MEMORANDUM

DATE: February 6, 2001

TO: Members, Peripheral and Central Nervous Systems Drugs Advisory Committee and Invited Guests

FROM: Staff
Division of Neuropharmacological Drug Products

SUBJECT: Background Document for PCNS Meeting of March 13, 2001: Issues Related to the Development of Treatment for Mild Cognitive Impairment

1 Background

As you know, a meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration will be held on March 13, 2001 to discuss the entity of Mild Cognitive Impairment. This paper has been prepared in an effort to brief you on the specific issues that we believe need to be addressed by the Agency when considering the regulation of drugs being developed to treat this putative clinical entity. In addition to this memo, we are forwarding a number of articles from the literature addressing several important aspects of this issue, which we hope will provide a more detailed background for the meeting.

1.1 Purpose Of Meeting

The purpose of this Advisory Committee meeting is to achieve a consensus on a number of issues related to the proposed entity of Mild Cognitive Impairment (MCI). These issues, which are discussed further below, are being raised in the context of the development of drugs intended for the treatment of that putative disorder.

1.2 Mild Cognitive Impairment

MCI is a widely referred-to concept in publications that deal with age-related cognitive disorders and dementia.

Several operational definitions of MCI have been proposed in the medical literature, and in drug trial protocols that our Division has reviewed. One such definition refers to a population that has isolated memory impairment, no other areas of cognitive abnormality, and normal or only slightly impaired functional abilities. Other definitions use criteria that are based on scores achieved on cognitive and global rating instruments, and are not necessarily restricted to isolated memory impairment.

Populations considered to have MCI based on these definitions have, in prospective studies, been reported to have a variable, but increased risk of developing overt Alzheimer's Disease over time, as compared with age-matched controls. Such reports appear to be the main reason why MCI has been considered a target for pharmacological intervention.

Clinical drug trials for the proposed entity of MCI have had 2 main objectives when assessing the efficacy of a putative treatment. These consist of evaluating the benefit of the drug in:

- preventing or delaying the onset of Alzheimer's Disease in this population
- treating the cognitive abnormality of MCI

There can be no question that the goal of preventing or delaying the onset of Alzheimer's Disease, or of any other form of dementia, in a susceptible population, is a commendable and highly desirable one. However, from a regulatory perspective, a number of issues need to be addressed in regard to the development of drugs to treat this putative entity.

Currently both the concept and proposed definitions for MCI appear to be controversial, based on a reading of the medical literature.

1.3 FDA Role

The FDA approves a drug for marketing based on a determination that such a treatment is both effective and safe, when used to treat one or more specific clinical entities. The entity for which such a treatment is intended, is referred to as the "claim" or "indication" for that drug and is described in the "Indications and Usage" section of the label. Proposed labeling must accompany the New Drug Application (NDA) submitted by the sponsor.

The Federal Food, Drug, and Cosmetic Act (the Act) requires that the approval of a drug treatment for a specific condition be supported by (among other things) "…substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling…". Substantial evidence is further defined as evidence from "adequate and well controlled…clinical investigations…". These definitions make clear that approval of a drug product is inextricably linked to our ability to adequately describe the population for whom the drug is intended and the drug's effects in that population in labeling.

In order to do this, the following must generally be true:

- The condition can be defined without ambiguity using criteria that have wide acceptance, and are both valid and reliable
- Appropriate instruments be used for measurement of the clinical effect of the drug on that condition; such instruments must measure what they are intended to under the conditions under which they are actively employed

- Clinical trials should be appropriately designed to measure that effect
- The effect measured should be clinically meaningful

For the most part, 2 classes of clinical entities are considered appropriate for new drug claims

- Specific diseases or clinical syndromes, such as multiple sclerosis or chronic renal failure.
- Non-specific symptoms such as pain or urinary frequency

On occasion, claims may be also be directed at symptoms of specific diseases, e.g., excessive daytime sleepiness associated with narcolepsy.

The Act also states that the Secretary may refuse to approve an application "if based on a fair evaluation of all material facts, such labeling is false or misleading." Labeling that states that a particular drug is indicated for the treatment of a specific clinical entity could be considered misleading if the condition if not well-defined, the effect of the drug on that condition is not appropriately measured, or the clinical trial in which that effect was measured was not appropriately designed.

In deciding whether a proposed clinical entity justifies a new claim, criteria used by the FDA have generally consisted of the following

- The existence of the entity must be broadly accepted by medical experts representing the relevant clinical discipline
- The entity should be operationally definable

If a new claim is sought for a drug that is already approved for a specific indication, a sponsor would be required to establish that the new indication is meaningfully different from the existing claim. Otherwise, the implication in labeling that the 2 indications were different entities when, in fact, they were not, could be considered misleading.

1.4 Current Basis For Approving Drugs For Dementia

In the last 10 years 3 drugs have been approved by the FDA for the treatment of dementia: tacrine, donepezil and rivastigmine. All 3 drugs have been approved for an identical indication: the treatment of mild to moderate Alzheimer's Disease. Their approval has been based upon clinical trials, the key elements of which have been as follows

1.4.1 Diagnosis of Alzheimer's Disease

Patients enrolled in these trials have generally had "probable" Alzheimer's Disease as defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). Those criteria* are as follows

- Dementia established by clinical examination, and confirmed by a rating scale such as the Mini-Mental Status Examination, and by neuropsychological testing

- Deficits in two or more areas of cognition
- Progressive cognitive worsening
- No disturbance of consciousness
- Onset between ages 40 and 90
- Absence of systemic disorders, and other brain diseases that could account for the progressive cognitive impairment

*The NINCDS-ADRDA criteria for probable Alzheimer's Disease have been shown to be both valid and moderately reliable. They have a sensitivity of > 90%; their specificity is however lower (50 – 60%) and they are particularly lacking in specificity in distinguishing the frontotemporal dementias from Alzheimer's Disease, as well as in distinguishing those who have a combination of cerebrovascular neuropathology and Alzheimer's Disease from those who have pure Alzheimer's Disease.

1.4.2 Severity Of Dementia

Patients enrolled in these trials have been considered to have dementia of mild to moderate severity at study entry. The severity of their dementia has been assessed based on their Mini-Mental Status Examination scores; the range of such scores that have been considered to fit the "mild to moderate" category has been from 10-26.

1.4.3 Design And Duration Of Clinical Trials

These trials have so far invariably been randomized, double-blind, placebo-controlled, parallel-arm studies. The period of double-blind treatment has ranged from 3-6 months.

So far, the approval of drugs for the treatment of Alzheimer's Disease has been based upon demonstrating efficacy in at least 2 such studies, each of at least 3 months' duration.

1.4.4 Outcome Measures For Assessing Drug Efficacy

Draft guidelines issued by this Agency have recommended that the efficacy of putative drugs for dementia be determined using assessments of the following as pre-specified co-primary outcome measures.

- Cognitive functions. The standardized test battery used most widely for this purpose is the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog). This battery assesses a spectrum of cognitive functions believed to be impaired in Alzheimer's Disease with each such function being allotted a maximum score; higher scores indicate more severe impairment. The total score for this battery can range from 0 (no impairment) to 70 (severe impairment). Patients with Alzheimer's Disease decline on average 7 to 9 points on this scale every year, although this decline varies widely
- A clinician's overall impression of how the patient's cognition, behavior and function have changed over the course of the study; this has been referred to as a "global" assessment. Several different methods of making such an assessment have been proposed. The most widely used method is the Clinician Interview Based Impression of Change-Plus (CIBIC-Plus). The CIBIC-Plus is based upon information obtained from an interview of the patient and caregiver, and the recall of the patient's earlier condition, by an independent clinician who is blinded to the results of more formal

assessments of cognitive function, such as the ADAS-Cog or Mini-Mental Status Examination, carried out by others. The CIBIC-Plus is rated on a scale from 1 (marked improvement) to 7 (marked worsening); a rating of 4 denotes no change.

A cognitive rating scale has been recommended as a primary outcome measure since the core symptoms of dementia are cognitive. However, since the clinical significance of a change on a cognitive rating scale may not be clear, a global scale has been recommended as a second primary outcome measure. For approval to be granted it has been required that superiority of the drug over placebo be demonstrated separately on each of these 2 types of measures.

For most clinical trials completed over the last 10 years, the ADAS-Cog and CIBIC-Plus have been the primary outcome measures.

1.4.5 Symptomatic Effect Versus Disease Modification

The clinical trials on which the approval of drugs for Alzheimer's Disease have been based have thus far been considered not to be designed to distinguish between a purely symptomatic effect of the drug in question and a disease-modifying effect. In this context, the term "disease modifying" refers to an effect on the underlying pathology of the disease.

Accordingly, the class labeling for these drugs states: "There is no evidence that -------(name of drug) alters the course of the underlying dementing process."

Two theoretical study designs that have been proposed for making this distinction are further described below. Both designs apply to studies that are randomized, double-blind, placebo-controlled and parallel-arm throughout. Each proposed design has 2 study segments:

- Randomized withdrawal design. In the initial segment patients are randomized to either active drug or placebo. This segment is then allowed to continue for a sufficient duration to allow the active drug to demonstrate efficacy in relation to placebo. At the beginning of the second study segment those randomized to active drug in the initial phase are further randomized to either continue active drug or receive placebo. The second study segment then continues for an appropriate period. If at the end of the second segment, those receiving placebo, in that phase only, maintained their difference from those who received placebo through both segments, a disease-modifying effect would be assumed. On the other hand should those receiving placebo in the second segment only deteriorate to the level of those who received placebo throughout, a purely symptomatic effect would be inferred
- Randomized start design. In the initial segment patients are again randomized to active drug or placebo. This segment is then allowed to continue for a sufficient duration to allow the active drug to demonstrate efficacy in relation to placebo. At the end of that period those who received placebo during the initial segment are re-randomized to receive active drug or placebo for the entire duration of the second segment, as are those who initially received active drug. If at the end of the second segment the group which received placebo initially "catches up" with those who received active drug throughout a symptomatic effect is inferred; on the other hand if

a difference between the groups is maintained, the active drug is assumed to have a disease-modifying effect

Both study designs can still be considered theoretical and have yet to be adequately assessed in a clinical trial setting. The appropriate durations of each segment, the frequency of assessments, and a number of analytical issues need to be resolved.

The use of brain imaging measures (such as volumetric magnetic resonance imaging of hippocampal and whole brain atrophy) have been proposed as surrogate markers to assess the effects of putative disease-modifying agents in Alzheimer's Disease. While a detailed review of regulatory considerations that pertain to surrogate markers is beyond the scope of this paper, it would be highly desirable for the following questions to be answered prior to such a marker being considered acceptable for use in key clinical trials that are intended to assess the effects of disease-modifying agents in Alzheimer's Disease.

- What clinical outcome is the imaging marker a surrogate for?
- Does the imaging marker reliably predict the desired clinical outcome?
- Is the desired clinical outcome based on the drug effect on the surrogate?

2 Issues For Discussion

Drug trial protocols in MCI that have been reviewed by this Division have had the following common features

- All have been randomized, double-blind, placebo-controlled, and parallel-arm in design
- Key selection criteria have consisted of the following
  - Complaints of memory impairment, confirmed by objective testing using a standardized measure
  - Mild or no cognitive impairment (e.g., a Mini-Mental Status Examination score > 24)
  - Preserved or only slightly impaired activities of daily living
  - A total score on the Clinical Dementia Rating scale (a structured measure of global function) of 0.5
  - Exclusion of depression based on scores on the Hamilton Depression Scale or similar measure
- Trials have been of 24-36 months' duration
- Active drug treatment arms have had sample sizes between 240 and 650 subjects
- Key efficacy measures have consisted of
  - Incidence or time to diagnosis of Alzheimer's Disease
  - Composite scores on a cognitive test battery

2.1 Can the entity be clearly defined in a clinical setting?

When a drug is approved by this Agency for treatment of a specific entity, it is implied that there is broad agreement within the relevant medical discipline(s) that

- such an entity exists
- is sufficiently homogenous
- the condition can be identified by practicing clinicians with a reasonable degree of consistency using accepted operational criteria

In the case of MCI, a fundamental question is whether that entity is a distinct clinical syndrome or a non-specific symptom complex accompanying a variety of underlying pathologies. In deciding whether MCI does represent a new distinct clinical syndrome, conventional criteria for determining its clinical validity could be used. Such criteria might include the following

- The existence of a cluster of related symptoms with a characteristic time course, identified by cluster analysis or clinical observation, and
- A distinct separation of the entity of interest from related conditions by discriminant function analysis.

It has been suggested that MCI can be distinguished clinically from a reportedly much more common (if not universal) memory impairment accompanying "normal" aging. Clinical terms that have been used over the years to describe age-related cognitive impairment short of dementia have included "benign senescent forgetfulness", "age-associated memory impairment", "aging-associated cognitive decline", "aging-related cognitive decline" and others. The nosological status of MCI in relation to these other entities also warrants further discussion.

2.2 Are there valid criteria for its diagnosis?

When clinical trials of a drug are conducted to evaluate its efficacy for a specific indication, criteria should be available for defining that entity so that a sufficiently homogenous population is selected for such trials. Such criteria should ideally have a high degree of sensitivity and specificity when compared with a "gold standard". While the specific diagnostic criteria used in clinical trials may not always be applicable in their entirety to the clinical setting, they should be broadly representative of that entity as identified by a practicing clinician.

For any set of diagnostic criteria that are being proposed for use in clinical trials a high degree of inter-rater reliability is also desirable.

In the case of the proposed entity of MCI, finding a gold standard may however be problematical as such a standard does not appear to exist. Whereas the sensitivity and specificity of the NINCDS-ADRDA criteria for probable Alzheimer's Disease have been compared against the histopathological diagnosis as the gold standard, such an approach does not seem practical in MCI even if the pathological substrate of that entity could be clearly defined.

Instead of determining the sensitivity and specificity of a set of diagnostic criteria for MCI, assuming that the existence of that entity is valid, against a non-existent gold standard, the appropriateness of such criteria for use in clinical trials could conceivably be determined based on whether or not they are sufficiently predictive of an outcome that an intervention is intended to counter. For example, if the prevention of overt Alzheimer's Disease is the desired outcome of such an intervention, diagnostic criteria for MCI that are reasonably predictive of the subsequent development of Alzheimer's Disease could be used to select patients

for such a study. Such an approach to validating the diagnosis would require a robust experience of the longitudinal course of MCI.

The use of diagnostic criteria for MCI that are highly predictive of the subsequent development of Alzheimer's Disease, however, makes it even more likely that those defined as having MCI by such criteria may have an early stage of Alzheimer's Disease (see Section 2.3).

It has also been suggested that diagnostic criteria for MCI that are based on clinical and neuropsychological assessments, could be further refined so as to be more predictive of the development of subsequent Alzheimer's Disease by using genotyping, cerebrospinal fluid biomarkers, and brain imaging. However, if such a population can be defined only with the aid of relatively sophisticated diagnostic techniques that may not be widely available, the applicability of efficacy data from such clinical trials to routine clinical practice may also be questionable.

2.3 Does Mild Cognitive Impairment merely represent an early stage of Alzheimer's Disease in a significant proportion of those with the former condition?

This is a critical issue in regard to whether the putative entity of MCI justifies a claim that is distinct from that already granted by this Agency to the sponsors of tacrine, donepezil, and rivastigmine. The claim for those 3 drugs is for "treatment of mild-to-moderate dementia of the Alzheimer's type."

As noted earlier, the approved claims for tacrine, donepezil, and rivastigmine have been based upon studies carried out in patients with probable Alzheimer's Disease, as defined by the NINCDS-ADRDA criteria. In essence these criteria require the presence of progressive deterioration in 2 or more cognitive domains, and the absence of disturbances of consciousness, or of any other systemic or brain disorder that could explain the patient's cognitive impairment.

There appears to be some evidence that MCI, as that proposed entity is currently viewed, may, at least in a substantial proportion of such a population, be an early stage of Alzheimer's Disease that is not yet advanced enough to satisfy the NINCDS-ADRDA criteria for diagnosing that entity.

- Several prospective studies have suggested that a significant proportion of those with so-called MCI will develop full-fledged Alzheimer's Disease if observed for a sufficient period of time.
- An isolated decline in memory, especially verbal episodic memory, which is considered by some to be the sine qua non of Mild Cognitive Impairment, is also considered to be a common early sign of Alzheimer's Disease
- The limited contemporaneous autopsy data that is available for those diagnosed to have MCI appears to indicate that a number of these individuals have histopathological changes in the brain that are qualitatively similar to those of Alzheimer's Disease, even if they are quantitatively less-pronounced.

- Brain imaging (CT, MRI and SPECT) shows abnormalities in those diagnosed to have MCI that are similar in quality and location to those seen in Alzheimer's Disease, although such abnormalities may be quantitatively less pronounced.

It further could seem logical that if the objective of clinical drug trials in MCI is to prevent or delay the development of overt Alzheimer's Disease, then, at least in theory, it is being assumed that such drugs are treating an earlier stage in the pathogenesis of the latter condition.

If MCI is to a large extent the same as early Alzheimer's Disease, pathologically and pathophysiologically, and if a drug can be demonstrated to have efficacy, however that is determined, in treating MCI, in what way would such a claim differ from one for mild Alzheimer's Disease (that satisfies the NINCDS-ADRDA criteria)? The Division has to date adopted the view that a separate claim for MCI distinct from that for Alzheimer's Disease may not be justified.

If Mild Cognitive Impairment is not, in large measure, an early form of Alzheimer's Disease, but merely a manifestation of a variety of underlying diseases, then the issue that needs to be addressed is whether Mild Cognitive Impairment is sufficiently homogenous to justify a separate claim.

2.4 Mild Cognitive Impairment as a non-specific symptom of a variety of underlying diseases

As noted above, it is possible that the entity called MCI by some is (if not early Alzheimer's Disease or another specific clinical entity) a symptom, or symptom complex, common to a number of other illnesses, (analogous to fever or pain, which can occur in the setting of a number of conditions). Ordinarily, in such a case, the Agency grants a claim for a drug as a treatment for the symptom, but only after a showing that the drug effectively treats the symptom in a representative number of clinical settings in which it occurs (for example, the Agency will grant a claim for a drug as an analgesic once it is shown that the treatment is effective in treating dental pain, surgical pain, muscle contraction headache, etc.). Of course, it is possible that a treatment may be approved for a "symptom" in a particular clinical setting, even though the "symptom" appears to occur in multiple settings (as noted earlier, a claim for the excessive daytime sleepiness of narcolepsy would be an example of such a claim). However, in these cases, the sponsor must ordinarily show that the treatment is ineffective against that symptom in the other clinical settings in which it appears to occur, or present other evidence (pathophysiologic, etc.) that the symptom in the sought after clinical setting is specific to that setting, even though it may appear to be identical clinically to a symptom seen in other clinical settings.

Failure to demonstrate the specificity of the symptom to the clinical setting in the latter case can give rise to a so-called pseudospecific claim, which arises as an artifact of the population studied, and can be misleading. For example, if a sponsor studied the effects of their drug only in Alzheimer's patients with

headache, and showed the treatment to be effective against the headache in these patients, they would not be entitled to a claim for their drug as a treatment for headache in patients with Alzheimer's Disease. Such a claim would be pseudospecific, in that it arises entirely from the fact that the sponsor chose to study only Alzheimer's Disease patients with headache. Unless the sponsor could present compelling evidence that the headaches treated were specific to Alzheimer's Disease, and that the drug differentially treats such headaches, such a claim would be considered misleading, and would be unacceptable.

It will be important for the Committee to discuss the possibility that MCI is a non-specific symptom of several underlying pathologies, and, if it is, what an appropriate development program for such a symptom might be.

2.5 What outcome measures are appropriate to use in clinical drug trials conducted in Mild Cognitive Impairment? Should clinical drug trials in Mild Cognitive Impairment incorporate any special features in their design?

If it can be assumed that Mild Cognitive Impairment is a distinct clinical syndrome, and that there are widely accepted and validated criteria for its diagnosis, a number of further questions arise as to the design and conduct of such trials.

One such issue is what key outcome measure(s) should be used in clinical trials for that entity. The few protocols that we have reviewed so far have used the incidence, or time to diagnosis, of overt Alzheimer's Disease (using the NINCDS-ADRDA or similar criteria) as a primary outcome measure, supplemented in at least one instance by a composite score on a cognitive measure. However as already indicated in Section 2.3, if the clinical diagnosis of Alzheimer's Disease is to be the primary endpoint in such studies, and if on that basis the drug is shown to be effective, it could be argued that the drug is in fact treating an earlier stage of Alzheimer's Disease that is, at the time of study entry, not sufficiently advanced to satisfy the NINCDS-ADRDA criteria.

In this case, preventing (or delaying the time to diagnosis of) AD might be considered an inappropriate claim, first, because it might be interpreted to imply an effect on the underlying pathology of the disease, and second, because the effect would really be an effect on the symptoms of AD (the indication for which the current drugs are approved); the delaying of the time to diagnosis of AD would merely be an artifact of our inability to diagnose AD earlier in its course, and would inappropriately imply that MCI is fundamentally different from AD.

A further issue concerns the appropriate sample size and duration for such studies; unless data from completed studies are available, such estimates will be need to be based upon what is known about the natural history of Mild Cognitive Impairment and what would be considered a desirable clinical effect.

Protocols for Mild Cognitive Impairment that have come to the attention of this Division have not been designed so as to distinguish between symptomatic and disease-modifying effects of the study drugs that have been proposed for use. Whether designs similar to those proposed for overt Alzheimer's Disease (see Section 1.4.5) are applicable to Mild Cognitive Impairment is unclear.

The use of brain imaging (most specifically, volumetric magnetic resonance imaging of hippocampal and whole brain atrophy) has been proposed as a surrogate marker to assess the effects of putative disease-modifying agents in MCI. For a brief regulatory perspective on surrogate markers, please see Section 1.4.5. In clinical protocols that this Division has seen, volumetric magnetic resonance imaging has been proposed as a measure for use only in a small proportion of the study centers enrolled.

In this memo, we have outlined the issues we would like the Committee to discuss in advising the Division about the development of treatments for the symptom complex currently referred to by some as MCI. Of course, we are eager to hear your views not only on the issues we have identified, but on any other issue you believe to be relevant. We very much appreciate your thoughts on this matter, and look forward to seeing you and to a lively discussion.