PETITION FOR HEALTH CLAIMS:

PHOSPHATIDYLSERINE AND COGNITIVE DYSFUNCTION

PHOSPHATIDYLSERINE AND DEMENTIA

SUBMITTED TO THE FOOD AND DRUG ADMINISTRATION

APRIL 18, 2002

PETITIONER:

DR. KYL SMITH

02P.0413

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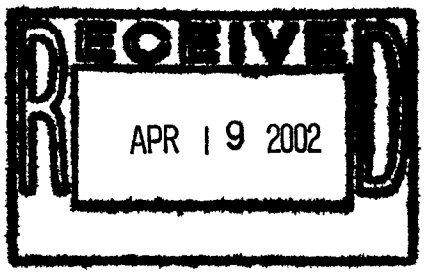

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BACKGROUND OF THE PETITIONER

Dr. Kyl Smith is a Doctor of Chiropractic. He received a post-doctoral Diplomate in Pediatrics and has engaged in over eight years of clinical practice and post-doctoral study in the field of nutrition. Dr. Smith is the President and CEO of Creative Health Institute Inc., a company engaged in research and development of natural wellness products and the development of complementary educational programs. CHI also contributes articles to trade magazines and provides reference material for product substantiation through peer-reviewed science. Dr. Smith formulates dietary supplement products containing phosphatidylserine and licenses them for sale by dietary supplement companies.

April 18, 2002

PETITIONER: Kyl Smith, D.C.

ADDRESS: c/o Emord & Associates, P.C.
5282 Lyngate Court
Burke, VA 22015

SUBJECT: Petition for Health Claims: Phosphatidylserine and Cognitive Dysfunction; Phosphatidylserine and Dementia

Food and Drug Administration
Office of Nutritional Products, Labeling, and Dietary Supplements
HFS-800
5100 Paint Branch Parkway
College Park, MD 20740

I. Introduction and Statement of Purpose

Dr. Kyl Smith (hereinafter "Petitioner"), pursuant to Section 403(r)(5)(D) of the Federal Food, Drug & Cosmetic Act ("FDCA")(21 U.S.C. §343(r)(5)(D)), submits this petition for two health claims concerning, respectively, the relationship between the consumption of phosphatidylserine and cognitive dysfunction and the relationship between the consumption of phsophatidylserine and dementia. The proposed claims are contained in section V below. Attached hereto, and constituting a part of this petition, are all of the items specified in 21 C.F.R § 101.70(f). The text of the proposed model claims are set forth in section IV of this petition.

This petition presents a logical and valid evaluation of the scientific studies and clinical trials concerning the relationship between phosphatidylserine and cognitive dysfunction and phosphatidylserine and dementia. The attached scientific studies demonstrate that (1) evidence of cognitive decline reflects neuropathological changes in hippocampal and cerebral functioning; (2) cognitive decline is not a mandatory component of human aging and, in the absence of symptoms of dementia, the progression of cognitive decline to dementia is not universal; (3) cognitive decline, in the absence of symptoms of dementia, is a modifiable risk factor for later

development of dementia; and (4) supplementation with phosphatidylserine decreases the risk of dementia by interrupting accelerated cognitive decline. The scientific evidence justifies permitting a health claim that links consumption of phosphatidylserine with a reduction in the risk of cognitive dysfunction and the risk of dementia. See Glade Report attached as Exhibit (Exh.) 1.

The proposed health claim responds to a major public health concern in the United States: cognitive failure among persons of all ages, but more particularly for persons over 65 years of age. 21 C.F.R. § 101.75(b). An estimated 4 to 5 million Americans have some form and degree of cognitive dysfunction. Merck Manual of Diagnosis and Therapy, Section 14 Neurologic Disorders, Chapter 171 Delirium and Dementia, (2002). An estimated 1.8 million Americans have severe dementia and another 1.5 million Americans have mild to moderate dementia. Exh. 5. It is believed that nearly half of all people age 85 and older have some form of dementia. Fact Sheet: Dementia, Family Caregiver Alliance, http://www.caregiver.org/factsheets/dementiaC.html (Last visited 3/27/02); attached as Exh. 6.

Phosphatidylserine is present in cell membranes in humans, animals, and plants. Exh. 1at 6; Exh. 2 at 354. Phosphatidylserine is found in significant quantities in the human brain (10-100 mg/gm tissue). Exh 1. While phosphatidylserine is a ubiquitous natural component of the American diet it is virtually impossible for any one person to consume daily those foods in conventional form that contain enough phosphatidylserine (50-500 mg/day) to affect a reduction in the risk of cognitive dysfunction and in the risk of dementia. Only a supplemental source of phosphatidylserine can ensure that efficacious quantities are ingested daily. The scientific studies described in this petition directly address this important public health issue and further national

and DHHS policies by identifying low cost means of reducing cognitive dysfunction and dementia risk.

The Petitioner believes that the truthful and succinct health information conveyed by his proposed health claims will enable consumers to make prudent and effective dietary choices. Labeling dietary supplements with the proposed phosphatidylserine claim would inform consumers at the point of sale of current scientific evidence concerning means to lessen risk of cognitive dysfunction and dementia. The petitioned claim will accurately impart to consumers the scientific understanding about the relationship between phosphatidylserine and the risks of cognitive dysfunction and dementia.

Consistent with the decision in Pearson v. Shalala, 164, F.3d 650 (D.C.Cir. 1999), reh'g denied en banc, 172 F.3d 72 (D.C.Cir. 1999); see also Pearson v. Shalala, 130 F.Supp.2d 105 (2001), the Petitioner respectfully requests that if the agency finds the proposed claims do not satisfy its "significant scientific agreement" standard, that the agency authorize the claims nevertheless, with such short, succinct, and accurate disclaimers as are reasonably necessary to avoid a potentially misleading connotation. The Petitioner will accept reasonable short, succinct, and accurate disclaimers that achieve that objective.

II. Preliminary Requirements

A. Phosphatidylserine meets the definitions of 21 C.F.R. 101.14(a)

The Petitioner seeks FDA approval of the proposed claim for use on dietary supplements containing phosphatidylserine. Phosphatidylserine meets the definition of a "substance" provided by 21 C.F.R. § 101.14(a): "Substance means a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement that includes vitamins, minerals, herbs, or other similar nutritional substances." 21 C.F.R. § 101.4 (2002). Phosphatidylserine is a glycerophosphate skelaton linked to two fatty acid molecules and the amino acid L-serine. Exh. 2 at 354.[1] Phosphatidylserine is the major acidic phospholipid in the brain and is a basic structure component of cell membranes in plants, animals and other life forms. Exh. 1 at 6; Exh. 2 at 354. Phosphatidylserine is located in the internal layers of biological membranes, facing the cytoplasm with its polar head group. Exh. 2 at 354. In animal tissues, phosphatidylserine is formed from phosphatidylethanolamine by the exchange of the ethanolamine head for L-serine. Id. It has been isolated from soya and egg yolks. Id. Phosphatidylserine can be derived from bovine brain or soya lecithin and is available as a dietary supplement. Exh. 1 at 9; Exh. 2. The Petitioner derives phosphatidylserine from soya lecithin. Thus, phosphatidylserine is a "substance" as defined by 21 C.F.R. § 101.14(a).

B. Phosphatidylserine meets the definitions of 21 C.F.R. 101.14(b)

The proposed health claim meets the relevant eligibility requirements of 21 C.F.R. § 101.14(b). Section 101.14(b) requires:

(b) Eligibility. For a substance to be eligible for a health claim:

[1] Phosphatidylserine is "the condensation product of phosphatidic acid and serine." PDR Medical Dictionary, at 1355; Medical Economics, NJ (1st Ed. 1995). It is known chemically as 1,2-diacyl-sn-glycerol-(3)-L-phosphoserine. Exh. 2 at 354.

(1) the substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup (e.g., the elderly) is at risk, or, alternatively, the petition submitted by the proponent of the claim otherwise explains the prevalence of the disease or health-related condition in the U.S. population and the relevance of the claim in the context of the total daily diet and satisfies the other requirements of this section.

(2) If the substance is to be consumed as a component of a conventional food at decreased dietary levels, the substance must be a nutrient listed in 21 U.S.C. 343(q)(1)(C) or (q)(1)(D), or one that the Food and Drug Administration (FDA) has required to be included in the label or labeling under 21 U.S.C. 343(q)(2)(A); or

(3) If the substance is to be consumed at other than decreased dietary levels:

(i) The substance must, regardless of whether the food is a conventional food or a dietary supplement, contribute taste, aroma, or nutritive value, or any other technical effect listed in § 170.3(o) of this chapter, to the food and must retain that attribute when consumed at levels that are necessary to justify a claim; and

(ii) The substance must be a food or a food ingredient or a component of a food ingredient whose use at the levels necessary to justify a claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Federal Food, Drug and Cosmetic Act.

1. Phosphatidylserine is associated with a disease for which the general U.S. population is at risk.

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 (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition (claims pertaining to such diseases are thereby not subject to § 101.13 or § 101.70)." 21 C.F.R. § 101.14(a)(5). The proposed health claim associates the substance, phosphatidylserine, with two diseases and health-related conditions, cognitive dysfunction and dementia.

Cognitive dysfunction is the declining ability to perform effortful cognitive processing. Exh. 1 at 1. Cognitive processing is divided into two categories: automatic (requiring little attention) and effortful (requiring considerable attentional capacity). Id. The early signs of

declining ability to perform effortful cognitive processing typically includes reduced ability to perform on tests of reaction time, language, declarative memory, working memory, free recall, isuospatial/reasoning skills, executive functions, and problem solving. Id. The presence of mild cognitive decline is not predictive of later dementia. Id. at 4. Over the age of 70 cognitive performance declines with advancing age irrespective of health status. Id. However, cognitive changes that differ from the changes seen in normal aging precede the appearance of signs of dementia. Id. Dementia is characterized most typically by accelerated deficits in effortful processing with little or no decline in automatic processing. Id. By contrast, cognitive decline in the absence of dementia typically accompanies aging and may become "converted" within the brain to dementia only after a threshold of accumulation of small pathological changes occurs. Id. at 5.

The general U.S. population is at significant risk of cognitive dysfunction and dementia. The elderly U.S. population (age 65 and over) is at a high risk of cognitive dysfunction and dementia. An estimated 4 to 5 million Americans (about 2% of all ages and 15% of those age 65 or older) have some form and degree of cognitive dysfunction. Merck Manual of Diagnosis and Therapy, Section 14 Neurologic Disorders, Chapter 171 Delirium and Dementia, (2002). In 1990 the U.S. Congressional Office of Technology Assessment estimated that 1.8 million Americans have severe dementia and another 1.5 million Americans have mild to moderate dementia. Exh. 5. The Alzheimer's Association estimates that of those persons with dementia, 4 million have Alzheimer's disease. Fact Sheet: Dementia, Family Caregiver Alliance, http://www.caregiver.org/factsheets/dementiaC.html (Last visited 3/27/02); Attached as Exh. 6. By the year 2040 the Alzheimer's Association estimates that the Alzheimer's disease population

may exceed 6 million. It is believed that nearly half of all people age 85 and older have some form of dementia. Id.

A 1985 report by the congressional Office of Technology Assessment, "Losing a Million Minds: Confronting the Tragedy of Alzheimer's Disease and Other Dementia," reported that the economic, social and health problems associated with disorders that cause deterioration of mental function (dementia) are growing rapidly. See Exh. 6. The 1983 estimate of the cost of providing long-term care nationwide was approximately $44 billion yearly with $12 billion derived from federal sources. Id. Disorders leading to dementia account for an estimated 30-50% of those costs, $14-22 billion dollars annually. Id. Reduction of the risk of cognitive dysfunction and dementia is, thus, an economic and health necessity for the U.S. population.

2. Phosphatidylserine contributes nutritive value at the levels present in supplements

In accordance with section 101.14(b)(3)(i), phosphatidylserine contributes nutritive value. While there is no Reference Daily Intake (RDI) for phosphatidylserine, the nutritive contribution of phosphatidylserine is widely recognized. See Exhs. 1 and 2. "Phosphatidylserine has demonstrated some usefulness in treating cognitive impairment, including Alzheimer's disease, age-associated memory impairment and some non-Alzheimer's dementias." Exh. 2 at 355.

Phosphatidylserine is a naturally occurring nutritive component in a wide variety of foods such as eggs and soy products. Exh. 2 at 354. Oral phosphatidylserine has been reported to be highly bioavailable in humans and to cross the blood-brain barrier. Exh. 1 at 7. The proposed health claim does not identify specific intake quantities for phosphatidylserine. Studies have shown phosphatidylseine supplementation to have nutritive value from 75 mg to 500 mg a day.

Exh. 1 at 7-9. Phosphatidylserine is typically supplied in solid oral dosage form in capsules containing 50 mg, 100 mg or 500 mg. Exh. 2 at 356.

3. Phosphatidylserine is safe and lawful under the FDCA

"For each such ingredient listed, the petitioner should state how the ingredient complies with the requirements of § 101.14(b)(3)(ii), e.g., that its use is generally recognized as safe (GRAS), listed as a food additive, or authorized by a prior sanction issued by the agency, and what the basis is for the GRAS claim, the food additive status, or prior sanctioned status." 21 C.F.R. § 101.70(f)(A). In accordance with section 101.14(b)(3)(ii), phophatidylserine is both a food and food ingredient and is safe and lawful at the levels necessary to justify the proposed health claim. As mentioned above, phosphatidylserine is a natural ingredient of common foods such as meats and soy products. Phosphatidylserine is also commonly sold as a dietary supplement. The FDCA deems dietary supplements a food under 21 U.S.C. § 321(ff). Accordingly, phosphatidylserine is both a food and food ingredient under 21 C.F.R. § 101.14(b)(3)(ii).

Phosphatidylserine is generally recognized as safe and lawful at the levels necessary to justify the proposed health claim. General recognition of safety is based on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. 21 C.F.R. § 170.30(a). The basis for such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food. Id.

> Safe or safety means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered:

(1) the probably consumption of the substance and of any substance formed in or on food because of its use.
(2) The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet.
(3) Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients are generally recognized as appropriate.

21 C.F.R. § 170.3.

Phosphatidylserine has been a naturally occurring ingredient in foods consumed in the United States prior to January 1, 1958. There is no evidence that phosphatidylserine consumed either in foods or as a dietary supplement has a cumulative effect in the diet that affects its safety. See Exh. 1 at 9. There are no reported drug, nutritional supplement, food or herb interactions with phosphatidylserine. Exh. 2 at 355. Moreover, there is an absence of reports of adverse reactions in the published scientific literature concerning oral supplementation with phosphatidylserine. Exh. 1 at 9. The PDR for Nutritional Supplements states that occasional gastrointestinal side effects, such as nausea and indigestion, are reported. Exh. 2 at 355. The safety of phosphatidylserine has been documented in detail through clinical trials by several investigators. Exh. 1 at 9.[2] The PDR indicates no significant contraindications, only a general statement that it is contraindicated for persons that are hypersensative, i.e. allergic, to any component of the preparation. Id. Finally, phosphatidylserine extracted from plant sources exclusively has been reported to be without side effects and poses no risk as a vector of viral pathogens. Id.

The maximum (safe) daily intake of phosphatidylserine is generally limited to the amount reasonably required to accomplish the intended nutritive effect. 21 C.F.R. § 172.5. The safe upper limit for phosphatidylserine has not been established but it has been shown to be safe at

intake levels up to 500 mg per day. Id. at 8. Therefore, the proposed health claims comply with the safety and lawfulness requirements of 21 C.F.R. § 101.14(b)(3)(ii).

In summary, since phosphatidylserine meets the requirements set forth in 21 C.F.R. § 101.14(b), the preliminary requirements of 21 C.F.R. § 101.70 are fully satisfied.

[2] The PDR cautions that there is a lack of long-term safety studies so phosphatidylserine should be avoided by children, pregnant women and nursing mothers. Id. at 355. It also states that persons with antiphospholipid-antibody syndrome should take phosphatidylserine only under medical supervision and monitoring. Id.

III. Summary of Scientific Data Supporting the Proposed Claim

A. Significant scientific agreement exists to support the proposed claim

There is significant scientific agreement among experts who study the field of cognitive dysfunction and dementia that phosphatidylserine is an effective modifier of cognitive decline and reduces the risk of dementia.[3] See Exh. 1 at 10. The scientific literature shows that (1) a reduced ability to perform complex executive functions through effortful or controlled mental processing ("cognitive decline") is not a mandatory component of human aging; (2) evidence of cognitive decline reflects neuropathological changes in hippocampal and cerebral functioning; (3) in the absence of symptoms of dementia, the progression of cognitive decline to dementia is not universal; (4) an acceleration of cognitive decline is required in order for declining function to progress to dementia; (5) cognitive decline in the absence of symptoms of dementia represents a modifiable risk factor for later development of dementia; and (6) oral phosphatidylserine supplementation is an effective modifier of cognitive decline and reduces the risk for dementia. Id.

A number of pathophysiologic processes contribute to cognitive decline: 1) decreased cholinergic function; 2) altered neuronal membrane lipid composition; 3) cerebral atrophy; 4) white matter lesions, also known as leukoaraiosis; 5) hypoperfusion; 6) cerebrovascular disease; 7) hypertension; and 8) oxidative stress and failure of neuroprotection. Id. at 1-4. The presence of mild cognitive decline is not predictive of later dementia. Id. at 4. Studies have shown that mild cognitive decline in the elderly does not always lead inevitably to dementia. Id. Studies

[3] The summary must establish that, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), there is significant scientific agreement among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence. 21 C.F.R. § 101.70(f)(B).

suggest that cognitive decline in the absence of dementia typically accompanies aging and becomes "converted" to dementia only after small pathological changes in the brain reach a certain threshold. Id. Cognitive decline preceding dementia is characterized by accelerated deficits in effortful processing with little or no decline in automatic processing. Id. The best predictors of future dementia or later development of Alzheimer's disease in asymptomatic individuals without signs of dementia are declining performance on tests of short-term memory, particularly verbal memory, and decreasing ability to focus attention on attention-demanding tasks. Id.

Phosphatidylserine is incorporated into neuronal cell membranes, influencing the metabolism of the neurotransmitters acetylcholine, norephinephrine, serotonin and dopamine. Id. at 6. Phosphatidylserine must be present in neuronal cell membranes for the fusion of intraneuronal secretory granules with presynaptic membranes and the subsequent release of neurotransmitter molecules into the synaptic cleft and for proper postsynaptic neurotransmitter-receptor interactions. Id.

In animal studies phosphatidylserine has been shown to increase intercellular communication by increasing the fluidity of cell membranes, to eliminate the typical age-dependence decreases in stimulus-evoked acetylcholine release, to eliminate the cholinergic and cognitive problem-solving functions, and to stimulate enhanced performance on tasks that test learning ability and short term memory. Id. at 6. In those studies supplemental phosphatidylserine was shown to be rapidly incorporated into neuronal cell membranes, to increase cell membrane-associated ATPase activity, to increase intraneuronal synthesis of actylcholine and dopamine in the cerebral cortex, to increase cholinergic neurotransmission and signal transduction, to decelerate the rate of loss of dendritic connections in the hippocampus, to

attenuate the rate of loss of nerve growth factors receptors in the hippocampus, to arrest atrophy of cholinergic cells in the basal forebrain, and to reduce the frequency of the normal rodent age-associated episodes of erratic electroencephalographic patterns. Id.

B. Scientific evidence demonstrates the public health benefits of phosphatidylserine

Both open-label trials and double-blind placebo-controlled randomized human clinical trials have shown the effectiveness of oral phosphatidylserine supplementation on the public health problems of cognitive decline and dementia. Exh. 1 at 7-9. In open label trials for 60 days and 90 days respectively at 100 mg three times a day elderly subjects with mild degrees of decline in cognitive function responded with significant improvements in test of verbal learning, verbal recall, verbal fluency, visual learning, attention, communication skill, initiative, socialization and self-sufficiency. Id. at 7. In a study of elderly adults with more severe degrees of cognitive impairment (moderate levels) following two months of oral supplementation with phosphatidylserine at the same dosage, subjects showed significant improvements in verbal learning, verbal recall, attention span and ability to concentrate, vigilance, initiation, socialization, and self-sufficiency. Id. Those findings were repeated in double-blind placebo-controlled randomized clinical trials. Id. Moreover, in a longer study, six months, of elderly adults with moderately severe cognitive impairment supplemented with oral phosphatidylserine, subjects showed significantly greater improvements in verbal recall, initiation, withdrawal, apathy and overall cognitive functioning. Id. Long-term memory and ability to perform the activities of daily living were improved significantly. Id. Finally, patients with signs of chronic depression have responded well to phosphatidylserine supplementation. Id.

Phosphatidylserine has been tested on subjects with dementia and those at risk of dementia (with mild degrees of accelerated cognitive deterioration). Id. at 8. Both groups have

shown positive results. Id. In nondemented elderly patients with mild degrees of accelerated cognitive deterioration, phosphatidylserine supplementation improved performance of executive functions. Id. Electroencephalographic evidence showed normalization of some brain functions. Id. Both improvements persisted for the 16 weeks of follow-up after discontinuation of supplementation. Id.

In a study of subjects with more severe memory loss and cognitive decline six weeks of daily supplementation with phosphatidylserine stabilized cognitive function, improving recall, long-term memory, pattern recognition and performance of daily life activities. Id. Discontinuation of supplementation caused resumption of pre-supplementation rates of cognitive deterioration. Id. Thus, substantial scientific evidence shows that phosphatidylserine is a significant risk modulator of of cognitive decline and dementia. Moreover, there is significant scientific agreement among experts qualified by scientific training and experience to evaluate such claims that the proposed claims concerning the relationship of phosphatidylserine to the risk of cognitive dysfunction and dementia are supported by the evidence.

C. Scientific Summary Issues

FDA requests that health petitioners address the following questions in their petitions:

(1) Is there an optimum level of phosphatidylserine to be consumed beyond which no benefit would be expected?

Clinical trials have tested phosphatidylserine's effectiveness with doses as high as 500 mg per day. Exh. 1 at 8. There is no evidence of an optimum level of phosphatidylserine to be consumed beyond which no benefit is expected. Moreover, there are no reports of overdosage. Exh. 2 at 355.

(2) Is there any level at which an adverse effect from the substance or from foods containing the substance occurs for any segment of the population?

There is no level identified at which adverse events occur for any segment of the population. See Exh. 1 at 9. There is an absence of reports of adverse reactions in the published scientific literature and the safety of oral supplementation with phosphatidylserine has been documented in detail by several investigators. Id. The PDR for Nutritional Supplements reports occasional gastrointestinal side effects, such as nausea and indigestion, but there is no evidence of causality showing that those effects were the result of supplementation with phosphatidylserine. Exh. 2 at 355.

(3) Are there certain populations that must receive special consideration?

The PDR for Nutritional Supplements cautions that phosphatidylserine should be avoided by children, pregnant women and nursing mothers. Id. at 355. It also states that persons with antiphospholipid-antibody syndrome should exercise caution in the use of phosphatidylserine and only take it under medical supervision and monitoring. Id.

(4) What other nutritional or health factors (both positive and negative) are important to consider when consuming the substance?

There are no reported drug, nutritional supplement, food or herb interactions with phosphatidylserine. Id. All applicable nutritional and health factors to be considered when consuming phosphatidylserine have been discussed above.

D. Potential effect of the use of the proposed claim on food consumption, including significant alterations in eating habits and corresponding changes in nutrient intakes.

The proposed claims concerning the relationship between oral supplementation with phosphatidylserine and the risk of cognitive dysfunction and dementia may increase the use of

oral phosphatidylserine supplementation among the general population, including populations more at risk of cognitive decline and dementia. The Petitioner does not believe that the proposed claim will have an effect on food consumption or eating habits. The only change in nutrient intake resulting from the proposed claims would be for those who choose to supplement their diet with phosphatidylserine.

D. Prevalence of the disease or health-related condition in the U.S. population and the relevance of the claim in the context of the total daily diet.

As discussed above, the proposed health claim responds to a major public health concern in the United States: cognitive failure among persons of all ages, but more particularly for persons over 65 years of age. 21 C.F.R. § 101.75(b). An estimated 4 to 5 million Americans (about 2% of all ages and 15% of those age 65 or older) have some form and degree of cognitive dysfunction. Merck Manual of Diagnosis and Therapy, Section 14 Neurologic Disorders, Chapter 171 Delirium and Dementia, (2002). In 1990 the U.S. Congressional Office of Technology Assessment estimated that 1.8 million Americans have severe dementia and another 1.5 million Americans have mild to moderate dementia. Exh. 5. The Alzheimer's Association estimates that of those persons with dementia, 4 million have Alzheimer's disease. Exh. 6. By the year 2040 the Alzheimer's Association estimates that the Alzheimer's disease population may exceed 6 million. It is believed that nearly half of all people age 85 and older have some form of dementia. Id. Thus, phosphatidylserine offers a safe, inexpensive, readily accessible means for reducing the risk of cognitive dysfunction and dementia population wide.

IV. Analytical Method

The amount of phosphatidylserine contained in a dietary supplement that may be a candidate for bearing the health claims can be ascertained by high pressure liquid chromotography (HPLC) according to method AM 101 of the International Lecithin and Phospholipid Society. See Attachment 3. The assay method described in Attachment 3 is applicable to finished products.

V. Proposed Model Claims

Petitioner proposes the following model claims for phosphatidylserine:

- **The consumption of phosphatidylserine may reduce the risk of cognitive dysfunction in the elderly.**
- **The consumption of phosphatidylserine may reduce the risk of dementia in the elderly.**

Multiple studies have shown that oral supplementation with phosphatidylserine significantly reduces the risk of cognitive deterioration in persons with both mild and moderate cognitive dysfunction, in persons with pre-dementia accelerated decline, and in persons with more severe cognitive decline. Moreover, clinical trials have proven its safety for the general population.

VI. Attachments

Attached are copies of the scientific studies and other information referenced in, and constituting the basis for, this Petition. To the best of the Petitioner's knowledge, all non-clinical studies relied upon were conducted in compliance with the good laboratory practices regulations set forth in 21 CFR Part 58, and all clinical or other human investigations relied upon were either conducted in accordance with the requirements for institutional review set forth at 21 C.F.R. Part 56 or were not subject to such requirements in accordance with 21 C.F.R. § 56.104 or 56.105,

and were conducted in conformance with the requirements for informed consent set forth in 21 C.F.R. § 50 et seq. See generally, 21 C.F.R. § 101.7 (c)-(d).

VII. Environmental Impact

The requested health claim approval contained in this petition is categorically excluded from the environmental impact statement under 21 C.F.R. § 25.24.

VIII. Conclusion and Certification

For the foregoing reasons, the Petitioner requests that the FDA approve the proposed health claims. The Petitioner looks forward to working with the FDA in promulgating a regulation authorizing the use of dietary supplement health claims concerning the association between phosphatidylserine and cognitive dysfunction and dementia.

Any questions concerning this Petition may be directed to Jonathan W. Emord, Esq., Emord & Associates, P.C., 5282 Lyngate Court, Burke, VA, (202) 466-6937.

The undersigned certify on behalf of the Petitioner that to the best of their knowledge and belief, the Petition includes all information and views on which the Petitioner relies and is a representative and balanced submission that includes unfavorable information as well as favorable information known by the Petitioner to be pertinent to evaluation of the proposed health claims.

Sincerely,

KYL SMITH, D.C.

By: _____

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