DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

MAY 9 2006

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RE: Qualified Health Claim Petition - Green Tea and Reduced Risk of Cardiovascular Disease (Docket No. 2005Q-0297)

Dear Dr. Tarka:

This letter responds to the health claim petition dated June 9, 2005, submitted to the Food and Drug Administration (FDA or the agency) by Ito En, Ltd and Ito En (North America), Inc. 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 green tea and a reduction of a number of risk factors associated with cardiovascular disease (CVD) for use in the labeling of conventional foods and dietary supplements. This petition proposed as a model qualified health claim:

"Daily consumption of at least 5 fluid ounces (150 mL) of green tea as a source of catechins may reduce a number of risk factors associated with cardiovascular disease. FDA has determined that the evidence is supportive, but not conclusive, for this claim. (Green tea provides 125 mg catechins per serving when brewed from tea and 125 mg catechins as a pre-prepared beverage)."

FDA filed the petition on July 28, 2005 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.[1] The agency did not receive any comments on this 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 green tea or green tea extract and a reduction of a number of risk factors associated with CVD.

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

[1] "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/nuttf-e.html]

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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.[2] 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.[3] FDA considers the data and information 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.[4]

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.[5]

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,[6] review articles,[7] 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[8] 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.

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[2] 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).
[3] See guidance entitled "Interim Evidence-based Ranking System for Scientific Data," July 10, 2003. [http://www.cfsan.fda.gov/~dms/hclmgui4.html]
[4] For brevity, "disease" will be used as shorthand for "disease or health-related condition" in the rest of the section.
[5] 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]
[6] A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).
[7] Review articles summarize the findings of individual studies.
[8] Other examples include book chapters, abstracts, letters to the editor, and committee reports.

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 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.[9] The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional),

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[9] See *supra*, note 3.

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. population or target subgroup, whether study results supporting the proposed claim have been replicated[10], and the overall consistency[11] of the total body of evidence.[12] 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 a dietary supplement (21 CFR 101.14(a)(2)). The petition identified green tea as the substance that is the subject of the proposed claim. Green tea is an article used for drink and, therefore, meets the definition of food under the Act (21 U.S.C. § 321(f)(1)).

Although the model claim proposed in the petition refers only to green tea consumed as an article for drink, the discussion in the petition makes clear that the proposed claim is based on a body of evidence encompassing studies of green tea in both a beverage and an extract form. In this instance, it is not necessary for FDA to determine whether green tea extract should be considered a subject of the proposed claim, in addition to green tea, because including studies of green tea extract 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 much of the evidence submitted with the petition consisted of studies of green tea in extract form, the agency has decided to treat both forms of green tea, beverage and extract, as subjects of the proposed claim.

Green tea is a brewed beverage made by infusing hot water with the dried natural tea leaves of *Camellia sinensis* (also referred to as *Thea sinensis*). Green tea differs from other types of tea, such as black or oolong, in that green tea is made with unfermented tea leaves, while black and oolong tea are made with fermented leaves. The extracts of green tea used in the studies cited by the petitioner were described as being mainly comprised of green tea catechins.[13] The agency

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[10] 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).

[11] 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."

[12] See *supra*, note 3.

[13] The proposed claim in the petition identified the substance that is the subject of the claim as "green tea as a source of catechins." None of the scientific data evaluated by the agency measured the relationship of individual catechins

concludes that green tea, in either beverage or extract form, is a specific food or component of food and thus meets 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 CVD as the disease that is the subject of the proposed qualified health claim. CVD refers to disease of the cardiovascular system, and encompasses a number of diseases of the heart and the blood vessels. The agency concludes that CVD is a disease and therefore the petitioner has satisfied the requirement in 21 CFR 101.14(a)(5).

C. Safety

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 green tea or green tea extract 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

FDA has identified the following disease endpoints to use in identifying CVD risk reduction for purposes of a health claim evaluation: the incidence of coronary events (MI, ischemia), cardiovascular death, coronary artery disease, atherosclerosis, and coronary heart disease (CHD). High blood pressure, blood (serum or plasma) total cholesterol, and blood LDL-cholesterol levels are considered surrogate endpoints for all CVDs.[14] These disease and surrogate endpoints were used to evaluate the potential effects of green tea or green tea extract consumption on CVD risk.

The petition cited 105 publications as evidence to substantiate the relationship for this claim. These publications consisted of: 18 review articles; 24 *in vitro* articles; two animal articles; five

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and CVD. Therefore, the agency considered the relationship between green tea and green tea extract and a reduced risk of CVD.

[14] National Heart, Blood and Lung Institute (NHLBI), Heart and Blood Vessel Diseases (http://www.nhlbi.nih.gov/health/dci/Diseases/Atherosclerosis/Atherosclerosis_WhatIs.html) and National Cholesterol Education Program, Page 3 (U.S. Department of Health and Human Services, 2001, http://www.nhlbi.nih.gov/guidelines/cholesterol/atp_iii.htm).

publications from the USDA, NIH, and American Heart Association; one book chapter from the Institute of Medicine; two letters; seven intervention studies that did not evaluate the substance and disease relationship (i.e., bioavailability or pharmacokinetic articles); one meta-analysis; nine observational studies that did not evaluate the substance and disease relationship;[15] 27 intervention studies on green tea or green tea extract consumption and CVD risk;[16] and nine observational studies that evaluated green tea consumption and risk of CVD.

In addition to the studies included in the petition, FDA identified from a literature search one additional observational study (Tsubono and Tsugane, 1997) and one additional intervention study (Hirano-Ohmori et al., 2005) that evaluated the relationship between green tea consumption and risk of CVD.

A. Assessment of Review Articles, Meta-Analysis, Book Chapters, Letters, and Government Reports

Although useful for background information, review articles, meta-analyses, book chapters, letters, and government reports do not contain sufficient information on the individual studies which they reviewed and, therefore, FDA could not draw any scientific conclusions from this information. FDA could not determine factors such as the study population characteristics or the composition of the products used (e.g., food, dietary supplement). Similarly, the lack of detailed information on studies summarized in review articles, meta-analyses, book chapters, letters, and government reports 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. As a result, the review articles, meta-analyses, book chapter, letters, and government reports 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

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[15] One study examined dietary patterns of green tea drinkers (Tsubono et al., 1997) and one study examined dietary patterns associated with risk factors for CVD (Tsubono et al., 1997; Kerver et al., 2003). Seven observational studies evaluated a general category of food (e.g., tea) and not the specific substance of the claim (i.e., green tea) (Yang et al., 2004; Hertog et al., 1993; Geleijnse et al., 1999; Hertog et al., 1995; Arts et al., 2001; Rimm et al., 1996; Mukamal et al., 2002).

[16] One intervention study (Princen et al., 1998) evaluated the relationship of both green tea and green tea extract on risk factors of CVD. That study's results for green tea and green tea extract are considered separately below with the other intervention studies on green tea and green tea extract respectively.

reduction of CVD, nor can the studies mimic the human body's response to the consumption of green tea or green tea extract. Therefore, FDA cannot draw any scientific conclusions from the animal or *in vitro* studies regarding green tea or green tea extract and the risk of CVD.

C. Assessment of Intervention Studies

Green tea

FDA identified 18 intervention studies for its evaluation of the relationship between green tea consumption and risk of CVD. Scientific conclusions could not be drawn from 13 studies regarding the substance/disease relationship for one or more of the following reasons discussed below.

Nine studies did not measure a validated surrogate endpoint of CVD (i.e., blood total cholesterol, blood LDL cholesterol, blood pressure) (Gomikawa et al., 2002; Hodgson et al., 2000; Hodgson et al., 2002;Leenen et al., 2000; Nagaya et al., 2004; Serfini et al., 1996; Serfini et al., 2000; Sung et al., 2000; van het Hof et al., 1999). Because these studies did not measure a validated surrogate endpoint, scientific conclusions about the relationship between green tea consumption and risk of CVD cannot be drawn.

Two copies of one study (de Maat et al., 2000) were submitted in the petition. Furthermore, de Maat et al. (2000) was a republication of Princen et al. (1998). Thus, the two articles submitted by de Maat et al. (2000) provided no new scientific data to evaluate the proposed qualified health claim.

Two studies did not include a control group for comparing the relative effects of green tea consumption (Lee et al., 2005; Sung et al., 2005). Therefore, it could not be determined whether changes in the endpoint of interest were due to green tea consumption or to unrelated and uncontrolled extraneous factors. Hence, scientific conclusions could not be drawn from these two studies (Spilker, 1991).

One study did not conduct statistical analysis between the control and intervention group (Erba et al., 2005). Statistical analysis of the relationship is a critical factor because it provides the comparison between subjects consuming green tea and those not consuming green tea to determine whether there is a reduction in CVD risk. When statistics are not performed on the specific substance/disease relationship, it cannot be determined whether there is a difference between the two groups. As a result, because this study provided no information about whether green consumption reduces the risk of CVD, no scientific conclusions could be drawn from it.

Four intervention studies evaluated the relationship between green tea consumption and reduced risk of CVD (Hodgson et al., 1999; Princen et al., 1998; van het Hof et al., 1997; Hirano-Ohmori et al., 2005). Hodgson et al. (1999) was an Australian randomized cross-over intervention study of moderate quality in which 13 men and women consumed water and caffeine (control group) or green tea (1,000 milliliters (mL)), each for seven days. There was no significant difference in

systolic or diastolic blood pressure between the group who consumed green tea and control group.

Princen et al. (1998) was a four week randomized single blind, placebo controlled parallel design intervention study of high quality in which Dutch male and female smokers (n=15 per group) consumed 900 mL mineral water (control group) or 900 mL green tea (3 grams (g) green tea solids) for four weeks. There was no significant difference in total blood cholesterol and LDL cholesterol concentration between the green tea group and the control group.

van het Hof et al. (1997) was a four week parallel comparative design intervention study of moderate quality in which Dutch men and women (n=14 to16 per group) consumed mineral water (control group), or 900 mL green tea (3 g green tea solids). Participants were matched for age, sex, and body mass index. There was no significant difference in blood total cholesterol and LDL cholesterol concentration between the green tea and control group.

Hirano-Ohmori et al. (2005) was a randomized Japanese crossover intervention study of moderate quality in which 22 men consumed 700 mL green tea or water (control group) each for two weeks. There was no significant difference in total blood cholesterol and LDL cholesterol concentration between the green tea and the control group.

Green tea extracts

FDA identified 11 intervention studies for its evaluation of the relationship between the consumption of green tea extracts and risk of CVD. Scientific conclusions could not be drawn from eight studies for the reasons discussed below.

Two studies did not measure a validated surrogate endpoint of CVD (i.e., total cholesterol, LDL cholesterol, blood pressure) (Dullo et al., 1999; Samman et al., 2001). Instead, these studies measured endpoints, such as LDL oxidation and antioxidant activity, that are not validated surrogate endpoints of CVD. Because these studies did not measure a validated surrogate endpoint, scientific conclusions about the relationship between green tea extract consumption and risk of CVD cannot be drawn.

Four studies did not include a control group for comparing the relative effects of green tea extract consumption (Chantre and Lairon, 2002; Nakagawa et al., 1999; Kajimoto et al., 2003; Kajimoto et al., 2005). Therefore, it could not be determined whether changes in the endpoint of interest were due to green tea extract or to unrelated and uncontrolled extraneous factors. Hence, scientific conclusions could not be drawn from these studies (Spilker, 1991).

Two studies did not conduct statistical analysis between the control and intervention group (Maron et al., 2003; Miura et al., 2000). Statistical analysis of the relationship is a critical factor because it provides the comparison between subjects consuming green tea extract and those not consuming green tea extract to determine whether there is a reduction in CVD risk. When statistics are not performed on the specific substance/disease relationship, it cannot be

determined whether there is a difference between the two groups. As a result, because this study provided no information about whether green tea extract consumption reduces the risk of CVD, no scientific conclusions could be drawn from it.

Three intervention studies measured the effect of green tea extract consumption on risk of CVD. Young et al. (2002) was a three week randomized, double blind cross-over study of high quality with 16 Danish men (eight nonsmokers, eight smokers). Subjects were divided into two groups with four smokers and four nonsmokers in each group. Each group consumed a standardized diet low in flavonoids (control group) or a standardized diet with green tea extract added to meat patties for three weeks each. No significant difference in blood total cholesterol levels was found between the green tea extract group and control group.

Freese et al. (1999) was a four week randomized, double blind, placebo controlled intervention study of moderate quality that provided Finnish women a diet rich in linoleic acid and a gelatin capsule containing 3 g of green tea extract or diet rich in linoleic acid and a placebo capsule. Ten additional control subjects who consumed their habitual diets were also used. There was no significant difference in blood total cholesterol concentration between the green tea extract, placebo, and control groups.

Princen et al. (1998) was a four week randomized, single blind, placebo controlled parallel design intervention study of high quality in which Dutch male and female smokers consumed 900 mL mineral water (control group, n=15), or 3.6 g green tea polyphenol supplement (n=13) for four weeks. There was no significant difference in blood total cholesterol and LDL cholesterol levels between the green tea supplement group and the control group.

D. Assessment of Observational Studies

FDA identified ten observational studies that evaluated the relationship between green tea consumption and risk of CVD. Scientific conclusions could not be drawn from six of these studies for the reasons discussed below.

Four studies provided no information as to whether the food frequency questionnaires in the studies, which were used for the collection of green tea consumption data from study subjects, had been validated (Nakachi et al., 2000; Nakachi et al., 2003; Hirano et al., 2002; Sano et al., 2004). Validation of the food frequency questionnaire method is essential in order to be able to draw conclusions from the scientific data, as the failure to validate may lead to false associations between dietary factors and diseases or disease-related markers.[17] As a result, these studies

[17] "Validation of the food frequency questionnaire method is essential, as incorrect information may lead to false associations between dietary factors and disease or disease-related markers." Cade, J., Thompson, R., Burley, V., and Warm D. Development, Validation and Utilization of Food-Frequency Questionnaires-A Review. *Public Health Nutrition*, 5: page 573, 2002. See, also, Subar, A., et al., Comparative validation of the Block, Willett, and National Cancer Institute Food Frequency Questionnaires, *American Journal of Epidemiology*, 154: 1089-1099, 2001.

provided no information on the accuracy of how green tea intake was measured, and hence, no scientific conclusions could be drawn from them.[18]

Two studies did not use statistics to evaluate the specific relationship between green tea and CVD risk (statistics measured other parameters in each study) (Imani et al., 1995; Kono et al., 1992). Statistical analysis of the relationship is a critical factor because it provides the comparison between subjects consuming green tea and those not consuming green tea, to determine whether there is a reduction in CVD risk. Thus when statistics are not performed on the specific substance/disease relationship, it is not possible to determine if there is a difference between the two groups. As a result, this study provided no information about how green tea consumption may reduce the risk of CVD risk; hence, no scientific conclusions could be drawn from it.

Four observational studies evaluated the relationship between green tea consumption and risk of CVD (Sasazuki et al., 2000; Kono et al., 1996; Tsubono and Tsugane, 1997; Tokunaga et al., 2002).

Three cross-sectional[19] studies of moderate methodological quality evaluated the relationship between green tea consumption and blood lipids (Kono et al., 1996; Tsubono and Tsugane, 1997; Tokunaga et al., 2002). Kono et al. (1996) correlated blood total and LDL cholesterol levels and green tea intake in 2,062 Japanese males. The study identified a significant decrease in blood total and LDL cholesterol levels with the consumption of ten cups of green tea per day.

Tsubono and Tsugane (1997) correlated blood total cholesterol levels and green tea intake in 1,000 Japanese men and women. There was no association between green tea intake and blood total cholesterol concentration. Tokunaga et al. (2002) correlated blood total cholesterol and green tea intake in 13, 916 Japanese men and women. There was a significant decrease in blood total cholesterol reported in men and women with increased consumption of green tea.

Sasazuki et al. (2000) was a Japanese study described by its authors as a cross-sectional study. However, it appears to have used a hybrid design applying case-control analysis to data obtained through cross-sectional methods.[20] The study is of high methodological quality and included 167

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[18] "Food frequency questionnaires require validation prior to or as a part of dietary research. The approach taken in most studies is to examine the concordance of food frequency responses with reference instruments such as multiple 24 hour recalls or diet records using measurement error models to estimate the correlations between nutrient intakes measured by food frequency questionnaires and truth." Subar, A., et al., Comparative validation of the Block, Willett, and National Cancer Institute Food Frequency Questionnaires, *American Journal of Epidemiology*, 154: 1089-1099, 2001.

[19] A cross-sectional study design is a sample of a reference population examined at a given point in time. (Szklo and Nieto, Epidemiology Beyond the Basics, page 38, Aspen Publishers, 2000)

[20] In a case-control study, a group of cases are identified as the individuals in whom the disease of interest was diagnosed during a given year and controls are selected from individuals who do not have the disease in the same time period (Szklo and Nieto, Epidemiology Beyond the Basics, page 29 Aspen Publishers, 2000).

coronary artery disease[21] cases and 345 controls. There was no significant association between green tea intake and coronary artery disease for the entire group. However, in a subgroup analysis which excluded subjects that were under dietary or drug therapy for diabetes (126 cases of coronary artery disease and 323 controls), there was a significant association between the consumption of four or more cups of green tea per day and decreased incidence of coronary artery disease in men. No association was found in women.

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,[22] and the overall consistency[23] 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.

Based on the discussion in Section II above, the totality of the scientific evidence in this case includes the four intervention studies on green tea finding no evidence of an effect on CVD; the four observational studies on green tea, three of which (two cross-sectional studies and one hybrid design) reported a correlation between green tea and a reduced risk of CVD; and the three intervention studies on green tea extract finding no evidence of an effect. As discussed below, FDA has determined that this evidence is not credible to support the relationship between consumption of green tea or green tea extract and a reduced risk of CVD.

There were four intervention studies on green tea that established no evidence of an effect. Three of these four studies (Hodgson et al., 1999; Princen et al., 1998; Hirano-Ohmori et al., 2005) were randomized, controlled intervention studies. The fourth (van het Hof et al., 1997) did not randomize, but used an alternative to randomization called "minimization."[24]

Randomized, controlled intervention studies are considered the "gold standard" for establishing the presence or absence of an effect (Barton, 2005). In such studies, one group of subjects is randomly assigned to be the treatment group and another group is randomly assigned to be the

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[21] Coronary artery disease was defined in this study as at least one significant coronary artery stenosis. The authors defined coronary artery stenosis as when 75% or greater luminal narrowing occurred at one or more major coronary arteries or when 50% or greater narrowing occurred at left main coronary artery (Sasazuki et al., 2000).
[22] See *supra,* note 10.
[23] See *supra,* note 11.
[24] See Altman et al. (2001) ("Minimization is an acceptable alternative to random assignment."). Minimization tries to balance intervention groups for specific factors. In van het Hoff et al. (1997), the participants were matched for age, sex and body mass index (BMI).

control group (Sempos et al., 1999). Both groups are followed over time and the effect of the substance on the disease or surrogate marker of the disease is evaluated.

Randomized, controlled intervention studies provide the strongest evidence of whether or not there is a relationship between a substance and a reduced risk of a disease.[25] Intervention studies test effects on a condition from exposure to a substance in a very controlled environment, that is, the investigator controls whether the subjects receive the substance. Through random assignment of subjects to the treatment and control groups, these studies avoid selection bias -- that is, the possibility that those subjects most likely to have a favorable outcome independent of an intervention are preferentially selected to receive the intervention. Potential bias is also reduced by "blinding" the study so that the subjects do not know whether they are receiving the intervention, or "double blinding," in which neither the subjects or the researcher who assesses the outcome know who is in the treatment group and who is in the control group. By controlling the test environment, including the amount and composition of substance consumed and all other dietary factors, these studies also can minimize the effects of variables or confounders on the results.[26] For these reasons, such studies can provide convincing evidence of a cause and effect relationship between an intervention and an outcome (Kraemer et al., 2005 at 113).

In this case, there are four such studies for green tea. These studies, which were specifically designed and controlled to address the question of whether there is a relationship between green tea and reduced risk of CVD, found no evidence to support the relationship. Therefore, these studies establish that there is no credible evidence to support the proposed claim.

In addition, there were three randomized, controlled intervention studies that evaluated the relationship between green tea extract consumption and risk of CVD (Young et al., 2002; Freese et al., 1999; Princen et al., 1998). These studies found no evidence of a relationship between green tea extract and the reduced risk of CVD. Therefore, there is no credible evidence to support a relationship between green tea extract and reduced risk of CVD.

As stated above, the totality of the evidence included four observational studies on green tea and CVD. These studies (three cross-sectional studies and one hybrid design applying case-control analysis to data obtained through cross-sectional methods), which are all retrospective studies, had inconsistent results. Two of the cross-sectional studies and the one hybrid study reported a correlation between green tea consumption and CVD (Kono et al., 1996; Tokunaga et al., 2002, Sasazuki et al., 2000). One cross-sectional study reported no correlation (Tsubono and Tsugane, 1997). Because of the presence of the intervention studies discussed above, which were designed and controlled to test the relationship and found no evidence, any potential hypotheses of a correlation between green tea and CVD that were generated by the observational studies here have not been borne out.

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[25] See *supra*, note 5.

[26] Confounders are factors associated with both the disease in question and the intervention, and that if not controlled for, prevent an investigator from being able to conclude that an outcome was caused by an intervention. 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]

Even the best-designed observational studies cannot establish cause and effect between an intervention and an outcome (Kraemer et al, 2005 at 114). Observational studies are studies in which the investigator simply observes what happened to participants (Kraemer et al., 2005 at 114). The investigator does not control the consumption of the substance by the subjects. In such studies, nutritional exposure is estimated from a food frequency questionnaire frequency of disease is observed, and associations between a suspected nutritional exposure and disease risk are estimated using statistical techniques (Sempos et al., 1999).

All of the observational studies here are retrospective, rather than prospective.[27] In retrospective studies, investigators review the records of subjects and interview subjects after the outcome has occurred. A common weakness of observational studies is the limited ability to determine the actual food or nutrient intake for the population studied. Retrospective studies are particularly vulnerable to measurement error and recall bias, because they rely on subjects' recollections of what they consumed in the past. Because of the limited ability of observational studies to control for variables, they are often susceptible to confounders, such as complex nutrient/disease interactions. Well-designed observational studies can provide useful information for identifying possible associations to be tested by intervention studies, but they cannot provide convincing evidence of cause and effect (Kraemer et al., 2005 at 107). However, as discussed above, intervention studies can test whether there is evidence to show a cause and effect between a substance and a reduced risk of a disease.

Cross-sectional studies, such as the studies on green tea here,[28] are a particular type of retrospective observational study in which the exposure to the substance and the disease risk are measured at the same time.[29] Such studies may consist, for example, of a single interview or examination, or a survey administered once (Kraemer et al., 2005 at 113-14). These studies can be useful for identifying possible correlates and can be useful for providing baseline information for subsequent prospective studies (Kraemer et al., 2005 at 99-100). However, because cross-sectional studies measure the exposure to the substance and the disease risk at the same time, they cannot establish that consumption of the substance came before the health-related outcome, and therefore cannot show a cause and effect relationship. Further, cross-sectional studies are considered to be a "relatively weak method for studying diet-disease associations" because they can be subject to significant potential measurement error regarding dietary intake due to inaccuracy of survey methods used and limited ability to control for dietary intake variations (Sempos et al., 1999). For these reasons, cross-sectional study results "have the potential to mislead as errors of interpretation are very common" (Kraemer et al., 2005 at 103).

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[27] Observational studies may be prospective or retrospective. In prospective studies, investigators recruit subjects and observe them prior to the occurrence of the outcome. 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]

[28] As previously noted, three of the four observational studies here are cross-sectionals and the fourth, a hybrid design, relies on data obtained through cross-sectional methods.

[29] Reference Manual on Scientific Evidence, Reference Guide on Epidemiology at 343. *See also* Kraemer et al. (2005), at. 99-103.

Where randomized, controlled intervention studies exist on a substance/disease relationship, they trump the findings of any number of observational studies (Barton, 2005). This is because such studies are designed and controlled to test whether there is evidence of a cause and effect relationship between the substance and the reduced risk of a disease, whereas observational studies are only able to identify possible associations.[30] There are numerous examples -- such as vitamin E and CVD, folate and CVD, and beta-carotene and lung cancer -- where associations identified in observational studies have been publicized. However, when randomized, controlled intervention studies were later conducted to test these possible associations, the intervention studies found no evidence to support the relationships.[31] In this particular case, the totality of the evidence already includes intervention studies that tested the relationship between green tea or green tea extract and a reduced risk of CVD and those studies found no evidence of a relationship.

Therefore, for the reasons discussed above, the agency concludes, based on the totality of the evidence, that there is no credible evidence to support a relationship between consumption of green tea or green tea extract and a reduced risk of CVD.

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 consumption of green tea or green tea extract and a reduction of a number of risk factors associated with CVD. 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

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[30] In a situation where the totality of the evidence consists of observational studies identifying a possible association, without intervention studies showing no evidence of an effect, it may be possible that the totality of the existing evidence supports an appropriately qualified health claim.

[31] See Lichtenstein and Russell (2005) (citing these and other examples in which publicized observational study results suggested a beneficial dietary substance/disease association, but it was subsequently demonstrated in randomized, controlled intervention studies that the substance did not confer a benefit or actually increased the risk of the disease).

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 green tea or green tea extract and a reduction of a number of risk factors associated with CVD. Thus, FDA is denying your petition for a qualified health claim based on the following proposed claim:

Daily consumption of at least 5 fluid ounces (150 mL) of green tea as a source of catechins may reduce a number of risk factors associated with cardiovascular disease. FDA has determined that the evidence is supportive, but not conclusive, for this claim. (Green tea provides 125 mg catechins per serving when brewed from tea and 125 mg catechins as a pre-prepared beverage).

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 Schneeman

Barbara O. Schneeman, Ph.D.
Director
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Appendix 1

Please See Docket # 2005Q-0297, QHC1, for the following studies:

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