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Food and Drug Administration
Rockville MD 20857

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Dear Mr. Emord:

This letter is in response to your letter dated December 3, 2003 to Daniel E. Troy, Chief Counsel, Food and Drug Administration (FDA or the agency). In this letter, which presented your position concerning the use of disease treatment studies as evidence of risk reduction, you stated, "In the phosphatidylserine/dementia and phosphatidylserine/cognitive dysfunction claim context, the scientific evidence supporting the risk reduction claims there in issue came from treatment studies (dealing with patients suffering from Alzheimer's, dementia, and senility)."¹

In response to your letter, the agency re-evaluated the scientific evidence for the qualified health claims characterizing the relationship between phosphatidylserine and cognitive dysfunction, and phosphatidylserine and dementia, which FDA had originally evaluated in a letter dated May 13, 2003 (the May 2003 letter).² In that letter, the agency concluded that very limited and preliminary scientific research suggested that phosphatidylserine may reduce the risk of both cognitive dysfunction and dementia. In light of that conclusion, the agency stated its intention to consider the exercise of enforcement discretion for qualified claims regarding these relationships under certain circumstances described in the letter.³

This letter outlines FDA's rationale for its determination that the current evidence for the proposed health claims is still appropriate for consideration of a qualified health claim. FDA was in error in its May 2003 letter of enforcement discretion stating that all the studies were in a diseased population. Although FDA characterized all the intervention studies submitted with your petition as mitigation studies in a diseased population (i.e., studies of whether phosphatidylserine could treat dementia or cognitive dysfunction by reducing their symptoms), the agency erred in that characterization. In fact, four studies were conducted in subjects who were without diagnosed dementia or cognitive dysfunction, but who had mild to moderate cognitive deterioration, age-associated memory impairment or age-associated cognitive decline and were therefore at risk of dementia and cognitive dysfunction beyond what occurs with the normal aging process. FDA was also in error in concluding that mitigation studies in diseased populations alone constituted credible evidence to substantiate

¹ Letter from Jonathan W. Emord, Esq., Emord & Associates, P.C., to FDA Chief Counsel Dan Troy (December 3, 2003).

² Letter from Christine L. Taylor, Ph.D., FDA to Jonathan W. Emord, Esq., Emord & Associates, P.C. (May 13, 2003) <<http://www.cfsan.fda.gov/~dms/ds-ltr36.html>>.

³ Letter from Christine L. Taylor to Jonathan W. Emord, *supra* note 2, pp. 11-12.

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the proposed claims. In fact, for mitigation studies to be considered relevant, additional evidence from non-diseased populations is needed to demonstrate that the mechanisms for the mitigation effects measured in the diseased populations are the same as the mechanisms for risk reduction effects measured in non-diseased populations. Such additional evidence is lacking. However, because there are studies conducted in non-diseased populations demonstrating beneficial effects of phosphatidylserine on subjects at risk of dementia and cognitive dysfunction, there is some credible evidence for a risk reduction relationship.

I. Overview of Data and Eligibility for a Qualified Health Claim

The petition cited 278 publications as evidence to substantiate the relationship for this claim (see attached bibliography). These publications consisted of 49 review articles, 41 animal studies, 62 articles on prediction of and risk factors of dementia or cognitive dysfunction, 4 treatment/drug studies, 1 letter, 1 article on the prevalence of dementia, 2 meta-analyses, 1 abstract, 97 articles on the mechanism, progression and diagnosis of dementia or cognitive dysfunction, 5 articles on the effect of outcomes other than dementia or cognitive dysfunction, and 15 articles on the effect of phosphatidylserine on the risk or treatment of dementia or cognitive dysfunction in humans. FDA focused its review of the evidence to primary reports from human intervention studies that measured the incidence of the disease or health-related condition.

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of food (21 CFR 101.14(a)(2)). The petition identified phosphatidylserine as the substance that is the subject of the proposed claims and stated that it can be derived from two sources, bovine brain cortex and soy lecithin. Phosphatidylserine is found in food. As a component of food, phosphatidylserine is a substance; however, as the agency indicated in the May 2003 letter,⁴ soy lecithin phosphatidylserine (S-PS) and bovine brain cortex phosphatidylserine (BC-PS) may not be the same substance since they significantly differ in their fatty acid composition. As explained in the May 2003 letter,⁵ these differences, along with differences in the non-phosphatidylserine components of these ingredient sources, lead to uncertainty in generalizing results from studies done with BC-PS containing products to products containing S-PS, and vice versa.

B. Disease or Health-Related Condition

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition identified dementia and cognitive dysfunction as the diseases or health-related conditions that are the subjects of the proposed claims.

⁴ Letter from Christine L. Taylor to Jonathan W. Emord, *supra* note 2, p. 4.

⁵ Letter from Christine L. Taylor to Jonathan W. Emord, *supra* note 2, p. 5.

As was stated in the May 2003 letter,⁶ FDA could not find a standard definition of cognitive dysfunction and therefore considered it to mean a disturbance of cognitive function. Cognitive function is “an intellectual process by which one becomes aware of, perceives, or comprehends ideas. It involves all aspects of perception, thinking, reasoning, and remembering.”⁷ Therefore, the terms “cognitive function” or “cognitive functions” subsume a number of interrelated brain activities. Examples of such activities include memory, learning, abstract thinking, language, visuospatial perception, and higher executive functions (planning, organizing, and sequencing).

The May 2003 letter⁸ described dementia as a development of multiple cognitive deficits that include memory, and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive functioning.⁹ The cognitive deficits must be sufficiently severe to cause impairment in occupational or social functioning and must represent a decline from a previous higher level of functioning. Therefore, dementia indicates the presence of cognitive decline/deterioration (defined below) that is severe enough to impair occupational or social functioning.¹⁰ In FDA’s view, dementia and cognitive dysfunction are states of brain dysfunction resulting from the process of cognitive decline/deterioration.

FDA’s scientific analysis in this letter refers to a number of diseases or health-related conditions other than dementia and cognitive dysfunction. Cognitive decline, sometimes referred to as cognitive deterioration, is a progressive worsening of one’s cognitive abilities that may eventually lead to cognitive dysfunction and dementia. The Global Deterioration Scale for the assessment of dementia identifies various levels of cognitive status and progression of cognitive decline, beginning with the normal older adult (level 1) and progressing to severe cognitive decline/late dementia/severe Alzheimer’s disease (level 7) (Reisberg et al., 1982).

For purposes of this current health claim evaluation, FDA identified four terms representing various levels of cognitive decline that occur before the onset of dementia and that are associated with increased risk of dementia and cognitive dysfunction: 1) age-associated memory impairment (AAMI), 2) mild cognitive impairment (MCI), 3) moderate cognitive decline/deterioration, and 4) age-associated cognitive decline (AACD). The scientifically credible phosphatidylserine studies available to FDA for review involved subjects in all of the categories except MCI.

⁶ Letter from Christine L. Taylor to Jonathan W. Emord, *supra* note 2, p. 5.

⁷ Mosby’s Medical, Nursing and Allied Health Dictionary, 4th edition, 1994.

⁸ Letter from Christine L. Taylor to Jonathan W. Emord, *supra* note 2, p. 5.

⁹ Aphasia is defined as defect or loss of the power of expression by speech, writing, or signs, or of comprehending spoken or written language, due to injury or disease of the brain (Dorland’s Medical Dictionary, 2002). Apraxia is defined as loss of ability to carry out familiar, purposeful movements in the absence of paralysis or other motor or sensory impairment (Dorland’s Medical Dictionary, 2002). Agnosia is defined as loss of the power to recognize the import of sensory stimuli; the varieties of agnosia correspond with the several senses and are distinguished as auditory, visual, olfactory, gustatory, and tactile (Dorland’s Medical Dictionary, 2002.). Executive functioning is defined as planning, prioritizing, sequencing, self-monitoring, self-correcting, inhibiting, initiating, controlling or altering behavior (About Brain Injury. A Glossary of Terms, 2003; <http://www.waiting.com/glossary.html>).

¹⁰ Mani, 2002

AAMI is a term established by a National Institute of Mental Health Working Group for the purpose of calling attention to the concept of memory changes with normal aging (Crook et al., 1986). AAMI is a common condition in individuals greater than 50 years of age. It is characterized by complaints of gradual memory impairment (subjective memory decline and objective memory loss) in everyday life within the limits of what is considered normal for age and in the absence of dementia. Individuals are required to score one standard deviation below the mean established for young adults on at least one of several standardized tests. Based on the Global Deterioration Scale for assessment of dementia, individuals with AAMI have very mild cognitive decline (level 2) (Reisberg et al., 1982). Individuals with AAMI have been shown to have a three-fold greater risk for development of dementia than individuals who do not meet AAMI criteria (Goldman and Morris, 2001).

Individuals with MCI complain of impaired memory, while their daily living activities are normal. Based on the Global Deterioration Scale for assessment of dementia, individuals with MCI have mild cognitive decline/deterioration (e.g., early confusional state) (level 3) (Reisberg et al., 1982). While not all people with MCI develop dementia, people with this condition have a significantly increased risk of dementia compared to the rest of the population.¹¹ Based on a review of various studies, subjects with MCI progress to dementia at a rate between 10 to 15 percent per year (Petersen et al., 2001). Because none of the scientifically credible phosphatidylserine studies available for FDA's consideration involved subjects with MCI, we are defining that condition here only to provide an additional reference point on the continuum between normal aging and dementia.

The diagnosis of AACD, also known as age-related cognitive decline (ARCD), is based on a more comprehensive evaluation of cognition than AAMI (Levy, 1994). In addition to memory, AACD/ARCD criteria include learning, attention, concentration and thinking. Individuals are required to score one standard deviation below the norm for their own age group (rather than the norm for young adults, which is used as the reference for AAMI) on standardized tests. Therefore, individuals with AACD/ARCD are considered to have a further progression in cognitive decline than those with AAMI, and have also been categorized as having moderate cognitive decline (Jorissen et al., 2001). Individuals classified as having AACD/ARCD progressed to dementia at a rate of 28.6 percent over 3 years (Ritchie et al., 2001). The Global Deterioration Scale for assessment of dementia defines moderate cognitive decline/deterioration as being a late confusional state and without dementia (level 4) (Reisberg et al., 1982). Some of the symptoms of moderate cognitive decline include some deficit in memory of one's personal history and decreased knowledge of current and recent events. If progression of cognitive decline occurs, then one begins to experience moderately severe cognitive decline/early dementia (level 5).

As discussed in the May 2003 letter,¹² because the possible causes of dementia are likely the same as those for cognitive decline/deterioration¹³ that may result in cognitive dysfunction,

¹¹ http://www.ninds.nih.gov/disorders/alzheimersdisease/detail_alzheimersdisease.htm

¹² Letter from Christine L. Taylor to Jonathan W. Emord, *supra* note 2, p. 6.

¹³ See footnote 10.

FDA considered dementia and cognitive dysfunction together in re-evaluating the scientific evidence for the relationship with phosphatidylserine.

II. The Agency's Reconsideration of a Qualified Health Claim

A. Assessment of Intervention Studies

In FDA's original review, the agency evaluated 15 human intervention studies submitted with your petition for review of these qualified health claims (Crook et al., 1992; Heiss et al., 1994; Heiss et al., 1993; Amaducci and the SMID Group, 1998; Delwaide et al., 1986; Engel et al., 1992; Schreiber et al., 2000; Crook et al., 1991; Cenacchi et al., 1993; Palmieri et al., 1987; Villardita et al., 1987; Granata and DiMichele, 1987; Allegro et al., 1987; Caffarra and Santamaria, 1987; and Sinfiorani et al., 1987). The agency located through a literature search another intervention study (Jorissen et al., 2001).

Of these 16 studies, 7 studies included subjects diagnosed with dementia or severe cognitive deterioration, a characteristic of dementia (Crook et al., 1992; Cenacchi et al., 1993; Heiss et al., 1994; Heiss et al., 1993; Amaducci, 1988; Delwaide et al., 1986; and Engel et al., 1992).

Although a number of animal studies have been conducted to ascertain the mechanism by which phosphatidylserine may help mitigate the symptoms of dementia, the petition provided no evidence to indicate that the mechanism for treating dementia is the same as for risk reduction of dementia and/or cognitive dysfunction. Therefore, FDA does not consider these 7 studies relevant to a claim for risk reduction in the general population.

Of the 9 remaining studies, 5 were open-label designs (Schreiber et al., 2000; Granata and DiMichele, 1987; Allegro et al., 1987; Caffarra and Santamaria, 1987; and Sinfiorani et al., 1987). For reasons discussed in the May 2003 letter,¹⁴ these uncontrolled studies are not scientifically credible and therefore were not considered in the present FDA review.

The agency considers the 4 remaining intervention studies relevant because they evaluated subjects who were at risk of dementia and cognitive dysfunction but did not have these conditions. Two of these studies involved subjects with moderate cognitive deterioration (Palmieri et al., 1987; Villardita et al., 1987) and two studies involved subjects diagnosed with age-associated memory impairment (Jorissen et al., 2001; Crook et al., 1991). Some of the subjects in the Jorissen study also fulfilled the criteria for AACD. None of the subjects in these 4 studies was diagnosed with dementia or cognitive dysfunction. Thus, FDA considers these 4 studies relevant for evaluating whether phosphatidylserine intake reduces the risk of dementia and cognitive dysfunction.

Palmieri et al. (1987) was a 2 month randomized double blind, placebo controlled trial. Based on the Clifton Assessment Procedures method, Italian men (n= 30) and women (n=57) (55-80 years of age) were determined to have moderate cognitive deterioration and to be without dementia. These men and women received either a placebo or 300 mg/day of BC-PS. Compared to the placebo, supplementation with BC-PS significantly improved memory (as

¹⁴ Letter from Christine L. Taylor to Jonathan W. Emord, *supra* note 2, pp. 6-7.

measured by the Five-Word Test (acquisition and recall method), daily activities, orientation and spontaneity (as measured by Plutchik Geriatric Scale rating).

Villardita et al. (1987) was a 3 month multi-center, double-blind, placebo controlled trial. Based on the Mini-Mental Status Examination, Italian men (n = 85) and women (n=85) (55-80 years of age) were determined to have early, moderate cognitive deterioration and to be without dementia. These men and women received either a placebo or 300 mg/day of BC-PS. Compared to the placebo, supplementation with BC-PS significantly improved 14 of the 24 outcome measures that tested for attention, memory, and verbal skills.

Crook et al. (1991) was a 3 month double-blind placebo controlled study. U.S. men and women (total n = 149) (50-75 years of age) were determined to have AAMI based on the Memory Complaint Questionnaire, the Weschler Memory Scale, and the Benton Visual Retention Test, and to be without dementia (Mini-Mental Status Examination score > 27). These men and women received either a placebo or 300 mg/day of BC-PS. Two subgroups were identified retrospectively based on the level of performance across all measures at baseline (92 subjects with relatively good memory and 57 subjects with relatively impaired memory). Compared to the placebo, supplementation with BC-PS significantly improved 6 of the 20 outcome measures for the total sample, which included 5 primary outcome variables (acquisition, delayed recall, facial recognition, telephone number recall and misplaced objects recall) at 4 evaluation points. For the relatively impaired subgroup, there was significant improvement for 12 of the 20 outcome measures with BC-PS supplementation.

Jorissen et al. (2001) was a 3 month double-blind, placebo controlled study. Dutch men and women (total n = 120) (> 57 years of age) were determined to have AAMI based on the Memory Complaint Questionnaire and to be without dementia (Mini-Mental Status Examination score > 24). These men and women received either a placebo, 300 mg/day of S-PS, or 600 mg/day of S-PS. Compared to the placebo, no significant differences were observed for any of the efficacy variables measured (e.g., visual verbal learning test, memory scanning test, verbal fluency test) for either of the groups that received S-PS.

Although these four studies were all double-blind, placebo-controlled intervention studies, their scientific reliability is limited by flaws in design and analysis. As discussed in the May 2003 letter,¹⁵ significant flaws present in one or more of these studies included the following, among others: 1) demographic and other baseline characteristics were not statistically compared (Palmieri et al., 1987); 2) multiple comparisons were made among the measured variable in the authors' analysis of the study, without applying appropriate statistical corrections to reduce the possibility of finding statistically significant relationships by chance alone (Palmieri et al., 1987; Villardita et al., 1987; Crook et al., 1991); 3) a dataset on those who completed the study was not provided (Villardita et al., 1987); 4) lack of information as to whether outcome measures used in the study had been standardized, validated, and generally accepted (Crook et al., 1991; Jorissen et al., 2001), and 5) randomization of subjects was not based on subgroup category, making the interpretation of the subgroup results unclear (Crook et al., 1991).

¹⁵ Letter from Christine L. Taylor to Jonathan W. Emord, *supra* note 2, pp. 8-9.

B. Strength of the Scientific Evidence

The current FDA reanalysis identified four intervention studies relevant for evaluating a possible relationship between phosphatidylserine and dementia and cognitive dysfunction (Crook et al., 1991; Jorissen et al., 2001; Palmieri et al., 1987; Villardita et al., 1987). These 4 studies included individuals, aged 50 years or more, who were at risk of dementia and cognitive dysfunction beyond what occurs with the normal aging process because they suffered from AAMI, AACD and/or moderate cognitive deterioration (Petersen et al., 1999; Ritchie et al., 2001; Goldman and Morris, 2002; Reisberg et al., 1982). None of the subjects in the four studies was diagnosed with dementia or cognitive dysfunction. Three of the four studies supported a relationship between intake of BC-PS and reduced risk of dementia and cognitive dysfunction by demonstrating a significant benefit from intake of BC-PS in subjects with AAMI or moderate cognitive deterioration (Palmieri et al., 1987; Villardita et al., 1987; Crook et al., 1991). The one study that showed no benefit involved the use of S-PS (Jorissen et al., 2001).

Based on FDA's reanalysis of the strength of the total body of scientific evidence for qualified health claims about phosphatidylserine and reduced risk of dementia and cognitive dysfunction, FDA concludes that the credible scientific evidence regarding these substance-disease relationships, while sufficient to support a qualified health claim, is very limited and preliminary. Furthermore, for the reasons discussed in FDA's May 2003, letter,¹⁶ there is still considerable uncertainty about whether the effects of BC-PS and S-PS on reduced risk of dementia and cognitive dysfunction are similar or different. Thus, there is considerable uncertainty in generalizing results from studies done with BC-PS containing products as the test substance to products containing S-PS, and vice versa.

III. Conclusions

Based on the agency's reanalysis of the credible intervention studies relevant to the relationship between phosphatidylserine and dementia and cognitive dysfunction, FDA continues to believe that the science provides very limited and preliminary evidence sufficient for qualified health claims about phosphatidylserine and reduced risk of these conditions, with the same qualifying language and enforcement discretion factors as outlined in the May 2003 letter.¹⁷

Please note that scientific information is subject to change, as are consumer consumption patterns. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may

¹⁶ Letter from Christine L. Taylor to Jonathan W. Emord, *supra* note 2, p. 5.

¹⁷ Letter from Christine L. Taylor to Jonathan W. Emord, *supra* note 2, pp. 11-12.

become available that will support significant scientific agreement or that will no longer support the use of a qualified claim, or that raises safety concerns about the substance that is the subject of the claim.

Sincerely,

A handwritten signature in black ink, appearing to read "William K. Hubbard", written over a horizontal line.

William K. Hubbard
Associate Commissioner for Policy and Planning

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