DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD

MAY 13 2003

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Jonathan W. Emord
Andrea G. Ferrenz
Emord and Associates, P.C.
5282 Lyngate Court
Burke, Virginia 22015

RE: Health Claim Petition - Phosphatidylserine and Cognitive Dysfunction; Phosphatidylserine and Dementia

Dear Mr. Emord and Ms. Ferrenz:

This letter responds to your health claim petition submitted on April 19, 2002, on behalf of Doctor Kyl Smith, requesting the Food and Drug Administration (FDA or the agency) to authorize two health claims concerning the relationship between the consumption of phosphatidylserine as a dietary supplement and dementia and the relationship between the consumption of phosphatidylserine as a dietary supplement and cognitive dysfunction. Specifically, your petition requests that FDA authorize the following claims: 1) consumption of phosphatidylserine may reduce the risk of cognitive dysfunction in the elderly, and 2) consumption of phosphatidylserine may reduce the risk of dementia in the elderly. After mutual agreement to extend the 100-day deadline, FDA filed the petition for comprehensive review on September 13, 2002, in accordance with section 403(r)(4)(A)(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 343(r)(4)(A)(i)).

Under 21 CFR 101.70(j)(3), the deadline for FDA action on your petition was December 12, 2002, 90 days after it was filed for comprehensive review. By mutual agreement, the deadline was extended three times. The final agreed-upon deadline was February 24, 2003.

On January 28, the agency sent you a letter explaining its concerns about each of the two referenced health claims set out above. We discussed these concerns with you and your client at a February 3 meeting. In a letter sent to you on February 11, the agency offered two disclaimers (one for each claim) and explained the circumstances under which it would consider the exercise of enforcement discretion for the proposed claims, if accompanied by an agreed upon disclaimer. The two disclaimers offered in FDA's letter were identical except for the name of the disease (dementia or cognitive dysfunction). On February 13, you sent us an electronic letter suggesting alternative disclaimer language acceptable to your client. On February 21, the agency sent to you an electronic letter amending our offer of a disclaimer for the proposed claims. After negotiations about the wording of the disclaimers, your client agreed to the terms proposed by FDA, as modified during the negotiations. On February 24, FDA issued a letter memorializing the agreement and stating its intention to issue within 60 days its formal decision on the phosphatidylserine health claim petition. We regret the delay in issuing that decision.

02P-0413

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After reviewing the scientific evidence in your petition and other evidence relevant to your proposed claims, FDA evaluated the claims under the "significant scientific agreement" standard. FDA's current regulations, which mirror the statutory language in 21 U.S.C. 343(r)(3)(B)(i), provide that the agency may issue a regulation authorizing a health claim only "when it determines, 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), that 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 CFR 101.14(c)). For reasons set forth below, your petition does not meet the "significant scientific agreement" standard.

FDA next considered whether it would be appropriate to consider the exercise of enforcement discretion for qualified claims about the substance-disease relationship consistent with the agency's approach to evaluating proposed health claims for use on dietary supplements when the significant scientific agreement standard is not met. This letter outlines FDA's rationale for its determination that the evidence supporting your proposed health claims for phosphatidylserine does not meet the significant scientific agreement standard, the agency's rationale for why the evidence is appropriate for consideration of qualified health claims for phosphatidylserine, and the conditions under which the agency intends to consider the exercise of its enforcement discretion for certain qualified health claims in the labeling of phosphatidylserine dietary supplements.

I. Safety Review

Under 21 CFR 101.14(b)(3)(ii), the proponent of a health claim must demonstrate to FDA's satisfaction that the use of a substance at levels necessary to justify a claim is safe and lawful under applicable food safety provisions. For dietary supplements, the applicable safety provisions require, among other things, that the dietary ingredient not present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling or, if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use (section 402(f)(1)(A) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 342(f)(1)(A)). Further, a dietary supplement must not contain a poisonous or deleterious substance which may render the supplement injurious to health under the conditions of use recommended or suggested in the labeling (21 U.S.C. 342(f)(1)(D)).

Phosphatidylserine is a phospholipid that is a structural component of biological membranes of plants, animals and other life forms. The petition identifies two sources of phosphatidylserine: 1) bovine brain cortex (BC-PS), and 2) soy lecithin (S-PS). The petition provided evidence that

phosphatidylserine is safe and lawful. This evidence is derived from human studies, and the petition also cites the absence of reports of adverse reactions in the published literature. However, the petition noted that the "safety of phosphatidylserine obtained from animal sources has come under criticism" because of the risk of virus transmission (Scientific Report of Dr. Michael Glade, Attachment 1 to Petition, at 9).[1]

FDA concludes that the use of phosphatidylserine as a dietary supplement is safe and lawful under 21 C.F.R. § 101.14 provided that bovine-derived sources, if used, are not derived from bovine tissues from cattle born, raised, or slaughtered in any country where BSE exists.[2]

II. Scientific Evaluation

FDA reviewed the scientific evidence from your petition and other publicly available sources to evaluate the potential benefits of phosphatidylserine. FDA also reviewed the literature for generally recognized definitions and measures related to the evaluation of dementia and cognitive dysfunction that are the focus of your proposed health claims. FDA focused its review of the evidence for the relationships between phosphatidylserine and reduction of risk of cognitive dysfunction and dementia on primary reports of human experimental data.

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[1] FDA concern about the need for vigilance in the documentation and handling of bovine-derived ingredients from countries with cattle infected with bovine spongiform encephalopathies (BSE) is a matter of record (See FDA Action Plan April 24, 2001. http://www.fda.gov/oc/oca/roundtable/bse/fda_actionplan.html). The group of human and animal diseases known as transmissible spongiform encephalopathies (TSEs) is characterized by a sponge-like appearance of the brain and is associated with deposits in the brain of unique proteins called prions. The prions can be transmitted from one host to another, not only between members of a single species, but also from one species to another. In the mid-1980s, a new TSE, bovine spongiform encephalopathy (BSE), was first described in cattle in the United Kingdom. Humans are also susceptible to TSEs, one form of which is Creutzfeldt-Jakob disease (CJD). In 1996, a new variant of CJD (vCJD) was described in patients in the United Kingdom. Epidemiological data implicate the consumption of beef products contaminated with the agent of BSE as the probable cause of vCJD in humans. Unfortunately, there is no sensitive, specific pre-mortem diagnostic test in either humans or animals. Diagnosis is confirmed only by post-mortem examination of brain tissue. At present, animal and human TSEs have no treatments or preventative vaccines. All are invariably fatal. Routine materials and processes that destroy traditional human and animal pathogens do not appear to destroy prions, and no established methods can reliably decontaminate or sterilize articles contaminated with prions. For all these reasons, FDA recommends that firms that manufacture or import dietary supplements or dietary ingredients containing specific bovine tissues, including extracts or substances derived from such tissues, take all necessary steps to ensure that such ingredients do not come from cattle born, raised, or slaughtered in countries where BSE exists. (See letter from FDA to Manufacturers and Importers of Dietary Supplements and Dietary Supplement Ingredients, November 14, 2000, or visit http://www.cfsan.fda.gov/~dms/dspltr05.html).

[2] A list of countries where BSE is known to exist is maintained by the U.S. Department of Agriculture and codified in Title 9, Code of Federal Regulations, Part 94.18.

A. Substance

In your petition, you noted two sources of phosphatidylserine: bovine brain cortex and soy lecithin (Petition at page 4). Your petition also states that the "petitioner derives phosphatidylserine from soy lecithin" (Petition at page 4). FDA evaluated whether, for purposes of the proposed health claims, BC-PS and S-PS are the same substance or are different substances because of differences in their overall composition. Chemically, the phosphatidylserine molecule consists of a glycerol-phosphate backbone, serine, and two fatty acids. Information included in your petition showed that the fatty acid composition of the bovine and soy phosphatidylserine molecules differ (PDR® for Nutritional Supplements, Attachment 2 to Petition, at 354). For example, the phosphatidylserine molecule from soy lecithin contains mainly polyunsaturated acids, while the phosphatidylserine molecule from bovine brain cortex contains mainly saturated and monounsaturated fatty acids and long-chain polyunsaturated fatty acids (e.g., docasahexaenoic acid). Additionally, the relative proportions of fatty acids from the omega-3 and omega-6 series[3] vary in the phosphatidylserine molecules from bovine and soy products. For example, the phosphatidylserine molecule from soy has 7% alpha-linolenic acid (omega-3) and 47% linoleic acid (omega-6), while the phosphatidylserine molecule derived from bovine brain cortex has 8% docasahexaenoic acid (omega-3) and 2% arachidonic acid (omega-6) (see Phosphatidylserine (Sodium Salt), Attachment 2). Different fatty acids differ in their metabolism, biological activity, and potency (Food and Nutrition Board, 2002). Because the phosphatidylserine molecules from bovine brain cortex and soy lecithin differ significantly in their fatty acid composition, they may not be the same substance.

In addition to the differences in the fatty acid composition of the phosphatidylserine molecules from bovine brain cortex and soy lecithin, there are also differences in the non-phosphatidylserine components of these ingredient sources. These non-phosphatidylserine components are primarily other phospholipids and free fatty acids. BC-PS is prepared by extracting and separating the phospholipid classes from brain material. The final extract will contain up to 8% of its weight as non-phosphatidylserine components (Folch, 1948). S-PS is prepared from soy lecithin that has been treated with serine and an enzyme to convert the native phospholipids in soy lecithin to phosphatidylserine (Sakai et al., 1996). The resulting phosphatidylserine content depends on the composition of starting soy lecithin product and processing conditions such as enzyme activity. For S-PS from one manufacturer, the non-phosphatidylserine components can range from 15% to 80% (Degussa, 2002). The non-phosphatidylserine components are free fatty acids and phospholipids which, as noted above, may have biological activity independent of phosphatidylserine. These other components outside the phosphatidylserine molecule of the soy sources of phosphatidylserine differ incomposition and amounts, and perhaps also in biological activity, from the non-

[3] Omega-3 fatty acids include α-linolenic acid (18:3), eicosapentaenoic acid, (20:5) docosapentaenoic acid (22:5), and docosahexaenoic acid (22:6). Omega-6 fatty acids include linoleic acid (18:2), γ-linolenic acid (18:3), dihomo-γ-linolenic acid (20:3), arachidonic acid (20:4), adrenic acid (22:4) and docosapentaenoic acid (22:5). (Food and Nutrition Board, 2002).

phosphatidylserine components in BC-PS. For products of high purity (i.e., relatively low amounts of non-phosphatidylserine components), uncertainties as to any biological effects of the non-phosphatidylserine components would be minimized .

For the reasons summarized above, FDA considers that bovine brain cortex- and soy lecithin-sources of phosphatidylserine may be different substances and may, therefore, have different biological activities. 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.

B. Dementia and Cognitive Dysfunction as a Disease or Health-related Condition

To define dementia and cognitive dysfunction, the subjects of the proposed health claims, FDA looked for generally accepted definitions of these two conditions. The essential feature of dementia is the 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.[4] 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. A diagnosis of dementia should not be made if the cognitive deficits occur exclusively during the course of "delirium" (American Psychiatric Association, 2000). Therefore, in effect, the term "dementia" indicates the presence of cognitive decline/deterioration that is sufficient to impair occupational or social functioning (Mani, 2002).

FDA did not find any standard definition of "cognitive dysfunction." Therefore, FDA considered it to mean a disturbance of "cognitive function." "Cognitive" is defined as "Pertaining to the mental processes of comprehension, judgment, reasoning, as contrasted with emotional and volitional processes" (Mosby's Medical, Nursing and Allied Health Dictionary, 1994). "Cognitive function" is defined as "An intellectual process by which one becomes aware of, perceives, or comprehends ideas. It involves all aspects of perception, thinking, reasoning, and remembering" (Mosby's Medical, Nursing and Allied Health Dictionary, 1994). 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) (Mani, 2002). "Cognitive dysfunction" may be considered to mean a disturbance of cognitive function.

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[4] 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 centers; Apraxia is defined as 1) loss of previously acquired ability to perform intricate skilled acts, and 2) mind blindness; a condition in which there is a lack of a proper apprehension of the true nature of things, leading to the performance of preposterous acts; 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, 1957); Executive functioning is defined as planning, prioritizing, sequencing, self-monitoring, self-correcting, inhibiting, initiating, controlling or altering behavior (About Brain Injury, 2003.)

FDA considered dementia and cognitive dysfunction together in evaluating the scientific evidence for the relationship with phosphatidylserine because the possible causes of dementia are likely the same as those for cognitive decline and deterioration (Mani, 2002).

C. Phosphatidylserine and Reduced Risk of Dementia or Cognitive Dysfunction

FDA focused its review of the evidence for the relationships between phosphatidylserine and reduced risk of dementia and cognitive dysfunction on primary reports of human experimental data. You submitted 15 intervention studies that evaluated the effects of phosphatidylserine on dementia or impaired cognitive function (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., 1987; 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). In each of these 16 studies, the individuals enrolled were diagnosed with some form of dementia or cognitive dysfunction. The purpose of these studies was to examine the effect of phosphatidylserine on mitigating (reducing) the symptoms of various levels of severity of dementia and cognitive dysfunction in a diseased population, not on reducing the risk of dementia or cognitive dysfunction in the general population. Thus, none of the studies directly evaluated the relationship that is the subject of the claims, phosphatidylserine and reduced risk of dementia or cognitive dysfunction.

Most of the studies identified BC-PS as their test product (Crook et al., 1992; Amaducci and the SMID Group, 1998; Delwaide et al., 1986; Engel et al., 1992; Palmieri et al., 1987; Villardita et al., 1987; Crook et al., 1991; Cenachi et al., 1993; Caffarra and Santamaria, 1987; Allegro et al., 1987; Sinforiani et al., 1987; and Granata and DiMichele, 1987). Two studies used a soy-derived of phosphatidylserine (Jorissen et al., 2001; Schreiber et al., 2000), and two did not identify the source of the phosphatidylserine (Heiss et al., 1993; Heiss et al., 1994). Only one of the studies (Jorissen et al, 2001) provided any information on the overall composition or purity of the test or placebo products.

Of the studies, five 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). FDA did not include these studies in its evaluation of the relationship between phosphatidylserine and dementia or cognitive dysfunction. In open-label studies, both the investigator and subjects know what substance is being tested and know that subjects are receiving the test substance. Placebo effects alone may be responsible for any apparent changes in outcome measures. Open label trials are uncontrolled, as they involve only a treatment group. Without a concurrent control group that receives a placebo and is evaluated according to the same measures as the

treatment group, it is not possible to determine whether effects on outcome measures are due to the test substance or to other extraneous factors. For example, because subjects took tests of cognitive function several times throughout the course of these studies, the repeated measures and increased familiarity with the testing protocols and content alone may have resulted in improved scores regardless of whether the subjects were consuming S-PS.

Randomization (assigning subjects randomly to the control and test groups) is an important study design feature because it ensures that extraneous factors that might influence the results are equally divided between control and test groups (Spilker, 1991). For example, the baseline cognitive abilities of study participants might vary greatly. Without randomization, the test and control groups might differ in their baseline cognitive abilities. Unequal baseline differences in cognitive abilities would cause test results to inappropriately appear to favor one protocol over another protocol. In an open-label study, there is no randomization because there is no concurrent control group. Thus, there is no way to control for extraneous variables independent of the test substance that might be affecting results. Studies using controlled, and blinded, as well as randomized procedures provide the most compelling evidence to minimize and attempt to eliminate most, if not all biases (Spilker, 1991). An open-label study is flawed in that none of these types of controls is included. Thus, open-label studies are subject to serious biases and false results (Spilker, 1991), and cannot provide credible evidence for relating intakes of phosphatidylserine to reduced risk of dementia or cognitive dysfunction.

Additionally, one study was a cross-over design (Engel et al., 1992). FDA also did not include this study in its evaluation because cross-over designs are not considered appropriate for evaluating the relationship between phosphatidylserine and dementia or cognitive dysfunction (Mani, 2002). Dementia and cognitive dysfunction are characterized by progressive declines in status. Cross-over studies, to be valid, must be able to have the baseline levels of participants be equal at the beginning of each phase (Spilker, 1991). In a cross-over study, half of the subjects start with the treatment phase followed by the control phase; the other half of the subjects start with the control phase followed by the treatment phase. If the dementia is progressive, then the group that starts with the placebo phase will be in worse shape at the beginning of their treatment phase than they were at the beginning of the control phase. Thus, the basic premise of a cross-over study, i.e., that the baseline levels of subjects at the beginning of both the placebo and treatment phases are equal, cannot be met for progressive diseases such as dementia or cognitive dysfunction. Additionally, study results may be uninterpretable if the effects of a test product from the treatment phase carry over to the control phase. Indeed, the authors of this study (Engel et al., 1992) conclude that, "In retrospect, the requirements of the cross-over design were not fulfilled in this study."

Of the 10 intervention studies that formed the basis of FDA's evaluation, all were seriously flawed or limited in their reliability in one or more ways. Therefore, generalization of the results from these studies to the proposed health claims involved numerous uncertainties. For example, as discussed above, none of these studies directly evaluated the risk reduction relationship that is the subject of the proposed health claims. There is considerable uncertainty about whether the

effects of phosphatidylserine in the general population for which risk reduction is claimed are similar to the effects of phosphatidylserine in the diseased populations that served as the participants for all of the available intervention studies. Only one of the studies (Jorissen et al., 2001) provided data on the composition of the phosphatidylserine-containing product used.

Thus, generalizability of results for products of unknown or different composition to marketed products is uncertain. Several of the intervention studies had very small sample sizes, making generalizability of results questionable (e.g., n=10, Heiss et al., 1993; n=17-18, Heiss et al., 1994; n= 21, Delwaide et al., 1986). Each of the 10 studies conducted analyses on "completers" rather than on an "intent to treat" basis, thus potentially causing bias in results if the original randomization assignments were altered by the drop-outs. This is particularly problematic in those studies where the number of drop-outs was relatively large and somewhat uneven across treatment and placebo groups (e.g., Cenachi et al., 1993), or when information on numbers of completers and the data set used for analysis is unclear (e.g., Villardita et al., 1987). Several of the studies used outcome measures in which it was unclear whether the measures represented standardized, validated, and generally accepted instruments (Crook et al, 1992; Crook et al., 1991; Jorissen et al., 2001). Without such instruments, interpretation of results is questionable since it is not possible to predict how changes on the instrument will relate to changes in disease status. Most studies made multiple comparisons among measured variables in their analysis steps but failed to apply appropriate statistical corrections to reduce the possibility of finding statistically significant relationships by chance alone (Crook et al., 1992; Amaducci and the SMID Group, 1988; Delwaide et al., 1986; Heiss et al., 1993; Heiss et al., 1994; Palmieri et al., 1987; Villardita et al., 1987; Crook et al., 1991; Cenacchi et al., 1993; and Jorissen et al., 2001). Thus, nominally statistically significant results in an analysis uncorrected for multiple comparisons could become non-significant when the appropriate statistical procedures are applied. Several studies conducted subgroup analyses that appeared to show stronger relationships between phosphatidylserine and outcome measures than were observed for the overall group results (Crook et al, 1992; Crook et al., 1991). However, these subgroup analyses are of questionable validity, given that randomization was not based on subgroup category (Spilker, 1991). Thus, interpretation of results is unclear. Finally, several studies included evaluation of outcome measures that were not relevant to the proposed health claims (EEG and cerebral metabolic rate for glucose in Heiss et al, 1993; Heiss et al., 1994). These irrelevant outcome measures were not considered in FDA's evaluation.

Of the 10 studies that formed the basis of FDA's evaluation, three found no statistically significant effect ($p<0.05$) of phosphatidylserine on outcome measures of dementia or cognitive dysfunction (Amaducci and the SMID group, 1988; Heiss et al., 1993; and Jorissen et al., 2001). Additionally, although the Heiss et al. (1994) study observed nominally significant relationships for several measures at weeks 8 and 16, these effects were apparently transient or not real, as they were not sustained beyond 16 weeks. Thus four of the 10 studies showed no effect of phosphatidylserine on any outcome measures of dementia or cognitive dysfunction when followed for the full duration of the study.

The six remaining studies found no statistically significant relationship for many of the outcome measures evaluated but did find that a relatively small number of the evaluated measures were nominally significant (Crook et al., 1992; Delwaide et al., 1986; Palmieri et al., 1987; Villardita et al., 1987; Crook et al., 1991; and Cenacchi et al., 1993). As noted above, however, the analysis of results in these studies involved numerous comparisons. When making multiple comparisons such as this, it is necessary to use statistical procedures to "correct" for the probability that multiple comparisons will, by chance alone, result in some relationships appearing to be statistically significant. Since these studies did not make the appropriate corrections for multiple comparison effects, the validity of nominally statistically significant results is uncertain. For example, given the information reported on statistical significance (i.e., "p values" at or near the cut-off level of $p<0.05$), it is uncertain whether the nominally statistically significant results reported in the Delwaide et al., 1986, study would remain statistically significant if appropriate statistical procedures were applied.

Thus, only five of the 10 intervention studies included in the FDA evaluation might be considered to show any evidence of effectiveness (Palmieri et al., 1987; Villardita et al., 1987; and Cenachi et al., 1993; Crook et al., 1992; and Crook et al., 1991). In all cases, the effects that might remain statistically significant after statistical corrections for multiple comparisons were seen in only one or a few outcome measures. In the two Crook et al. studies (1991 and 1992), information on the statistical significance (i.e., "p values") of individual variables is missing, making it difficult to evaluate whether the few nominally statistically significant findings would remain significant with appropriate statistical procedures. None of these studies showed statistically significant effects on multiple endpoints, across the broad spectrum of cognitive functions and impairment of daily living activities that together characterize dementia and cognitive dysfunction. Additionally, it is not clear what data set was used for analysis of the Villardita et al. (1987) or Palmieri et al. (1987) reports, making it difficult to interpret results. The Cenacchi et al. (1993) analysis was based on completers only, despite the fact that the study had a significant number of drop-outs during the course of the study. It was unclear whether the instruments used to assess outcome measures in the Crook et al. (1992 and 1991) studies represented standardized, validated, and generally accepted instruments.

In summary, the scientific evidence available consists of mitigation studies. There is considerable uncertainty about whether data on mitigation effects apply to the risk reduction relationships that are the subject of your proposed claims for phosphatidylserine. Moreover, all of the studies had serious flaws or limitations that warrant caution in applying their results to the proposed health claims. In the few cases in which nominally statistically significant relationships were reported, the relationships were limited to a few selective cognitive functions and did not demonstrate an effect on the range of cognitive and functional components that are characteristic of dementia and cognitive dysfunction. Thus, generalization of the limited results from these studies to the proposed health claims is fraught with considerable uncertainty.

III. Agency's Consideration of Significant Scientific Agreement

FDA reviewed information about the composition of the two ingredient sources of phosphatidylserine (i.e., bovine brain cortex and soy), definitions of the diseases of interest (i.e., dementia and cognitive dysfunction), and the intervention trials that evaluated the relationship of phosphatidylserine to dementia and cognitive dysfunction. The compositional information identified differences between BC-PS and the S-PS products, suggesting that BC-PS and S-PS may be different substances. Thus, there is considerable uncertainty about whether their effects on dementia and cognitive dysfunction are similar or different. The only intervention trial in which S-PS was the test product showed no effect on the disease outcome. As noted above, there is also considerable uncertainty as to whether results from trials done with BC-PS are relevant to products containing S-PS as the source of the phosphatidylserine.

The definitions of cognitive dysfunction and dementia describe an integrated relationship among various disturbances in cognitive functions and impairments in daily activities that together characterize these disease conditions. Three intervention studies showed very limited findings of statistical significance in a few selected measures of cognitive functioning, but not in the majority of outcome measures or concurrently with impairments in daily activities.

Finally, none of the intervention studies directly evaluated the proposed health claims, i.e., the effect of phosphatidylserine in reducing the risk of dementia or cognitive dysfunction in the general population. All the studies were mitigation studies in persons already diagnosed with dementia or cognitive dysfunction. There is considerable uncertainty about whether phosphatidylserine will act similarly in the general population relative to disease risk reduction as it does in diseased populations where mitigation of existing symptoms is the outcome of interest. Moreover, all the intervention studies were flawed in some way, thus limiting the usefulness of any results that they may have reported.

Therefore, based on its evaluation of the totality of the publicly available scientific evidence, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between phosphatidylserine and reduced risk of dementia or cognitive dysfunction.

IV. Agency's Consideration of a Qualified Health Claim

For claims that do not meet the significant scientific agreement standard, FDA considers whether to exercise enforcement discretion for qualified health claims about the relationship between the substance and the disease. After reviewing the scientific evidence in your petition and other relevant scientific evidence, FDA concludes that most of the evidence does not support a relationship between phosphatidylserine and reduced risk of dementia or cognitive dysfunction, and that the evidence that does support such a relationship is very limited and preliminary. This latter conclusion is based on the fact that in five of the 10 intervention trials, a very small number of outcome measures, out of the large number of measured outcomes, indicated statistically

significant relationships between intakes of phosphatidylserine and measures of cognitive function relating to mitigation of symptoms of dementia and cognitive dysfunction. Therefore, although most of the evidence does not support an effect of phosphatidylserine intake on reduced risk of dementia and cognitive dysfunction, a few nominally significant relationships provide a very limited and preliminary basis for suggesting a possible relationship between phosphatidylserine and reduced risk of dementia or cognitive dysfunction, and this evidence provides a basis for qualified claims. Additionally, the uncertainties as to whether results for BC-PS-containing products are relevant to S-PS-containing products will be minimized if manufacturers use S-PS products of high purity, thus assuring phosphatidylserine levels similar to those in BC-PS-containing products.

V. Other Requirements

Phosphatidylserine dietary supplements bearing the qualified claims for which FDA has indicated that it intends to exercise its enforcement discretion must still meet all applicable statutory and regulatory requirements under the Federal Food, Drug, and Cosmetic Act. For example, such supplements must be labeled consistent with 21 CFR §101.36 (b)(3). Dietary supplements also must not pose an unreasonable risk of illness or injury to consumers, contain substances that may render the product injurious to health, or be otherwise adulterated or misbranded.

VI. Conclusions

We have considered the scientific evidence submitted with your petition and, as appropriate, have also considered other pertinent scientific evidence. Our conclusion is that there is not significant scientific agreement that phosphatidylserine may reduce the risk of dementia or cognitive dysfunction in the elderly. However, the science provides very limited and preliminary evidence for qualified health claims about these relationships. Because such claims would be potentially misleading, however, they must be qualified so as not to mislead consumers. Thus, FDA proposed disclaimers to accompany your proposed claims. After a change made during negotiations regarding disclaimer wording, the qualified claims that you agreed to on behalf of your client are:

Dementia claim and disclaimer:

> "Consumption of phosphatidylserine may reduce the risk of dementia in the elderly.
>
> Very limited and preliminary scientific research suggests that phosphatidylserine may reduce the risk of dementia in the elderly. FDA concludes that there is little scientific evidence supporting this claim."

Cognitive dysfunction claim and disclaimer:

> "Consumption of phosphatidylserine may reduce the risk of cognitive dysfunction in the elderly.
>
> Very limited and preliminary scientific research suggests that phosphatidylserine may reduce the risk of cognitive dysfunction in the elderly. FDA concludes that there is little scientific evidence supporting this claim."

FDA intends to consider exercising enforcement discretion for the above qualified claims when: (1) the applicable disclaimer is placed immediately adjacent to and directly beneath your claims, with no intervening material, in the same size, typeface, and contrast as the claim itself; (2) the claim meets the general requirements for health claims in 21 CFR 101.14, except for the requirement that the evidence for the claim meet the significant scientific agreement standard, the requirement that the claim be made in accordance with an authorizing regulation, and the requirement that the claim specify the daily dietary intake necessary to achieve the claimed effect[5]; and (3) if S-PS is used, it is of very high purity.

Please note that scientific information is subject to change. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may later become available that will support significant scientific agreement or that will no longer support the use of a qualified claim. If and when such information becomes available, FDA intends to inform you of this new information and its implications by letter.

Sincerely,

Christine L. Taylor, Ph.D.
Director
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

Attachments:
(#)Reference list

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[5] FDA finds that the provision in § 101.14(d)(2)(vii) stating, "If the claim is about the effects of consuming the substance at other than decreased dietary levels,.... the claim must specify the daily dietary intake necessary to achieve the claimed effect...." does not apply to the qualified claim for phosphatidylserine and reduced risk of dementia or cognitive dysfunction. The scientific evidence for this relationship is very limited and preliminary and does not support the establishment of a level of effect that could serve as the basis for a recommended daily dietary intake level.