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RE: Qualified Health Claim Petition - Xangold® Lutein Esters and Age-Related  
Macular Degeneration and Cataract Formation (Docket No. 2004Q-0180)

Dear Dr. Tarka:

This letter responds to the health claim petition dated March 5, 2004, submitted to the Food and Drug Administration (FDA or the agency) by the Cognis Corporation pursuant to Sections 403(r)(4) and 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §§ 343(r)(4) and 343(r)(5)(D)). You are listed in the petition as the person to whom correspondence should be addressed. The petition requested that the agency authorize a qualified health claim characterizing the relationship between the consumption of Xangold® lutein esters and reduced risk of age-related macular degeneration and cataract formation for use in the labeling of conventional foods and dietary supplements. This petition proposed as a model qualified health claim: "Consumption of 12 mg of Xangold® lutein esters per day may reduce the risk of age-related macular degeneration and cataract formation. FDA has determined that the evidence is supportive, but not conclusive, for this claim. This food/dietary supplement provides \_\_\_ mg lutein esters per serving." According to the petition, Xangold® lutein esters comprise 93% lutein diesters (principally dipalmitate) and 7% zeaxanthin diesters.

FDA evaluated the scientific evidence provided with the petition and other evidence related to your requested health claim. The Oregon Health Sciences Evidence-Based Practice Center assisted FDA by doing an independent scientific review.<sup>1</sup>

FDA filed the petition on April 26, 2004 as a qualified health claim petition and posted the petition on the FDA website for a 60-day comment period, consistent with the agency's guidance on procedures for qualified health claims.<sup>2</sup>

The agency received a total of fifteen comments on the petition. Comments were from industry, academia, health professionals, and individual consumers. The comments addressed various issues, including free lutein vs. esterified lutein as the substance of the

<sup>1</sup> The report submitted by Oregon Health Sciences Evidence-Based Practice Center is included in the docket.

<sup>2</sup> "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements" (July 10, 2003). [<http://www.cfsan.fda.gov/~dms/nuttfe.html>]

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claim, using brand names to identify substances that are the subject of health claims, and the addition of zeaxanthin to any permitted lutein claim.

Out of the fifteen comments, there were thirteen comments opposed to the qualified health claim as proposed by the petitioner. The comments were supportive of a qualified health claim regarding lutein and certain eye diseases but considered the subject of the petitioner's proposed claim too restrictive. Most commented that the available evidence for a relationship between lutein and eye diseases involved the unesterified, "free" form of lutein, not the esterified form. The thirteen comments indicated that the subject of any authorized claim should be lutein and/or lutein-containing foods instead of lutein esters. Four of these thirteen comments went further and also opposed the use of a brand name in a qualified health claim. The reasons given for this opposition were that restricting the claim to any one brand name unnecessarily limited the use of a health claim that could be of benefit to the public health and also that use of a brand name would suggest an endorsement by the FDA of a specific company. One of the thirteen comments opposed to the claim also felt that zeaxanthin should be included in any authorized claim for lutein and eye diseases.

Of the remaining two comments, one comment supported the claim as submitted by the petitioner, stating that the petitioner had made a strong case for why the FDA should grant a claim. The other comment had no position for or against a lutein claim but advocated that the agency consider the inclusion of zeaxanthin in the evaluation of any qualified health claim for lutein. FDA considered all fifteen comments in its evaluation of the petition.

This letter sets out the basis for FDA's determination that there is no credible scientific evidence to support qualified health claims about consumption of Xangold® lutein esters (comprising lutein diesters and zeaxanthin diesters), lutein, or zeaxanthin and reduced risk of age-related macular degeneration or cataract formation.

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

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(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 is at risk (21 CFR 101.14(b)(1)). Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease.<sup>3</sup> In a review of a qualified health claim, the agency first identifies the substance and disease or health-related condition that is the subject of the proposed claim and the population to which the claim is targeted.<sup>4</sup> FDA considers the data and information

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<sup>3</sup> See *Whitaker v. Thompson*, 353 F.3d 947, 950-51 (D.C. Cir.) (upholding FDA's interpretation of what constitutes a health claim), *cert. denied*, 125 S. Ct. 310 (2004).

<sup>4</sup> See guidance entitled "Interim Evidence-based Ranking System for Scientific Data," July 10, 2003. [<http://www.cfsan.fda.gov/~dms/hclmgui4.html>]

provided in the petition, in addition to other written data and information available to the agency, to determine whether the data and information could support a relationship between the substance and the disease or health-related condition.<sup>5</sup>

The agency then separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.<sup>6</sup>

In addition to individual reports of human studies, the agency also considers other types of data and information in its review, such as meta-analyses,<sup>7</sup> review articles,<sup>8</sup> and animal and *in vitro* studies. These other types of data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease or health-related condition, or both, but cannot by themselves support a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-analyses, review articles, and similar publications<sup>9</sup> to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship. If additional studies are identified, the agency evaluates them individually.

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes such as digestion, absorption, distribution, and metabolism that affect how humans respond to the consumption of foods and dietary substances (IOM, 2005). Animal and *in vitro* studies can be used to generate hypotheses or to explore a

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<sup>5</sup> For brevity, "disease" will be used as shorthand for "disease or health-related condition" in the rest of the section.

<sup>6</sup> In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (i.e., disease). Intervention studies provide the strongest evidence for an effect. See Guidance entitled "Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements" (December 22, 1999).

[<http://www.cfsan.fda.gov/~dms/ssaguide.html>]

<sup>7</sup> A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

<sup>8</sup> Review articles summarize the findings of individual studies.

<sup>9</sup> Other examples include book chapters, abstracts, letters to the editor, and committee reports.

mechanism of action but cannot adequately support a relationship between the substance and the disease.

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors such as a control group or a statistical analysis means that scientific conclusions cannot be drawn from the study (Spilker et al., 1991, Federal Judicial Center, 2000). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these are eliminated from further review.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance-disease relationship.

Next, FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (e.g., use of a placebo control versus a non-placebo controlled group), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (e.g., selection bias and whether important information about the study subjects--e.g., age, smoker vs. non-smoker--was gathered and reported). For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Moderate or low quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria. Studies that are so deficient that scientific conclusions cannot be drawn from them cannot be used to support the health claim relationship, and these are eliminated from further review.

Finally, FDA evaluates the results of the remaining studies. The agency then rates the strength of the total body of publicly available evidence.<sup>10</sup> The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of the various types of studies and sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S.

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<sup>10</sup> See *supra*, note 4.

population or target subgroup, whether study results supporting the proposed claim have been replicated<sup>11</sup>, and the overall consistency<sup>12</sup> of the total body of evidence.<sup>13</sup> Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and, if so, determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

#### 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, regardless of whether the food is in conventional form or in the form of a dietary supplement (21 CFR 101.14(a)(2)). The petition identifies Xangold® lutein esters as the substance that is the subject of the proposed claim. "Xangold® lutein esters" is the brand name of a mixture of carotenoid xanthophyll esters, specifically esters of lutein (>93%) and esters of zeaxanthin (<7%).

Although the title of the petition and the model claim proposed in the petition refer only to Xangold® lutein esters (a specific mixture of lutein esters and zeaxanthin esters manufactured by the petitioner), the scientific discussion in the petition makes clear that the proposed claim is based on a broader body of evidence encompassing studies of lutein and/or zeaxanthin, in either free or esterified form, and that Xangold® lutein esters are intended as a source of these nutrients. In this instance, it is not necessary for FDA to determine whether lutein and/or zeaxanthin should be considered as subjects of the proposed claim, in addition to Xangold® lutein esters, because including studies of lutein and/or zeaxanthin does not change FDA's ultimate conclusion that the petition should be denied for lack of credible evidence. FDA is under no obligation to go beyond the scope of the claim requested in the petition. Nonetheless, because the majority of the available evidence consists of studies of lutein and/or zeaxanthin rather than studies of Xangold® lutein esters and because so many comments recommended that FDA not limit its consideration to Xangold® lutein esters, the agency has decided to treat lutein and zeaxanthin, in addition to Xangold® lutein esters, as subjects of the proposed claim.

According to the petition, Xangold® lutein esters are intended for use in dietary supplements and as a component of a variety of conventional foods, including baked goods, breakfast cereals, beverages, and dairy products. Lutein and zeaxanthin are used

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<sup>11</sup> Replication of scientific findings is important for evaluating the strength of scientific evidence (An Introduction to Scientific Research, E. Bright Wilson Jr., pages 46-48, Dover Publications, 1990).

<sup>12</sup> Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill A.B. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295-300); See also *Systems to rate the scientific evidence*, Agency for Healthcare Research and Quality [<http://www.ahrq.gov/clinic/epcsums/strengthsum.htm#Contents>], defining "consistency" as "the extent to which similar findings are reported using similar and different study designs."

<sup>13</sup> See *supra*, note 4.

as dietary ingredients in dietary supplements. They also occur naturally as components of a variety of foods, especially leafy green vegetables and yellow-orange fruits and vegetables. Therefore, Xangold® lutein esters, lutein, and zeaxanthin meet the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)).

## **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 has identified age-related macular degeneration (AMD) and cataracts as the diseases or health-related conditions that are the subject of the proposed claim. The National Eye Institute (NEI) of the National Institutes of Health describes AMD and cataracts as the diseases that are the leading causes of visual impairment and blindness in the United States.<sup>14</sup>

There are two types of AMD: “dry” and “wet”. Approximately 85 to 90% of AMD cases are dry AMD. Dry AMD is characterized by deterioration of the retina, which is associated with the formation of small yellow spots (drusen) under the macula.<sup>15</sup> This phenomenon leads to a thinning and drying out of the macula, causing the macula to lose its function and resulting in a gradual loss of vision. Dry AMD can progress to wet AMD when new blood vessels are formed to improve blood supply to oxygen-deprived retinal tissue. The development of new blood vessels results in hemorrhage, swelling and scar tissue.<sup>16</sup>

Dry AMD has three stages: 1) early AMD in which people have several small drusen or a few medium sized drusen, 2) intermediate AMD in which people have either many medium-sized drusen or one or more large drusen, and 3) advanced AMD, which includes drusen and a blurred spot in the center of one’s vision.<sup>17</sup> Age-related maculopathy (ARM), or “early AMD”, includes symptoms associated with dry AMD (Bartlett and Eperjesi, 2003a).

Cataracts are a clouding of the lens in the eye that affects vision.<sup>18</sup> If the lens is cloudy from a cataract, images will appear blurred. A cataract can occur in either or both eyes. Cataracts can form due to the clumping of protein on the lens, coloration of the lens to a brownish shade that can occur with age, or with certain diseases such as diabetes.

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<sup>14</sup> National Eye Institute, Age-Related Eye Disease Study—Results.

[<http://www.nei.nih.gov/amd/background.asp>]

<sup>15</sup> The macula is an oval yellow spot near the center of the retina of the human eye. Light is focused onto the macula, where millions of cells change the light into nerve signals that tell the brain what the eye is seeing.

<sup>16</sup> Age-Related Macular Degeneration: What you should know.

[[http://www.nei.nih.gov/health/maculardegen/armd\\_facts.asp](http://www.nei.nih.gov/health/maculardegen/armd_facts.asp)]

<sup>17</sup> See *supra*, note 16.

<sup>18</sup> Cataract: What You Should Know. [<http://www.nei.nih.gov/health/ataract/webcataract.pdf>]

The agency concludes that AMD and cataracts are diseases and therefore that the petitioner has satisfied the requirement in 21 CFR 101.14(a)(5).

### **C. Safety Review**

Under 21 CFR 101.14(b)(3)(ii), if the substance is to be consumed at other than decreased dietary levels, 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 the claim must be demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Act.

It is not necessary for FDA to make a determination about the safety of Xangold® lutein esters, lutein, or zeaxanthin in this letter because the agency is denying the proposed claims for lack of credible evidence, as discussed in sections II and III.

### **II. The Agency's Consideration of a Qualified Health Claim**

To date, no surrogate endpoints have been recognized for predicting the risk of AMD or cataracts. Moreover, the petition included no data demonstrating that any of the outcomes assessed in the supporting studies are surrogate endpoints for the risk of AMD or cataracts. Therefore, at this time the relationship between the intake of Xangold® lutein esters, lutein or zeaxanthin and reduced risk of AMD or cataracts can only be evaluated by measuring actual incidence of either disease.

A total of 139 publications were provided as evidence to substantiate the substance-disease relationships for this claim (see Docket No. 2004Q-0180)). These publications consisted of 29 review articles; 4 book chapters; 5 government documents (e.g., FDA correspondence and National Eye Institute statement; 2 commentaries; 1 abstract; 8 *in vitro* studies; 3 animal studies; 5 articles on food or nutrient consumption; 2 articles printed in German; 5 articles on lutein bioavailability; 9 articles on biomarkers for AMD or for intake of lutein and/or zeaxanthin; 21 articles on vision, the physiology of AMD or cataracts, or the structure of the eye/retina; 13 articles on risk factors for AMD, cataracts, or macular pigment density; 12 human intervention studies on intake of Xangold® lutein esters, lutein and/or zeaxanthin and AMD or cataracts; and 20 human observational studies on dietary lutein and/or zeaxanthin and AMD or cataracts.

In addition to the studies in the petition, FDA reviewed three additional observational studies obtained through a literature search (Taylor et al., 2002; Valero et al., 2002; Lyle et al., 1999b).

#### **A. Assessment of Review Articles and Abstracts**

Although useful for background information, the review articles and abstract submitted with the petition do not contain sufficient information on the individual studies described and, therefore, FDA could not draw any scientific conclusions from this information. For example, FDA could not determine factors such as the study population characteristics or the composition of the products used (e.g., conventional food, dietary supplement) in the individual studies from the description in the review articles and abstract submitted with the petition. Similarly, the lack of detailed information on studies summarized in the review articles and abstract prevented FDA from determining whether the studies were flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. As a result, the review articles and abstract supplied by the petitioner do not provide information from which scientific conclusions can be drawn regarding the substance-disease relationships claimed by the petitioner.

#### **B. Assessment of Animal and *In Vitro* Studies**

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease, and they can also be used to generate hypotheses or to explore a mechanism of action, but they cannot adequately support a relationship between the substance and the disease in humans. FDA did not consider the animal or *in vitro* studies submitted with the petition as providing any supportive information about the substance - disease relationships that are the subject of the petition because such studies cannot mimic the normal human physiology that may be involved in the risk reduction of AMD or cataracts, nor can the studies mimic the human body's response to the consumption of Xangold® lutein esters, lutein, or zeaxanthin. Therefore, FDA cannot draw any scientific conclusions from the animal or *in vitro* studies regarding the intake of Xangold® lutein esters, lutein, or zeaxanthin and the reduction of risk of AMD or cataracts.

#### **C. Assessment of the Intervention Studies**

There were a total of 12 intervention studies that evaluated the relationship between Xangold® lutein esters, lutein and/or zeaxanthin and AMD or cataracts (Falcini et al., 2003; Dagnelie et al., 2000; Hammond et al., 1997; Johnson et al., 2000; Landrum et al., 1997; Berendschot et al., 2000; Cardinault et al., 2003; Bone et al., 2003; Olmedilla et al., 2001; Olmedilla et al., 2003; Bartlett and Eperjesi, 2003b; Koh et al., 2004). FDA determined that scientific conclusions about the relationship between Xangold® lutein esters, lutein, or zeaxanthin and AMD or cataracts could not be drawn from these 12 studies for the reasons discussed below.

Three studies evaluated subjects who had ARM, AMD or cataracts (Falsini et al., 2003; Olmedilla et al., 2001; Olmedilla et al., 2003). These studies evaluated the treatment

effect of lutein and/or zeaxanthin, rather than their effect on reducing the risk of AMD or cataracts. Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease.<sup>19</sup> These claims involve reducing the risk of AMD or cataracts in people who do not already have these diseases. In evaluating health claim petitions for risk reduction, FDA considers evidence from studies in individuals already diagnosed with the disease only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. Given that such evidence was not available, the agency could not draw any scientific conclusions from these studies.

Eight studies measured macular pigment density, which is not recognized as a surrogate endpoint for risk of AMD or cataracts (Johnson et al., 2000; Landrum et al., 1997; Hammond et al., 1997; Cardinault et al., 2003; Berendschot et al., 2000; Bone et al., 2003; Bartlett and Eperjesi, 2003b; Koh et al., 2004). Macular pigment is an effective filter of damaging blue light, which causes retinal injury. Therefore, it has been hypothesized that increased macular pigment density may protect against AMD. However, while there is a body of evidence for an association between macular disease and low macular pigment density, there is no evidence to determine the nature of this association; i.e., whether low macular pigment density contributes to the development of AMD, whether AMD causes low macular pigment density, or whether the association is merely coincidental. In the absence of such evidence, one cannot simply assume that low macular pigment density is a risk factor or surrogate endpoint for AMD. For example, diabetes is associated with elevated levels of lipids (fatty acids) in the blood; however, elevated blood lipid levels are not a surrogate endpoint for diabetes. Furthermore, there is no evidence to show that high macular pigment density confers a protective effect (Davies and Morland, 2004). Although macular pigment density is "possibly associated" with the risk of AMD (Bone et al., 2003), study authors caution that "further research is necessary" to show whether increasing macular pigment density has a protective effect against AMD (Broekmans et al., 2002). Therefore, no scientific conclusions could be drawn about the role of Xangold® lutein esters, lutein, or zeaxanthin in reducing the risk of AMD or cataracts based on these studies.

Eight studies did not include a control group (Dagnelie et al., 2000; Johnson et al., 2000; Landrum et al., 1997; Berendschot et al., 2000; Cardinault et al., 2003; Bone et al., 2003; Olmedilla et al., 2001; Koh et al., 2004). Therefore, it could not be determined whether changes in the endpoint of interest were due to lutein or zeaxanthin intake or to unrelated and uncontrolled extraneous factors. Hence, scientific conclusions could not be drawn from these studies about the relationship between Xangold® lutein esters, lutein, or zeaxanthin intake and AMD or cataracts (Spilker et al., 1991).

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<sup>19</sup> See *supra*, note 3.

With regard to the claimed relationship between AMD risk reduction and intake of Xangold® lutein esters, lutein and/or zeaxanthin, six studies used a test substance that included other nutrients that could be responsible for any protective effect observed in the study (Falsini et al., 2003; Hammond et al., 1997; Johnson et al., 2000; Olmedilla et al., 2001; Bartlett and Eperjesi, 2003b; Cardinault et al., 2003). For intervention studies on foods and multi-nutrient supplements, it is not possible to accurately determine whether any observed effects on risk of AMD or cataracts are due to: 1) lutein and/or zeaxanthin; 2) interactions between lutein and/or zeaxanthin and other nutrients; 3) other nutrients acting alone or together; or, 4) for foods, decreased consumption of other nutrients or substances contained in foods displaced from the diet by the increased intake of lutein-and/or zeaxanthin-rich foods, unless the studies are controlled so that it can be determined that the effects are from lutein or zeaxanthin, alone or in combination, and it is known that there are no confounders (Lichtenstein and Russell, 2005). These studies were not controlled.

Moreover, in four of these studies, the subjects were given a supplement that contained nutrients other than lutein or zeaxanthin that have been suggested to have a role in protecting against retinal deterioration (e.g., vitamin C, vitamin E, and zinc) (Falsini et al., 2003; Olmedilla et al., 2001; Bartlett and Eperjesi, 2003b; Cardinault et al., 2003). As discussed above, these studies have other design flaws so serious that no scientific conclusions can be drawn from their findings (lack of a control group (Olmedilla et al., 2001; Cardinault et al., 2003); study evaluated treatment instead of risk reduction (Falsini et al., 2003; Olmedilla et al., 2001); unrecognized surrogate endpoint (all four studies)). As stated in Falsini et al. (2003) and Bartlett and Eperjesi (2003b), there is some evidence to suggest that vitamin C, vitamin E, and zinc may have a role in preventing AMD. Therefore, even without the other flaws discussed above, no scientific conclusions could be drawn about the relationship between Xangold® lutein esters, lutein, or zeaxanthin and risk of AMD based on these four studies.

In the other two studies (Hammond et al., 1997; Johnson et al., 2000), the subjects were given spinach, which contains nutrients such as antioxidant vitamins C and E, as well as lutein and zeaxanthin. As discussed above, these studies have other design flaws so serious that no scientific conclusions can be drawn from their findings (lack of a control group (Johnson et al., 2000); unrecognized surrogate endpoint (both studies)). Even without these other flaws, no scientific conclusions could be drawn about the relationship between Xangold® lutein esters, lutein, or zeaxanthin and risk of AMD based on these two studies because there is evidence to suggest that vitamins C and E may have a role in preventing AMD (Falsini et al. 2003; Bartlett and Eperjesi (2003b)).<sup>20</sup>

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<sup>20</sup> In *Pearson v. Shalala*, the D.C. Circuit noted that FDA had "logically determined" that the consumption of antioxidant vitamins in dietary supplement form could not be scientifically proven to reduce the risk of cancer where the existing research had examined only foods containing antioxidant vitamins, as the effect of those foods on reducing the risk of cancer may have resulted from other substances in those foods. 164 F.3d 650, 658 (D.C. Cir 1999). The D.C. Circuit, however, concluded that FDA's concern with granting antioxidant vitamins a qualified health claim could be accommodated by simply adding a prominent disclaimer noting that the evidence for such a claim was inconclusive, given that the studies supporting the

## B. Assessment of the Observational Studies

There were 23 observational studies that evaluated the relationship between lutein and/or zeaxanthin and cataracts or AMD. Scientific conclusions could not be drawn from these 28 studies for the reasons discussed below.

Fourteen observational studies estimated lutein intake by estimating dietary intake of lutein-containing foods (Mares-Perlman et al., 2001; Hammond et al., 1995; Hammond et al., 1996; Beatty et al., 2001; Seddon et al., 1994; Flood et al., 2002; Snellen et al., 2002; Vanden-Langenberg et al., 1998; Chasan-Taber et al., 1999; Brown et al., 1999; Jacques et al., 2001; Taylor et al., 2002; Valero et al., 2002; Lyle et al., 1999b). In observational studies that calculate nutrient intake from conventional foods, measures of lutein intake are based on recorded dietary intake methods, such as food frequency questionnaires, diet recalls, or diet records, in which the type and amount of foods consumed are estimated. Lutein and zeaxanthin concentration values are then estimated using typical lutein and zeaxanthin concentration values for the food product category, based on a source such as the USDA National Nutrient Database for Standard Reference, SR 16. A common weakness of observational studies is the limited ability to ascertain the actual food or nutrient intake for the population studied as a result of poor memory, over- or

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claim were based on foods containing other substances that might actually be responsible for reducing the risk of cancer. *Id.* The court noted that FDA did not assert that the dietary supplements at issue would "threaten consumer's health and safety." *Id.* at 656. There is, however, a more fundamental problem with allowing qualified health claims for individual nutrients based on studies of foods containing those nutrients (such as the two intervention studies that used spinach as the test substance) than the problem the D.C. Circuit held could be cured with a disclaimer. Even if the effect of the specific component of the food could be determined with certainty, recent scientific findings on the complex nature of nutrient-food interactions and on the relationship between diet, biological parameters, and disease indicate that nutrients found to have health benefits when consumed in one food or group of foods may not necessarily have the same beneficial effect when they are consumed in dietary supplement form or in other foods. See Lichtenstein and Russell (2005). For example, not only have studies on dietary supplements established that the benefits associated with the dietary intake of certain nutrients do not materialize when the nutrients are taken as a supplement, but some of these studies have actually indicated an increased risk for the very disease the nutrients were predicted to prevent. *Id.* Thus, a study based on intake of a specific food or foods provides no information from which scientific conclusions may be drawn for the nutrient itself. Further, even if the nutrients are consumed in other foods rather than in a dietary supplement, the physiological effects may be different because the food matrix can affect the bioavailability and bioactivity of the nutrients. *Id.*

Thus, studies in foods do not provide any credible evidence for a claim for risk reduction for a single food component because, in fact, the single food component may decrease, have no effect, or actually increase risk of the disease or health related condition. Additionally, the intervention studies using spinach as a source of lutein and zeaxanthin (Hammond et al., 1997; Johnson et al., 2000) do not provide credible evidence for the relationships claimed in the petition for other reasons, as discussed in the text. For the reasons set forth in Section IV, we have concluded that neither a disclaimer nor qualifying language would suffice to prevent consumer deception in these instances because studies in food do not provide credible evidence for qualified health claims for Xangold® lutein esters, lutein, or zeaxanthin, and there is no other credible evidence to support these claims.

underestimation of portion sizes and recall bias<sup>21</sup> (Flegal, 1999). Furthermore, the lutein content of foods can vary due to food processing and cooking procedures (Micozzi et al., 1990). Thus, it is difficult to ascertain an accurate amount of the nutrient consumed based on reports of dietary intake from conventional foods.

In addition, conventional foods contain not only lutein and zeaxanthin, but also other nutrients that may be associated with the metabolism of lutein or zeaxanthin or the pathogenesis of AMD or cataracts. Because foods consist of many nutrients and substances, it is difficult to study the nutrient or food components in isolation (Sempos et al., 1999). For example, spinach is abundant in lutein, zeaxanthin and beta-carotene. Cooked spinach was associated with a reduced risk of cataract extraction (i.e., risk of developing cataracts severe enough to require extraction); however, neither lutein, zeaxanthin, nor beta-carotene was associated with a reduced risk of cataract extraction (Brown et al., 1999). (See Sempos et al. (1999), Willett (1990) and Willett (1998) regarding the complexity of identifying the relationship between a specific nutrient within a food and a disease.) For studies based on recorded dietary intake of such foods, it is not possible to accurately determine whether any observed effects of lutein or zeaxanthin on AMD or cataract risk were due to: 1) lutein or zeaxanthin alone; 2) interactions between lutein or zeaxanthin and other nutrients; 3) other nutrients acting alone or together; or 4) decreased consumption of other nutrients or substances contained in foods displaced from the diet by the increased intake of lutein- or zeaxanthin-rich foods.

In fact, evidence demonstrates that in a number of instances, epidemiological studies based on the recorded dietary intake of conventional foods may indicate a benefit for a particular nutrient with respect to a disease, but it is subsequently demonstrated in an intervention study that the nutrient-containing dietary supplement does not confer a benefit or actually *increases* risk of the disease (Lichtenstein and Russell, 2005). For example, previous epidemiological studies reported an association between fruits and vegetables high in beta-carotene and a reduced risk of lung cancer (Peto et al., 1981). However, subsequent intervention studies, the Alpha-Tocopherol and Beta Carotene Prevention Study (ATBC) and the Carotene and Retinol Efficiency Trial (CARET), demonstrated that beta-carotene supplements increase the risk of lung cancer in smokers and asbestos-exposed workers, respectively (The Alpha-Tocopherol and Beta Carotene Cancer Prevention Study Group, 1994; Omenn et al., 1996).<sup>22</sup> These studies illustrate that the effect of a nutrient provided as a dietary supplement exhibits different health effects compared to when it is consumed among many other food components. Furthermore, these studies demonstrate the potential public health risk of relying on results from epidemiological studies, in which the effect of a nutrient is based on

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<sup>21</sup> In case-control studies, a participant who has been diagnosed with a disease (case) may recall the foods consumed differently than a healthy individual (control).

<sup>22</sup> Beta-carotene, lutein and zeaxanthin are members of the carotenoid family ("Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids," A Report of the Panel on Dietary Antioxidants and Related Compounds, Food and Nutrition Board of the Institute of Medicine, 2000).

recorded dietary intake of conventional foods, as the sole basis for concluding that a relationship exists between a specific nutrient and disease risk; the effect could actually be harmful.<sup>23</sup>

Evidence is also now available that epidemiological studies based on the recorded dietary intake of conventional foods may suggest a benefit for a particular nutrient in that food with respect to a disease, but it is subsequently demonstrated in an intervention study that the nutrient itself, when isolated from other nutrients in the food, does not confer a benefit ("Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acid," Institute of Medicine of the National Academies, 2002). For example, previous epidemiological studies (38 out of 48) reported an association between dietary fiber and reduced risk of colon cancer (Lanza 1990; Kromhout et al, 1982). Despite these and other positive findings, three recent clinical intervention trials found *no* association between dietary fiber and reduced risk of colon cancer (Alberts et al., 2000; Bonithon-Kopp et al., 2000; Schatzkin et al., 2000).

For the above reasons, FDA concludes that no scientific conclusions about the relationship between Xangold® lutein esters, lutein, or zeaxanthin and risk of AMD or cataracts can be drawn from observational studies on foods.<sup>24</sup>

Nine observational studies measured blood (serum or plasma), adipose tissue<sup>25</sup>, or retina concentration of lutein and/or zeaxanthin as a marker of intake (Bone et al., 2001; Broekmans et al., 2002; Gale et al., 2003; Eye Disease Case-Control Study, 1993; Mares-Perlman et al., 1995; Berendschot et al., 2002; Gale et al., 2001; Olmedilla et al., 2002; Lyle et al., 1999a). Observational studies have shown that dietary lutein and zeaxanthin intake are poorly correlated with levels of lutein and zeaxanthin in the blood (serum) (correlation coefficient range  $(r)^{26} = 0.03-0.24$ ) (El-Sohemy et al., 2002; Curran-Celentano et al., 2001; Gruber et al., 2004; Rock et al., 2002) and tissue ( $r = 0.06-2.5$ ) (Curran-Celentano et al., 2001; El-Sohemy et al., 2002). This poor correlation can be attributed to, in part, various factors associated with lutein and zeaxanthin levels including gender, race, age, smoking, alcohol consumption, serum cholesterol levels, and level of physical activity (Gruber et al., 2004; Rock et al., 2002). In addition, there are other factors that influencing the level of lutein and zeaxanthin that remain unknown

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<sup>23</sup> See footnote 20 for an analysis of these studies in relation to *Pearson v. Shalala*.

<sup>24</sup> Therefore, observational studies in foods do not provide any credible evidence for a claim for risk reduction for a single food component because, in fact, the single food component form may decrease, have no effect, or actually *increase* risk of the disease or health related condition. Additionally, the observational studies evaluated for this qualified health claim review do not provide credible evidence for the relationships claimed in the petition for other reasons, as discussed in the text. For the reasons set forth in Section IV, we have concluded that neither a disclaimer nor qualifying language would suffice to prevent consumer deception in these instances because observational studies in food do not provide credible evidence for qualified health claims for Xangold® lutein esters, lutein, or zeaxanthin, and there is no other credible evidence to support these claims.

<sup>25</sup> Adipose tissue is tissue that contains fat cells.

<sup>26</sup> Correlation coefficients range from -1 (negative correlation) through +1 (positive correlation). The closer to 1 the coefficient, the stronger the correlation; the closer to zero, the weaker the correlation.

(Gruber et al., 2004). Furthermore, serum lutein and zeaxanthin levels reflect intake over a short period of time, and therefore may not be representative of long-term consumption (Gruber et al., 2004). Because serum and tissue lutein and zeaxanthin levels are poorly correlated with dietary intake, and many known and unknown factors can alter these levels, no scientific conclusions about the relationship between intake of Xangold® lutein esters, lutein, or zeaxanthin and risk reduction of AMD or cataracts can be drawn from these 9 studies.

### **III. Strength of the Scientific Evidence**

Below, the agency rates the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of various types of studies and sample sizes), whether the body of evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,<sup>27</sup> and the overall consistency<sup>28</sup> of the total body of evidence. Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and if so, determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

#### ***Age-Related Macular Degeneration***

As discussed in section II, there were no interventional or observational studies from which scientific conclusions could be drawn about the relationship between intake of Xangold® lutein esters, lutein, or zeaxanthin and AMD. Based on its review of the totality of publicly available scientific evidence, FDA concludes that there is no credible evidence for a relationship between intake of Xangold® lutein esters, lutein, or zeaxanthin and reduced risk of AMD.

#### ***Cataracts***

As discussed in section II, there were no interventional or observational studies from which scientific conclusions could be drawn about the relationship between intake of Xangold® lutein esters, lutein, or zeaxanthin and cataracts. Based on its review of the totality of publicly available scientific evidence, FDA concludes that there is no credible evidence for a relationship between intake of Xangold® lutein esters, lutein, or zeaxanthin and reduced risk of cataracts.

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<sup>27</sup> See *supra*, note 11.

<sup>28</sup> See *supra*, note 12.

#### IV. Agency's Consideration of Disclaimers or Qualifying Language

We considered but rejected use of a disclaimer or qualifying language to accompany the proposed claim for Xangold® lutein esters and reduced risk of age-related macular degeneration and cataract formation. We also considered but rejected use of disclaimers or qualifying language to accompany claims for lutein and/or zeaxanthin and reduced risk of age-related macular degeneration or cataract formation. We concluded that neither a disclaimer nor qualifying language would suffice to prevent consumer deception in these instances, where there is no credible evidence to support the claim. Adding a disclaimer or incorporating qualifying language that effectively characterizes the claim as baseless is not a viable regulatory alternative because neither the disclaimer nor the qualifying language can rectify the message conveyed by the unsubstantiated claim. *See, e.g., In re Warner-Lambert Co.*, 86 F.T.C. 1398, 1414 (1975), *aff'd*, 562 F.2d 749 (D.C. Cir. 1977) (pro forma statements of no absolute prevention followed by promises of fewer colds did not cure or correct the false message that Listerine will prevent colds); *Novartis Consumer Health, Inc. v. Johnson & Johnson-Merck Consumer Pharms. Co.*, 290 F.3d 578, 598 (3d Cir. 2002) ("We do not believe that a disclaimer can rectify a product name that necessarily conveys a false message to the consumer."); *Pearson v. Shalala*, 164 F.3d 650, 659 (D.C. Cir. 1999) (where the weight of evidence was against the claim, FDA could rationally conclude that the disclaimer "The FDA has determined that no evidence supports this claim" would not cure the misleadingness of a claim). In such a situation, adding a disclaimer or qualifying language does not provide additional information to help consumer understanding but merely contradicts the claim. *Resort Car Rental System, Inc. v. FTC*, 518 F.2d 962, 964 (9th Cir.) (per curiam) (upholding FTC order to excise "Dollar a Day" trade name as deceptive because "by its nature [it] has a decisive connotation for which any qualifying language would result in contradiction in terms."), *cert denied*, 423 U.S. 827 (1975); *Continental Wax Corp. v. FTC*, 330 F.2d 475, 480 (2d Cir. 1964) (same); *Pasadena Research Labs v. United States*, 169 F.2d 375 (9th Cir. 1948) (discussing "self-contradictory labels"). In the FDA context, courts have repeatedly found such disclaimers ineffective. *See, e.g., United States v. Millpax, Inc.*, 313 F.2d 152, 154 & n.1 (7th Cir. 1963) (disclaimer stating that "no claim is made that the product cures anything, either by the writer or the manufacturer" was ineffective where testimonials in a magazine article promoted the product as a cancer cure); *United States v. Kasz Enters., Inc.*, 855 F. Supp. 534, 543 (D.R.I.) ("The intent and effect of the FDCA in protecting consumers from . . . claims that have not been supported by competent scientific proof cannot be circumvented by linguistic game-playing."), *judgment amended on other grounds*, 862 F. Supp. 717 (1994).

#### V. Conclusions

Based on FDA's consideration of the scientific evidence and other information submitted with your petition, and other pertinent scientific evidence and information, FDA concludes that there is no credible evidence to support qualified health claims for Xangold® lutein esters, lutein, or zeaxanthin and reduced risk of age-related macular

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degeneration or cataract formation. Thus, FDA is denying your petition for a qualified health claim based on the following proposed claim:

*Consumption of 12 mg of Xangold® lutein esters per day may reduce the risk of age-related macular degeneration and cataract formation. FDA has determined that the evidence is supportive, but not conclusive, for this claim. This food/dietary supplement provides \_\_\_ mg lutein esters per serving.*

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 become available that will support the use of a qualified health claim or that will support significant scientific agreement.

Sincerely,



Barbara O. Schneeman, Ph.D.  
Director  
Office of Nutritional Products, Labeling  
and Dietary Supplements  
Center for Food Safety  
and Applied Nutrition

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