March 6, 2000

Dr. Russell Katz, Director, Neuropharmacological Drug Products
Food and Drug Administration FDA 120
1451 Rockville Pike, Room 4049
Rockville, MD 20852-1420

SUBJECT: THE BEHAVIORAL COMMITTEE OF THE INTERNATIONAL WORKING GROUP FOR THE HARMONIZATION OF DEMENTIA DRUG GUIDELINES STATEMENT TO THE DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS (DNDP) ISSUE PAPER for March 9, 2000 Meeting of the Psychopharmacological Drugs Advisory Committee Meeting on the Various Psychiatric and Behavioral Disturbances Associated with Dementia.

Dear Dr. Katz:

We are writing in reference to the hearing the Food and Drug Administration is holding on March 9 concerning issues related to developing more effective interventions for the behavioral and noncognitive symptoms in dementia. We wish to highlight the international aspects of this issue. This statement has been prepared by the undersigned of this letter, as Chairpersons of the Behavioral and Steering Committees of the International Working Group for the Harmonization of Dementia Drug Guidelines (IWG), and it was approved by the IWG Steering Committee.

For five years, The International Working Group for the Harmonization of Dementia Drug Guidelines has been encouraging collaborative efforts amongst regulators, clinicians, and scientists to define and harmonize the methods for assessing and treating these symptoms. The FDA draft guidelines on antidementia drugs have been important in stimulating global discussions, particularly about cognitive symptoms. We now believe that the treatment of psychosis in dementia is recognized internationally as an appropriate target for drug development.

The symptoms in dementia are complex and there can be difficulties in differentiating cognitive and noncognitive symptoms. Certain symptoms such as apathy or withdrawal overlap with our traditional two category conceptual framework for symptoms. The differentiation of visual illusions and hallucinations can be challenging clinically when they coexist. Whereas, some behavioral symptoms in dementia can be categorized into standard psychiatric categories, others cannot. Moreover, the psychosis of dementia is different from the psychosis evident in other diseases such as schizophrenia. Depressive symptoms are frequent, but may overlap in phenomenology with cognitive impairment, and usually do not reach a level of major depression. Agitation or restlessness is an important practical problem and yet this symptom is difficult to fit into standard psychiatric categories. Nevertheless, operational criteria for psychosis associated with dementia have been developed and this type of psychosis is an appropriate target for drug therapy.

We recognize that the principal focus of the upcoming FDA hearing is for trials conducted in the United States, however, we urge that the international dimension of this problem be given attention.

In the spirit of the International Conference on Harmonization, the IWG is working with regulatory bodies around the world to improve the efficiency of global drug development. We note that the European Medicines Evaluation Agency (EMEA) Guidelines for dementia trials make direct references to behavior. However, the EMEA Guidelines do not specify the designs that might be appropriate for trials in this area. We expect that the Japanese guidelines may refer to behavioral symptoms at least in the questions and answers section that will follow the guidelines. In Canada, the proposed guidelines for the development of antidementia therapies outline the importance of behavioral symptoms at a target for symptomatic treatment with the need to demonstrate both clinically apparent and clinically meaningful treatment effects.

We encourage the FDA to support a consensual multifaceted approach to developing therapeutic agents in this field. We believe that psychosis in dementia can be characterized clearly and can be an appropriate and important target for drug therapy. However, we also believe that studying and developing treatments for other categories, such as agitation, is also appropriate.

Thank you for the opportunity to provide comments about this important topic of psychosis and behavioral symptoms in dementia, a major issue in the development of drugs to improve the quality of lives in patients with Alzheimer's disease.

Yours sincerely,

***Approved but not signed by Jeffrey Cummings**, **Akira Homma,**
and Peter J. Whitehouse
On behalf of the Members of the Steering Committee of the IWG

Name	Working Group	Country
Serge Gauthier	ADLs	Canada
Barry Reisberg	Clinical Global Measures	USA
Steven Ferris	Cognition	USA
Rachelle Doody	Cultural Issues	USA
Atwood Gaines	Cultural Issues	USA
Zaven Khachaturian	Diagnostic Criteria	USA
Stephen Post	Ethical Issues	USA
Bengt Winblad	Pharmacoeconomics	Sweden
Leon Thal	Prevention Protocols	USA
Martin Rossor	Slowing Progression Protocols	UK
Akira Homma	Behavioral Symptoms	Japan
Jeffrey Cummings	Behavioral Symptoms	USA
Jean-Marc Orgogozo	Quality of Life	France
Peter Whitehouse	Quality of Life	USA
Howard Feldman	Translation Issues	Canada
Luis Fornazzari	Translation Issues	Canada
Richard Harvey	Information Technology	UK
Timo Erkinjuntti	Vascular Dementia	Finland
Tohru Sawada	Vascular Dementia	Japan
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