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A) FDA PRELIMINARY REQUIREMENTS FOR HEALTH CLAIMS

In order for a substance to be eligible for a health claim, it must meet the eligibility requirements of 21 CFR §101.14 as follows:

21 CFR §101.14 (b) Eligibility. For a substance to be eligible for a health claim:

(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.

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(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 Sec. 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

1) 21 CFR §101.14(b)(1) Dietary intake of lutein or lutein esters is associated with reduction in risk of two diseases of the eye affecting the general U.S. population.

Age-related macular degeneration is an incurable eye disease that is the leading cause of blindness in those aged 55 and older in the United States, affecting as many as 15 million Americans (www.amd.org). As the population ages, we will continue to see the number of cases of AMD increase significantly. The disease is caused by the deterioration of the central portion of the retina known as the macula. The photoreceptors of the macular region of the retina are responsible for our ability to sense light and therefore the images of objects that we see. The nerves present in the retina convert the light image into nerve impulses and transmits them via the optic nerve from the eye to the brain. The macula is a small region, approximately 2mm in diameter, at the center of the visual field and it is especially rich in cones which are closely-packed, enabling objects to be seen in fine detail when an image falls on this section of the retina. Without a functional macula it is impossible to read, recognize faces, match colors, or to

perform many other common visual tasks that we take for granted (www.macular.org/disease/html). Macular degeneration results in degeneration of the nerves and photoreceptors in the macula and is an irreversible condition.

The role of nutritional supplementation in ocular health is of keen interest to eye care practitioners and consumers alike. Evidence that certain nutrients have a positive role by helping to delay the onset of certain eye disorders continues to surface as researchers unravel their contributions to eye health. This is especially apparent in the positive research outcomes for the xanthophylls, lutein and zeaxanthin. Considerable data now indicate that these components of the macular pigment may reduce the risk or delay onset of age-related macular degeneration (AMD) and the incidence of cataract formation.

Schalch et al., (1999)¹ recently reviewed the literature on the carotenoids of the human retina. The macula, or *macula lutea*, is a yellow pigmented area of the retina in the center of the visual field and contains a depression called the fovea. The fovea has a high density of cone photoreceptors that are closely packed and contribute to maximal visual acuity. Krinsky et al., (2003)² provides a brief review of the history of research on lutein and zeaxanthin in the eye and has pointed out that the pigmentation of the macula is due to the accumulation of these carotenoids that are the major xanthophylls found in plants. Further, they pointed out that while the mechanism of action of the macular pigments remains incompletely understood, there is an epidemiological association between both the level of dietary intake of lutein and zeaxanthin, and measured blood levels of lutein and zeaxanthin, and the risk of age-related macular degeneration (AMD). Krinsky et al.,(2003) also report on studies that demonstrate that dietary sources of lutein and zeaxanthin can contain either esterified or unesterified forms of these xanthophylls and it is well known that both are absorbed from the diet to increase serum levels.

As the life expectancy of the US population continues to increase over the next 25 years, a result of improved nutrition, improved medical care, and increased awareness of environmental factors, the number of individuals suffering AMD is expected to nearly double (Stone et al., 2001)³. Projections by the National Institute of Aging suggest that one in five people in the USA will be 65 or older by 2030. Individuals 85 and older could exceed 10 million at that time. The

incidence of AMD among individuals older than 65 years averages 1.7-2.1 % and by age 85 increases to 12-14 %.

Potential risk factors for macular degeneration include: smoking, obesity, race (data suggest that Caucasians are much more likely to suffer loss of vision from AMD than African Americans), family history, gender (women appear to be at a greater risk than men), light skin and eye color, cataracts and hypertension/history of cardiovascular disease (www.nei.nih.gov/health/index.htm ; www.blindness.org/).

There are two diagnostically separate forms of age-related macular degeneration. One form is known as the “dry form” or geographic atrophy and the other as the “wet form” or neovascular macular degeneration. The prevalent “dry” form, which affects 90% of the people with AMD, is characterized by the appearance of drusen and a loss or of the retinal pigment epithelial cells (RPE) in the macula. These RPE cells are present as a single cell layer underlying and in direct contact with the light sensitive outer segments of the photoreceptors of the cones and rods. RPE cells are responsible for transport of nutrient and metabolites to and from the photoreceptors and nerves that compose the retina and for the regeneration of shed discs from rods and cones. The uniquely high density of the photoreceptor cells found in the fovea makes this the only region of the retina where individual letters of fine print can be visually resolved when images are focused upon it. Thus the effect of damage to or loss of the RPE support cells is catastrophic and results in photoreceptor cell death and loss of vision. It is believed that drusen are lipophilic deposits of cell debris that accumulate with age between the RPE cell and the vascular choroid, the ultimate source of all nutrients and oxygen for the retina.

The “wet” or neovascular form of AMD is the more severe form of AMD and while it affects less than 10 % of those with AMD, it accounts for 90% of the severe loss of vision. It is likely that wet AMD is a later stage of AMD whereas the dry form is an early stage. In this wet form or stage of the disease, the Bruch’s membrane, which defines the boundary between the RPE cells and the retina, thickens. This is believed to disrupt oxygen flow to the macula and to result in the release of vascular growth factors that initiate the growth of new, abnormal capillaries into the normally avascular retina. These small vessels often leak fluid into subretinal

spaces distorting the retinal shape and frequently rupture releasing blood cells that absorb light. The result is the rapid onset of prolonged distorted vision and/or total loss of vision.

Formation of cataracts is a well-known consequence of aging. A cataract is a clouding of the lens in the eye due to oxidative damage and clumping of the protein in the eye's lens. This can be induced by environmental factors including exposure to ultraviolet light, radiation, or use of steroids. Cataracts are also associated with some genetic diseases. The resulting cloudiness of the lens results in vision loss. The prevalence of cataract increases dramatically with age. By age 80, more than half of all Americans either have had a cataract or have had cataract surgery (www.nei.nih.gov/health/cataract/cataract.facts.htm). The formation of cataract occurs more commonly in patients with a history of ocular trauma, uveitis or diabetes mellitus. The only treatment for cataract is surgical extraction of the opacified lens (Horton, 1998)⁴. Cataract remains the leading cause of visual loss, affecting approximately 20.5 million Americans older than 40 years. One in 20 Americans older than 40 years has undergone cataract surgery, and cataract care consumes approximately 60% of the Medicare budget for vision (Congdon et al., 2003)⁵.

Jacques, (1999)⁶; and Moeller et al., (2000)⁷ have reviewed several epidemiological studies evaluating cataract risk and intake of dietary nutrients. Evidence from these studies supports a role for nutritional antioxidants in delaying this age-related vision disorder. A significant, positive association between consumption of xanthophyll-rich foods and a reduction in risk of cataract was reported by these researchers.

As the above clearly demonstrates, a significant effect on the prevalence of age-related vision disorders in the U.S. is likely to be observed due to improvements in dietary, nutritional and lifestyle habits. However, despite years of public health and medical messages and advisories to the public regarding the health problems associated with excessive caloric intake, lack of exercise, diets high in fats and sugars and suboptimal fruit and vegetable intake, the great majority of Americans still consumed 300 calories more in 2000 than in 1985, mostly in refined grains or carbohydrates, added fats and added sugars (Putnam et al., 2002)⁸.

The reasons Americans continue to make such poor dietary choices and fail to heed sensible public health advice regarding our diet are strongly influenced by cultural and economic factors, as well as the choices presented to the consumer from modern agricultural and food processing practices. Obviously, taste and satiety are primary determinants in the types and amounts of food ingested. For some consumers, health and nutritional values of foods are very important, but, for most consumers, these rank behind taste, cost and convenience as purchasing criteria. Furthermore, in modern agriculture dominated by cereal grains such as wheat, corn and rice, it is not surprising that the most prevalent and economic foods in the market are based on these commodities.

In contrast to these negative dietary trends, there is an increased interest in the health benefits of foods and dietary supplements. This is largely associated with the maturing baby-boomers who are nearing retirement age and are becoming increasingly aware that health is a personal concern. One promising approach to providing consumer choices leading to healthier foods and which may reduce the risk of the vision disorders of AMD and cataract formation is to incorporate the desired substances, Xangold[®] lutein esters as a source of lutein, into conventional foods that that enjoy wide appeal. By fully informing the consumer of the benefits by health claim labeling of these foods they will be able to select preferred foods which incorporate this added nutritive value. In this case, even for the consumers who did not markedly change their normal diet, the consumption of foods supplemented with Xangold[®] lutein esters as a source of lutein would confer a positive health benefit including a reduction of risk for age-related macular degeneration and cataract formation. In this manner, it is possible to deliver physiologically important and beneficial nutrients into the daily diet without having to overcome longstanding cultural food preferences in the general population.

2) 21 CFR §101.14(b)(3)(i) Lutein esters contribute and retain nutritive value in conventional foods

Under Sec. 101.14(b)(3)(i), the substance that is the subject of a health claim must contribute taste, aroma, or nutritive value, or any other technical effect listed in Sec. 170.3(o) (21 CFR 170.3(o)), to the food and must retain that attribute when consumed at the levels that are necessary to justify a claim. Lutein esters do not contribute taste, aroma, or any other

technical effect listed in Sec. 170.3(o), and thus the lutein esters must contribute nutritive value to meet the requirement in Sec. 101.14(b) (3) (i).

Humans cannot synthesize lutein and the sole sources of xanthophylls and xanthophyll esters are dietary in origin. These include fruits, vegetables, and eggs, as well as dietary supplements.

The term “nutritive value” is defined in Sec. 101.14(a) (3) as “value in sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients, or providing energy.” In the proposed rule entitled “Labeling; General Requirements for Health Claims for Food” (56 FR 60537, November 27, 1991), FDA proposed this definition and explained its interpretation of nutritive value in the context of whether a substance is a food and thus appropriately the subject of a health claim (56 FR 60537 at 60542). The agency indicated that the definition was formulated based on the common meaning of the words that make up the term “nutritive value.” The agency also added that use of the phrase “such processes as” in the definition of nutritive value was intended to provide a measure of flexibility that the agency believed would be necessary in evaluating future petitions. In the final rule adopting the proposed definition, the agency noted that the evaluation of the nutritive value of substances would be done on a case-by-case basis to best ensure that the definition retains its intended flexibility (58 FR 2478 at 2488). In a subsequent final rule on health claims for dietary supplements (59 FR 395 at 407), FDA further explained that nutritive value “includes assisting in the efficient functioning of classical nutritional processes and of other metabolic processes necessary for the normal maintenance of human existence.”

A good working definition has been proposed for dietary antioxidants in a published National Academy of Sciences report, (2001)⁹ titled Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids as follows:

“A dietary antioxidant is a substance in foods that significantly decreases the adverse effects of reactive species, such as reactive oxygen and nitrogen species, on the normal physiological function in humans.”

This definition and the expert reviews referenced above clearly support Xangold® lutein esters as a source of lutein meeting the Agency's intended meaning of nutritive value in their use of the phrase "for nutritive value to include assisting in the efficient functioning of classical nutritional processes which are biochemically-based and of other metabolic processes necessary for the normal maintenance of human existence".

The scientific evidence suggests that the protective effects of lutein and zeaxanthin are derived from dietary lutein esters or unesterified lutein and zeaxanthin, on the macula of the eye and/or lens occur through a series of biological mechanisms in the eye. As a member of the carotenoid family, lutein is known to function as an effective antioxidant. Lutein is also known to absorb visible blue light acting as a filter in the retina. Reduction of intense blue light by the macular pigment decreases the ability to form blue-light generated oxyradicals. While not a direct antioxidant function per se, this filtering effect has the consequence of reducing photooxidative stress on the retina. Direct evidence indicates that pigmented regions of the macular have a significant level of protection from damage due to acute photic stress due to visible light not observed for other regions of the retina. Peroxyl radical-induced oxidative chain reactions can lead to irreversible damage to various cell structures. The presence of oxidative metabolites of lutein in the retina is consistent with a mechanism in which lutein acts as an antioxidant and is an active participant in oxidative metabolism within the retina. This putative antioxidant effect is reviewed in detail by Krinsky et al. (2003) as well as in the scientific summary of the studies supporting the protective role by lutein from derived from dietary lutein esters within this petition.

Thus, dietary lutein esters contribute nutritive value because the lutein derived from lutein esters is thought to function as an antioxidant in the retina. The studies discussed below demonstrate that the effects of lutein at intakes as high as 60mg/day from lutein esters result in increased macular pigmentation in the eye. The proposed food use levels and dietary supplement use levels of lutein esters would result in intakes of about 12mg per day of lutein esters. The level of lutein recommended for a food to qualify for the claim is 1.5 mg lutein per serving (3.0 mg lutein esters). This antioxidant function of lutein esters as a source of lutein is retained at the level proposed for use in food and dietary supplements and the levels proposed for a product to qualify for the proposed qualified health claim.

3) 21 CFR §101.14(b)(3)(ii) Lutein esters are safe and lawful under the FDCA.

The lutein esters such as the Xangold[®] lutein esters are composed of the xanthophylls lutein and zeaxanthin that are the subject of this petition. Lutein is found naturally at relatively high levels in green leafy vegetables, and in moderate amounts in yellow-orange fruits and egg yolks. In yellow-orange fruits and in edible flowers lutein is present as a mixture of fatty acid diesters. (www.nal.USDA.gov/fnic/foodcomp/data) The petitioner, Cognis Corporation submitted a GRAS Notification to FDA on July 17, 2002.¹⁰ This notification contained the unanimous concurrence from a panel of qualified experts that Xangold[®] lutein esters are GRAS, based on their expert evaluation of the scientific literature for addition to conventional foods as an ingredient to provide consumers with a supplementary source of lutein in their diets. The July 17, 2002 submission included the supporting data on which this conclusion was based. FDA responded to this submission in a letter dated January 21, 2003¹¹ stating “based on the information provided by Cognis, as well as other information available to FDA, the agency has no questions at this time regarding Cognis’ conclusion that lutein esters are GRAS under the intended conditions of use. The agency has not however, made its own determination regarding the GRAS status of the subject use of lutein esters”. In addition, a separate submission for lutein was received by the Agency on November 21, 2003 from Kemin Foods, L.C. for GRAS notification.

The Panel of independent qualified experts conducted an extensive review of all generally available scientific literature for safety and toxicity and evaluated all available data from dietary consumption of lutein and/or zeaxanthin. The typical U.S. daily consumption level of lutein plus zeaxanthin is 1.35-1.97 mg/day. No toxicity from lutein ester supplement consumption has been reported and human clinical studies indicate that long-term consumption of lutein esters is well tolerated. Seven clinical studies ranging from 84 days to 3 years have reported that consumption of between 18 and 60 mg/day lutein ester equivalents is safe. The Expert Panel established a conservative acceptable daily intake of Xangold[®] lutein esters of 40 mg/day. No evidence of toxicity or any safety issues were noted by the Panel in their review of all available toxicology and clinical studies.

The Expert Panel evaluated the proposed use of Xangold[®] lutein esters at specified levels seen in Table 1 in the following foods: baked goods and baking mixes, soy milk, beverages and

beverage substitutes, frozen dairy desserts and mixes, processed fruit and vegetable products, egg products and egg substitutes, breakfast cereals (ready-to-eat), fats and oils, hard candy, fruit snacks and dairy products. They concluded that such uses would result in an estimated daily intake that is below 40 mg/day lutein esters.

In its GRAS notification filing with the Agency on July 17, 2002, the petitioner provided proposed use levels, data from the United States Department of Agriculture (USDA) 1994-1996 Continuing Surveys of Food Intakes by Individuals, and the USDA carotenoid database to estimate that the intake of lutein esters from both dietary sources and its proposed uses would be approximately 12 milligrams per person per day (mg/person/day) at the mean and approximately 22 mg/person/day at the 90th percentile. The petitioner also estimated that the intake of lutein esters from consumption of dietary supplements ranges from 0.5 to 12 mg/person/day. Finally, the petitioner estimated that the potential maximum intake of lutein esters (i.e. combined from the diet, the uses that the petitioner proposed in conventional foods and dietary supplements) would be 34 mg/person/day at the 90th percentile.

The Expert Panel evaluated the combination of the 90th percentile lutein ester consumption levels from foods proposed to be supplemented with Xangold[®] lutein esters, with the 90th percentile current consumption of lutein esters from conventional foods. The estimated total daily intake of lutein esters from conventional foods would be 22.3 mg/day. In addition, the potential lutein ester consumption from dietary supplements may add an additional maximum intake of 12 mg/day. The Panel concluded that the maximum potential theoretical lutein ester consumption at the 90th percentile may reach 34.3 mg/day. They considered this to be a conservative estimate since it was highly unlikely that an individual would consume lutein from both conventional foods and dietary supplements at the 90th percentile level. Even this conservative estimate was well within the Acceptable Daily Intake of 40 mg/day established by the panel and was therefore deemed to be safe.

In the letter responding to the GRAS notice, FDA raised the issue of a potential requirement for a color additive petition. The Petitioner does not believe that the proposed uses for lutein esters would subject the ingredient to the color additive requirements. On January 8, 2003, the Petitioner's counsel sent a letter to FDA¹² discussing why lutein esters would not

require color additive approval. The reasoning presented in this letter is applicable to the determination in this petition that lutein esters is safe and lawful for the proposed uses and would not require color additive approval.

In summary, based on all the data presented above, the consumption of Xangold® lutein esters in conventional foods identified above (table 1) is safe and lawful and meets the requirements in [section]101.14(b)(3)(ii). Also, Xangold® lutein esters in dietary supplements do not present an unreasonable risk to the consumer and are therefore safe and lawful.

Xangold® lutein esters meet all of the eligibility requirements of 21 CFR §101.14(b); therefore, the preliminary requirements of 21 CFR §101.70 for a qualified health claim petition are acceptably met in the petition.