encompasses requisite duration, constancy over time, and severity of impact on functioning and quality of life. We anticipate and encourage the evolution of DSM criteria for the dementias similarly to the evolution that has occurred for other DSM-IV categories (e.g., schizophrenia, panic disorder) with further elaborated operationalized criteria. This will require a substantial effort and amount of time to complete. We contend that the current criteria provide a valid means to diagnose and select patients for clinical trials. Therefore, we are opposed to any suspension of drug development to await resolution of new diagnostic criteria as this would delay the availability of urgently needed new treatments.

Reliable and validated behavioral rating scales are currently available to evaluate the treatment efficacy in patients with psychosis associated with Alzheimer's disease. Thus, the availability of established DSM-IV criteria for diagnostic inclusion and validated rating scales to document cross-section severity and assess therapeutic response currently provide the necessary instruments to conduct registration quality clinical investigations of potential new treatments for psychosis associated with Alzheimer's Disease.

### **Agitation**

Similar to psychosis, specific behavioral disturbances associated with Alzheimer's disease are relatively common and create substantial hardships for patients and caregivers. Like psychosis, behavioral disturbances often are the precipitant that forces institutional care of patients who otherwise would be cared for at home or other community based outpatient programs. Although behavioral disturbances encompass a range of symptoms and signs which are potential targets for drug registration, it is reasonable to initially focus on one prominent behavior that is well known to clinicians, reliably identifiable, and causes significant adverse impact as a target for drug development. We propose that acute agitation is such a behavior. Unlike psychotic conditions, acute agitation has not been viewed historically as a specific diagnostic entity. Rather, it is a non-specific behavior that commonly occurs across a number of diseases including schizophrenia, bipolar disorder and the dementias. Thus, acute agitation is consistent with the established pain model. Accordingly, label indications for acute agitation should be supported with clinical data from a number of different patient types.

Like pain, agitation may be derived from different pathological processes. Pain may be derived from sources as distinct as acute appendicitis to headache. Similarly, agitation may be derived from clinical settings as diverse as the arousal and fear of a threatening

hallucinatory voice in schizophrenia to the disorientating impact of cognitive decline in Alzheimer's disease. Similar to psychosis, the field has not developed to the extent that would allow support of this perspective based on a common pathophysiology (ie, mediating neurochemical processes) since the pathophysiology of agitation is not known. However, the phenomenological characteristics of acute agitation across different disease states are relatively similar, readily recognizable by clinicians and able to be reliably and validly measured by current rating scales. Acute agitation generally encompasses excitement, tension, poor impulse control, hostility and uncooperativeness. These symptoms, for example, are contained in the Positive and Negative Syndrome Scale (PANSS) and comprise the PANSS Excited Component which has been validated in psychiatric populations and could be used across disease states in registration clinical trials of acute agitation. In addition, other validated scales such as the Corrigan Agitated Behavior Scale have been used to assess acute agitation in clinical trials of psychiatric patients including schizophrenia, and scales such as the Cohen-Mansfield Agitation Inventory have been designed specifically for and validated in patients with dementias and used in drug trials in these populations. Thus, there are currently available appropriate assessment tools that could be used either alone or in combination to conduct registration trials for acute agitation.

### **Conclusion**

In summary, the continually increasing elderly population, the substantial impact of Alzheimer's disease and other dementias on patients and their families, and the high degree of unmet need due to the inadequacies of currently available treatment options makes the development of new drug treatments in this area a public health priority. Clear guidance on acceptable approaches for the clinical evaluation and registration of new drug treatments for patients with various dementias is urgently needed and absolutely critical to successfully meet this public health challenge. We propose that current knowledge in the field, such as the availability of an appropriate diagnostic approach for patient selection for psychosis trials in patients with dementias and validated efficacy measures for both psychosis and acute agitation in these populations, is sufficient for the clinical evaluation of new and urgently needed treatments. We welcome the opportunity to meet with leaders of the medical and regulatory communities to discuss and reach consensus on acceptable clinical approaches to evaluate new treatments for patients with dementia.

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