DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

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RE: Health Claim Petition: Green Tea and Reduced Risk of Cancer Health Claim (Docket number 2004Q-0083)

Dear Dr. Lee:

This letter responds to the health claim petition dated January 27, 2004, submitted to the Food and Drug Administration (FDA or the agency), on behalf of Fleminger, Inc., as supplemented by your letter of May 21, 2004, pursuant to Section 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)). The petition requested that the agency authorize a qualified health claim characterizing the relationship between the consumption of green tea and a reduced risk of cancer. This petition proposed as a model qualified health claim: "Daily consumption of 40 ounces of typical green tea containing 710 μg/ml of natural (-)-epigallocatechin gallate (EGCG) may reduce the risk of certain forms of cancer. There is scientific evidence supporting this health claim although the evidence is not conclusive."

FDA filed the petition on March 18, 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 for procedures on qualified health claims.[1]

The agency received one comment on the petition. The comment was from a consumer. The comment expressed support for the approval of the petition in a one-sentence statement. FDA considered the comment in its evaluation of this petition.

This letter sets forth the results of FDA's scientific review of the evidence for the proposed qualified health claim related to consumption of green tea and the reduced risk of certain cancers. This letter also sets forth the factors that FDA intends to consider in the exercise of its enforcement discretion for qualified health claims regarding the consumption of green tea and a reduced risk of breast cancer and the consumption of green tea and a reduced risk of prostate cancer. Finally, this letter sets forth the basis for FDA's determination that there is not credible evidence to support a claim with respect to all other types of cancer.

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[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]

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.[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 can not 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

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[2] See *Whitaker v. Thompson*, 353 F.3d 947, 950-51 (D.C. Cir 2004) (Reh'g *en banc* denied on March 9, 2004) upholding FDA's interpretation of what constitutes a health claim.
[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.

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 (Institute of Medicine, National Academies of Science, 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), study category , 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 "typical green tea containing 710 mcg/ml of natural (-)-epigallocatechin gallate (EGCG)" as the substance that is the subject of the proposed claim. None of the scientific data evaluated by the agency identified specific amounts of EGCG in green tea. Therefore, the agency considered the relationship between green tea and a reduced risk of certain types of cancers. 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)). 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 is made with fermented leaves. Therefore the agency concludes that green tea is a specific 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 cancer as the disease that is the subject of the proposed claim. Cancer is a constellation of more than 100 different diseases, each characterized by the uncontrolled growth and spread of abnormal cells (American Cancer Society, 2004).

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[9] See *supra*, note 3.

[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.

Cancer is categorized into different types based on the specific organ site. Cancers at different organ sites have different risk factors, treatment modalities, and mortality risk (American Cancer Society, 2004). Both genetic and environmental risk factors may affect the risk of different types of cancers. Risk factors may include a family history of a specific type of cancer, cigarette smoking, alcohol consumption, overweight and obesity, exposure to ultraviolet or ionizing radiation, exposure to cancer-causing chemicals, and dietary factors. The etiology, risk factors, diagnosis, and treatment for each type of cancer are unique. [13] Since each form of cancer is a unique disease based on organ site, risk factors, treatment options, and mortality risk, each form of cancer must be individually evaluated in a health claim petition. As a result, the agency considered whether the studies supported the potential substance - disease relationship for any type of cancer, each of which constitutes a disease under 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 levels necessary to justify a claim must be demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under applicable food safety provisions of the Act.

FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the Act. For conventional foods, this evaluation involves considering whether the ingredient that is the source of the substance is GRAS, approved as a food additive, or authorized by a prior sanction issued by FDA (see 21 CFR 101.70(f)). Dietary ingredients in dietary supplements, however, are not subject to the food additive provisions of the act (see section 201(s)(6) of the Act (21 U.S.C. § 321(s)(6)). Rather, they are subject to the adulteration provisions in section 402 of the Act (21 U.S.C. 342) and, if applicable, the new dietary ingredient provisions in section 413 of the Act (21 U.S.C. 350b), which pertain to dietary ingredients that were not marketed in the United States before October 15, 1994. The term "dietary ingredient" is defined in section 201(ff)(1) of the Act and includes vitamins; minerals; herbs and other botanicals; dietary substances for use by man to supplement the diet by increasing the total daily intake; and concentrates, metabolites, constituents, extracts, and combinations of the preceding types of ingredients.

Tea is a beverage that is among the most ancient beverages in the world. It is the second most highly consumed beverage in the world, after water, with oolong tea making up about 2% of tea consumption, green tea about 20%, and black tea almost 80% (NCI, DCPC Chemoprevention Branch and Agent Development Committee, 1996). The petition proposes a qualified health claim for reduced risk of various types of cancer based on the consumption of 40 ounces (five cups) of green tea per day, and evidence cited in the petition shows that in some populations 10 cups of green tea per day is consumed regularly (Graham, 1992).

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[13] http://www.nci.nih.gov/cancertopics/commoncancers

The petition asserts that green tea is generally recognized as safe (GRAS) pursuant to section 409 of the Act. Tea (*Thea sinensis*) is listed in 21 CFR 182.20 as GRAS for its intended use. Although compounds found in green tea have been observed to have interactions with certain nutrients and drugs, inclusion of green tea as part of the diet has not generally been associated with having adverse affects. The polyphenols in green tea may interfere with the absorption of inorganic iron, and the vitamin K contained in green tea may influence the efficacy of the anticoagulant warfarin, although these interactions can be mediated by the addition of ascorbic acid to the diet and by the regulation of the drug dosage, respectively (Institute of Medicine, National Academies of Science, 2001).

Based on the above, FDA concludes under the preliminary requirements of 21 CFR 101.14(b)(3)(ii) that the use of green tea as described in the qualified health claims discussed in section IV, is safe and lawful.

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

FDA has identified the following markers to use in identifying risk reduction for purposes of a health claim evaluation involving cancer: incident cases of the particular cancer being studied, and recurrent colon/rectal polyps for colon/rectal cancer. Colon/rectal polyp recurrence has been used as a surrogate marker for colon/rectal cancer and has been used by the National Cancer Institute as a surrogate marker for colon cancer prevention (Schatzkin et al., 1994). To evaluate the potential effects of green tea consumption on cancer risk, FDA considered these markers as indicators or predictors of disease.

The petition cited 220 publications as evidence to substantiate the relationship for this claim (see Docket # 2004Q-0083). These publications consisted of 65 review articles, 2 abstracts, 1 meta-analysis, 12 *in vitro* studies, 12 animal studies, 92 observational studies that did not evaluate the substance and disease relationship, and 36 observational studies which did evaluate the relationship between green tea and cancer.

In addition to the studies in your petition that the agency considered, FDA considered three additional observational studies from a literature search which it conducted (Suzuki et al., 2004; Jian et al., 2004; Sonoda et al., 2004).

Below, we assess all of the available scientific information identified in relation to the proposed claim.

A. Assessment of Review Articles, Meta-Analyses and Abstracts

Although useful for background information, the review articles, meta-analysis, and abstracts 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 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. As a result, the review articles, meta-analysis, and abstracts 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 relationship because such studies cannot mimic the normal human physiology that may be involved in the risk reduction of any type of cancer, nor can the studies mimic the human body's response to the consumption of green tea. Therefore, FDA cannot draw any scientific conclusions from the animal or *in vitro* studies regarding green tea and the reduction of risk of any type of cancer.

C. Assessment of Intervention Studies

No intervention studies were submitted by the petitioner relating green tea and cancer risk reduction. Furthermore, the agency could not identify any relevant intervention studies from an independent literature search which it conducted.

D. Assessment of Observational Studies

There were 92 observational studies that evaluated a general category of food (e.g., tea) and not the specific substance of the claim (i.e., green tea). Because these studies did not assess the substance that is the subject of the proposed claim, they did not provide information from which scientific conclusions could be drawn regarding the substance - disease relationship.

FDA identified 39 observational studies that evaluated the relationship between green tea and one or more cancers. These studies consisted of seven prospective cohort studies,[14] one nested case-control study,[15] and 31 case-control studies.[16] Below, the agency discusses the

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[14] In a cohort study, a group of healthy people or cohort is identified and followed up for a certain time period to ascertain the occurrence of disease and or health related events. (Epidemiology Beyond the Basics, page 24, Aspen Publishers, 2000).

[15] A nested-case control study uses subjects from a defined cohort. Cases are subjects diagnosed with the disease (i.e. cancer) in the cohort and controls are subjects selected from individuals at risk each time a case (i.e. cancer) is diagnosed. (Epidemiology Beyond the Basics, page 34, Aspen Publishers, 2000).

[16] 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 (Epidemiology Beyond the Basics, page 29 Aspen Publishers, 2000).

observational studies for each specific cancer type, because each individual cancer is considered its own unique disease, as discussed Section I B above.

Breast Cancer
Five studies evaluated green tea consumption and breast cancer risk (Inoue et al., 2001; Nakachi et al., 1998; Suzuki et al., 2004 (consisting of two separate cohort studies); and Wu et al., 2003). The subjects in two of these studies (Inoue et al., 2001; Nakachi et al., 1998) had already been diagnosed with breast cancer. Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease.[17] These claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim. As a result, FDA considers evidence from studies in individuals already diagnosed with breast cancer 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 cannot draw any scientific conclusions from these two studies (Inoue et al., 2001; Nakachi et al., 1998).

The remaining three studies were considered to be of high methodological quality (Suzuki et al., 2004 (consisting of two separate studies); and Wu et al., 2003). Suzuki et al. (2004) included two separate cohort studies from Japan to evaluate the relationship between green tea consumption and the risk reduction of breast cancer. Cohort I contained 14,409 subjects and 103 cases were followed for nine years. Drinking up to five cups of green tea per day was not significantly associated with breast cancer risk; relative risk 0.96 (95% CI 0.50-1.86).[18] Cohort II contained 20,595 subjects and 119 cases with seven years of follow-up. Green tea consumption (greater than five cups per day) was not significantly associated with breast cancer incidence; relative risk 0.85 (95% CI 0.43-1.66).

Wu et al. (2003) was a case-control study that evaluated green tea intake and breast cancer risk in female Asian Americans living in Southern California, and used 501 cases and 504 controls. Drinking 85.7 milliliters of green tea per day was significantly associated with a decreased risk of breast cancer; odds ratio 0.47 (95% CI 0.25-0.85).

Prostate Cancer
Two case-control studies evaluated green tea and prostate cancer risk (Jian et al., 2004; Sonoda et al., 2004). Both studies received high methodological quality ratings. Jian et al. (2004) evaluated green tea intake and prostate cancer using 130 cases and 274 controls from China.

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[17] See *supra*, note 2.

[18] Relative risk is expressed as the ratio of the risk (incidence) in exposed individuals to that in unexposed individuals (Epidemiology Beyond the Basics, page 93, Aspen Publishers, 2000).
It is calculated in prospective studies by measuring exposure (e.g. green tea intake) in subjects with and without disease (e.g. specific type of cancer). An adjusted relative risk controls for potential confounders. Confidence intervals provide a statistical analysis (p value) of relative risk. 95% Confidence intervals that include 1.0 are not statistically significant. "CI" stands for a Confidence interval.

Drinking three cups of green tea per day was significantly associated with a reduced risk of prostate cancer; odds ratio 0.27 (95% CI 0.15-0.48).[19] Sonoda et al. (2004) included 140 Japanese prostate cancer cases and controls. Drinking two to ten cups of green tea per day was not significantly associated with prostate cancer risk; odds ratio 0.67 (95% CI 0.27-1.64).

Gastric Cancer

Sixteen studies evaluated the relationship between green tea and gastric cancer risk (Mu et al., 2003; Galanis et al., 1998; Hoshiyama et al., 2002; Koizumi et al., 2003; Tsubono et al., 2001; Hoshiyama et al., 2004; Hoshiyama et al., 1992; Inoue et al., 1998; Inoue et al., 1994; Ji et al., 1996; Kono et al., 1988; Lee et al, 1990; Setiawan et al., 2001; Tajima et al., 1985; Ye et al., 1998; and Yu et al., 1995). One of these studies did not use statistics to evaluate the specific relationship between green tea and gastric cancer risk (statistics measured other parameters in the study) (Mu et al., 2003). 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 cancer risk. Thus when statistics are not performed on the specific substance/disease relationship we are unable to determine if there is a difference between the two groups. As a result, this study provided no information about how green tea may reduce the risk of gastric cancer, hence, no scientific conclusions could be drawn from it.

Eleven of the 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 appropriately validated (Galanis et al., 1998, Hoshiyama et al., 2004; Hoshiyama et al., 1992; Inoue et al., 1998; Inoue et al., 1994; Ji et al., 1996;; Lee et al, 1990; Setiawan et al., 2001; Tajima et al., 1985; Ye et al., 1998; and Yu et al., 1995). 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.[20] As a result, these studies provided no information on the accuracy of how green tea intake was measured, and hence, no scientific conclusions could be drawn from them.[21]

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[19] Odds ratio is the odds of developing the disease in exposed compared to unexposed individuals (Epidemiology Beyond the Basics, page 29, Aspen Publishers, 2000). It is calculated in case control studies by measuring disease (e.g. specific type of cancer) development in subjects based on exposure (e.g. green tea). Adjusted odds ratio controls for potential confounders. Confidence intervals provide a statistical analysis (p value) of relative risk. 95% Confidence intervals that include 1.0 are not statistically significant. "CI" stands for a Confidence interval.

[20] "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.

[21] "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,

Of the four remaining studies (Hoshiyama et al., 2002; Koizumi et al., 2003; Tsubono et al., 2001; and Kono et al., 1988), three were prospectively designed cohort studies (Hoshiyama et al., 2002; Koizumi et al., 2003; Tsubono et al., 2001;) and the remaining study was case-control designed (Kono et al., 1988).

The three prospectively designed cohort studies received high methodological quality ratings. Hoshiyama et al. (2002) followed a cohort of 30,370 males and 42,481 females from Japan for approximately nine years of follow-up with the endpoint being stomach cancer death. The adjusted relative risk for drinking greater than ten cups of green tea and stomach cancer death was 1.0 for men (95% confidence intervals (CI) 0.5-2.0) and 0.7 for women (95% CI 0.3-2.0) and these associations are not statistically significant. Tsubono et al. (2001) included 26,611 Japanese men and women and evaluated the relationship between green tea intake and risk of gastric cancer. After a seven year follow-up, 419 subjects were diagnosed with gastric cancer. An adjusted relative risk of 1.4 (95% CI 1.0-1.9) was observed between drinking less than one cup of green tea per day and drinking five cups of green tea per day indicating that there was not a statistically significant association. Koizumi et al. (2003) included 39,604 Japanese men and women followed for nine years. In a combined analysis of Tsubono et al., (2001) cohort and Koizumi et al., (2003) cohort, there was no association between drinking more than five cups per day of green tea and gastric cancer risk; adjusted relative risk of 1.06 95% CI 0.86-1.30) (Koizumi et al., 2003).

One case-control study evaluated green tea consumption and gastric cancer risk. It received a moderate methodological quality rating (Kono et al., 1988). Kono et al. (1988) included 139 stomach cancer cases and 2,574 hospital controls (controls taken from hospitalized patients without cancer) as well as 278 population controls (controls from the general population) from Japan. There was no association between green tea intake and cancer risk when the cases were compared to the hospital controls; adjusted odds ratio of 0.5 (95% CI 0.3-1.1) but an association was reported when compared to the population controls; odds ratio 0.3 (95% CI 0.1-0.7).

Lung Cancer

Four case-control studies evaluated the relationship between green tea and lung cancer (Chengyu et al., 1992; Le Marchand et al., 2000; Tewes et al., 1990; Zhong et al., 2001). Three of the 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 appropriately validated. 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.

As a result, these studies provided no information on the accuracy of how green tea intake was measured, and hence no scientific conclusions could be drawn from them.[22]

Willett, and National Cancer Institute Food Frequency Questionnaires, *American Journal of Epidemiology*, 154: 1089-1099, 2001.

[22] See *supra*, note 21.

The remaining study, a case control, received a high methodological quality rating (Le Marchand et al., 2000). Le Marchand et al. (2000) conducted a case-control study in Hawaii with 582 lung cancer cases and 582 controls. Green tea intake had no association with lung cancer incidence, and the adjusted odds ratio for the highest quartile of green tea intake was 0.9 (95% CI 0.5-1.6) compared to the lowest quartile of green tea intake.

Colon/Rectal Cancer

Seven studies evaluated the relationship between colon/rectal cancer and green tea intake (Miller et al., 1983; Tajima et al., 1985; Watanabe et al., 1984; Kono et al., 1991; Ji et al., 1997; Inoue et al., 1998; and Kato et al., 1990). One study measured green tea consumption and colon/rectal cancer incidence. However, the study did not calculate the odds ratio[23] for colon/rectal cancer incidence and green tea intake. Without an odds ratio, it is not possible to determine if green tea intake reduced the risk of colon/rectal cancer. Therefore, the substance/disease relationship could not be evaluated in this study. As a result, this study provided no information about how green tea may reduce the risk of colon/rectal cancer, hence, no scientific conclusions could be drawn from it (Miller et al., 1983).

Five of the studies (Tajima et al., 1985; Watanabe et al., 1984; Ji et al., 1997; Inoue et al., 1998; and Kato et al., 1990) 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 appropriately validated. 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.[24] As a result, these studies provided no information on the accuracy of how green tea intake was measured, and hence no scientific conclusions could be drawn from them.[25]

The remaining study received a high methodological quality rating (Kono et al., 1991). Kono et al. conducted a case-control study with 80 Japanese men with adenoma colon/rectal polyps and 1,180 polyp-free men to evaluate green tea intake and risk of colon/rectal polyps, a surrogate marker for colon/rectal cancer. There was no association between green tea consumption (greater than or equal to five cups per day) and polyp occurrence.

Esophageal Cancer

Four studies evaluated the relationship between green tea and esophageal cancer risk (Mu et al., 2003; Wang et al., 1999; Inoue et al., 1998 and Gao et al., 1994). One of these studies did not use statistics to evaluate the specific relationship between green tea and esophageal cancer risk (statistics measured other parameters in the study) (Mu et al., 2003). 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 cancer risk. Thus, when statistics are not performed on the specific substance disease relationship we are unable to determine if there is a difference between the two groups. As a result, this study

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[23] See *supra*, note 19.
[24] See *supra*, note 20.
[25] See *supra*, note 21.

provided no information about how green tea may reduce the risk of esophageal cancer, hence, no scientific conclusions could be drawn from it.

The remaining three studies (Wang et al., 1999; Inoue et al., 1998 and Gao et al., 1994) 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 appropriately validated. 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.[26] As a result, these studies provided no information on the accuracy of how green tea intake was measured, and hence no scientific conclusions could be drawn from them.[27]

Pancreatic Cancer

Three case-control studies evaluated the relationship between pancreatic cancer and green tea consumption (Goto et al., 1990; Ji et al., 1997; and Mizuno et al., 1992). None of the three studies provided 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 appropriately validated. 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.[28] As a result, these studies provided no information on the accuracy of how green tea intake was measured, and hence no scientific conclusions could be drawn from them.[29]

Ovarian Cancer

One case-control study (Zhang et al. 2002) evaluated the relationship between green tea consumption and risk of ovarian cancer. It did not provide any information as to whether the food frequency questionnaire in the study, which was used for the collection of green tea consumption data from study subjects, had been appropriately validated. 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.[30] As a result, these studies provided no information on the accuracy of how green tea intake was measured, and hence no scientific conclusions could be drawn from them.[31]

Liver Cancer

One study (Mu et al., 2003) evaluated the relationship between green tea consumption and risk of liver cancer. This study did not use statistics to evaluate the specific relationship between green tea and liver cancer risk (statistics measured other parameters in the study) (Mu et al.,

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[26] See *supra*, note 20.
[27] See *supra*, note 21.
[28] See *supra*, note 20.
[29] See *supra*, note 21.
[30] See *supra*, note 20.
[31] See *supra*, note 21.

2003). 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 cancer risk. Thus when statistics are not performed on the specific substance disease relationship we are unable to determine if there is a difference between the two groups. As a result, this study provided no information about how green tea may reduce the risk of liver cancer, hence, no scientific conclusions could be drawn from it.

Bladder Cancer

One study (Wakai et al., 1993) evaluated the relationship between green tea consumption and risk of bladder cancer. However, the subjects in this study had already been diagnosed with bladder cancer. Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease.[32] These claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim. As a result, FDA considers evidence from studies in individuals already diagnosed with bladder cancer 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) that 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 cannot draw any scientific conclusions from this study (Wakai et al., 1993).

Skin Cancer

One study (Hakim et al., 2000) evaluated the measured green tea consumption and skin cancer incidence. This study measured green tea consumption and skin cancer incidence. However, the study did not calculate the odds ratio[33] for skin cancer incidence and green tea intake. Without an odds ratio, it is not possible to determine if green tea intake reduced the risk of skin cancer. Therefore, the substance/disease relationship could not be evaluated in this study. As a result, this study provided no information about how green tea may reduce the risk of skin cancer, hence, no scientific conclusions could be drawn from it.

Combined Analysis of Various Forms of Cancer

Two prospective cohort studies in Japan evaluated green tea intake and total cancer incidence (Nagano et al., 2002; Imai et al., 1997). These studies did not provide any information as to whether the food frequency questionnaire in the study, which was used for the collection of green tea consumption data from study subjects, had been appropriately validated. 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.[34] As a result, these studies provided no information on the accuracy of how green tea intake was measured, and hence no scientific

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[32] See *supra*, note 2.
[33] See *supra*, note 19.
[34] See *supra*, note 20.

conclusions could be drawn from them.[35] In addition the studies combined all forms of cancer into one single analysis. As discussed in Section I, each form of cancer is a unique disease based on organ site, risk factors, treatment options, and mortality risk. Hence it is not possible to draw any scientific conclusions regarding individual cancer risks from studies that combine multiple forms of cancer into a single analysis. Nagano et al., (2001) did evaluate the risk of some individual forms of cancer in this publication as well as total cancers combined (e.g., stomach, colon/rectal, liver/ pancreatic, lung, breast and bladder), however as stated above the study did not provide any information on the validation of the food frequency questionnaire and as a result the study provided no information on the accuracy of how green tea intake was measured, and hence no scientific conclusion could be drawn from it.

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), study category, 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[36], and the overall consistency[37] 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.

Breast Cancer

As discussed in Section II of this letter, three studies provided information about whether green tea may reduce the risk of breast cancer. Although two Japanese cohort studies found no association between green tea consumption and breast cancer (Suzuki et al., 2004 (consisting of two separate studies), one case-control study reported that, with green tea consumption, there was a reduction in breast cancer risk in Asian-Americans from California (Wu et al., 2003). FDA finds that there is very limited credible evidence for a qualified health claim specifically for green tea and breast cancer. However, the reported findings of Wu et al., 2003 have not been replicated, and replication of scientific findings is important in order to substantiate results.[38] Moreover, consistency of findings among similar and different study designs is important for evaluating the strength of the scientific evidence.[39] Furthermore, prospectively designed studies provide stronger evidence for an association than case-control studies since there are fewer forms of bias.[40]

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[35] See *supra*, note 21.
[36] See *supra*, note 10.
[37] See *supra*, note 11.
[38] See *supra*, note 10.
[39] See *supra*, note 11.
[40] See *supra*, note 3.

Based on FDA's review of the strength of the total body of publicly available scientific evidence for a claim about green tea and reduced risk of breast cancer, FDA ranks this evidence as the lowest level for a qualified health claim.[41] For the reasons given above, FDA concludes that it is highly unlikely that green tea reduces the risk of breast cancer.

Prostate Cancer

As discussed in Section II of this letter, two studies provided information about whether green tea may reduce the risk of prostate cancer. These involved two case-control studies from China and Japan, respectively (Jian et al., 2004; Sonoda et al., 2004). Each of the two studies were small (fewer than 150 cases each) in size and both received high methodological quality ratings. Although Sonoda et al. (2004) reported no association, Jian et al. (2004) reported a decrease in prostate cancer risk with green tea intake. FDA finds that there is very limited credible evidence for a qualified health claim specifically for green tea and prostate cancer. However, the reported findings of Jian et al., (2004) have not been replicated, and replication of scientific findings is important in order to substantiate results.[42] Moreover, consistency of findings among similar and different study designs is important for evaluating the strength of the scientific evidence.[43] Furthermore, both of the studies are retrospectively designed (case-control). Prospectively designed studies provide stronger evidence for an association than case-control studies since there are fewer forms of bias.[44] Based on FDA's review of the strength of the total body of publicly available scientific evidence for a claim about green tea and reduced risk of prostate cancer, FDA ranks this evidence as the lowest level for a qualified health claim.[45] For the reasons given above, FDA concludes that it is highly unlikely that green tea reduces the risk of prostate cancer.

Gastric Cancer

As discussed in Section II of this letter, four studies provided information about whether green tea may reduce the risk of gastric cancer. All of these studies were conducted in Japan. None of the three prospectively designed cohort studies that evaluated green tea and gastric cancer risk reported an association between green tea and gastric cancer risk reduction (Hoshiyama et al., 2002; Koizumi et al., 2003; Tsubono et al., 2001). The three cohort studies collectively represented well in excess of 100,000 men and women. The one case-control designed study had ambiguous results (Kono et al., 1988) in that there was a protective association for green tea consumption and gastric cancer when population controls were used (278 men and women), but not when hospital controls were used (2574 men and women). The more reliable and largest studies (the three prospective cohorts) reported no relationship between green tea consumption and gastric cancer. The reported findings from the case-control study (Kono et al., 1998) suggested a beneficial relationship for only the population based controls.

As previously mentioned, a health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)), and the substance for which the health

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[41] See *supra*, note 3.
[42] See *supra*, note 10.
[43] See *supra*, note 11.
[44] See *supra*, note 3.
[45] See *supra*, note 3.

claim is requested 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)).

The incidence of gastric cancer is high in Japan, while the incidence is very low in the United States (Hoenberger et al., 2003). Cancer is caused by external (e.g., dietary intake and infections)[46] and internal factors[47] (e.g., genetics, hormones, immune function). An estimated 50-80% of human cancer is caused by external factors.[48] Different external or internal causal factors may alter the etiology of cancer in different populations. The precise etiology of gastric cancer is unknown, however two factors, high salt intake and Helicobacter pylori (H. pylori) infection, are associated with an increased risk of the disease and are external risk factors of gastric cancer.[49] High salt intake and the incidence H. Pylori infection are more prevalent in Japan than in the United States (Hoenberger et al., 2003; Key et al., 2004). High salt intake and H. Pylori infection are forms of bias[50] for the green tea and gastric cancer relationship in Japan in that they each affect the risk of developing gastric cancer independent of green tea consumption. Therefore, because of these two external factors, subjects in the studies conducted in Japan are not appropriate subjects when trying to determine whether there may be a reduction in risk of gastric cancer in the U.S. population. Accordingly, results of studies on the Japanese population cannot be extrapolated to reach conclusions about potential effects on the U.S. population. Thus, studies from the U.S. or other applicable countries (countries with H. Pylori infection rates and salt intake that are similar to the United States) are needed as part of the total body of evidence to evaluate green tea consumption and gastric cancer risk. The agency could find no studies that evaluated green tea and gastric cancer risk in people in the United States or other applicable populations. Based on the above, FDA concludes that there is no credible evidence supporting a relationship between green tea consumption and gastric cancer.

Lung Cancer
As discussed in Section II of this letter, one study provided information about whether green tea may reduce the risk of lung cancer (Le Marchand et al., 2000). This case-control study found no association between green tea consumption and lung cancer. Based on the above, FDA concludes that there is no credible evidence supporting a relationship between green tea consumption and lung cancer.

Colon/Rectal Cancer
As discussed in Section II of this letter, one study provided information about whether green tea may reduce the risk of colon/rectal cancer (Kono et al., 1991). This case-control study found no

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[46] External causal factors are environmental, lifestyle, nutritional or cultural factors (e.g. smoking chemical, radiation, dietary factors socioeconomic factors, and specific viruses).
[47] Internal causal factors are genetic, gender, race or inherent factors (metabolism and pH).
[48] Cancer Prevention and Control, Chapter 6, page 83, edited by Greenwald P., Kramer B., Weed D. Marcel Dekker Publishing, 1995.
[49] http://www.nci.nih.gov/cancertopics/pdq/prevention/gastric/HealthProfessional/page1
[50] Bias is defined as the result of systematic error in the selection of study participants and as a consequence the observed results of a study may be different from the true results (Epidemiology Beyond the Basics, pages 125-126 Aspen Publishing, 2000).

association between green tea and colon/rectal cancer. Based on the above, FDA concludes that there is no credible evidence supporting a relationship between green tea consumption and colon/rectal cancer.

Esophageal, Pancreatic, Ovarian, Liver, Bladder, Skin Cancers, and Combined Analysis of Various Cancers
As discussed in Section II of this letter, no studies provided information about whether green tea may reduce the risk of any of these cancers. Based on the above, FDA concludes that there is no credible evidence supporting a relationship between green tea consumption and any of these cancers.

IV. Other Enforcement Discretion Factors

Qualified health claims on the label or in the labeling of green tea are required to meet all applicable statutory and regulatory requirements under the Federal Food, Drug, and Cosmetic Act, with the exception of the requirement that a health claim meet the significant scientific agreement standard and the requirement that the claim be made in accordance with an authorizing regulation. Other exceptions to the general requirements for health claims that FDA intends to consider in the exercise of its enforcement discretion for qualified claims about green tea and reduced risk of both breast cancer and prostate cancer are discussed below, along with enforcement discretion factors specific to the green tea qualified health claims.

A. Disqualifying Nutrient Levels

Under the general requirements for health claims (21 CFR 101.14(e)(3)), a food may not bear a health claim if that food exceeds any of the disqualifying nutrient levels for total fat, saturated fat, cholesterol, or sodium established in § 101.14(a)(4). Disqualifying total fat levels for individual foods are above 13.0 g per reference amount customarily consumed (RACC), per label serving size, and, for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying saturated fat levels for individual foods are above 4.0 g per RACC, per label serving size, and, for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying cholesterol levels for individual foods are above 60 mg per RACC, per label serving size, and, for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying sodium levels for individual foods are above 480 mg per RACC, per label serving size, and, for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g.

All types of non-herbal brewed teas are similar in nutrient composition and the nutrient profile is described in the USDA Nutrient Database for Standard Reference as one item (e.g. "Tea, brewed, prepared with tap water"). Non-herbal brewed tea is composed mostly of water; 99.7g per 100g and 236.29g per 8 fl. oz. (U.S. Department of Agriculture, Agricultural Research Service. 2004. USDA Nutrient Database for Standard Reference, Release 17. Nutrient Data Laboratory Home Page, http://www.nal.usda.gov/fnic/foodcomp). Green tea does not exceed the disqualifying nutrient levels for total fat, saturated fat, cholesterol, and sodium specified in 21 CFR 101.14(a)(4) and, therefore, FDA does not need to consider the exercise of its enforcement

discretion for qualified health claims concerning green tea and breast cancer and green tea and prostate cancer to be used on the label or in the labeling of green tea when not used as an ingredient in other foods.

Green tea is also present as an ingredient for other foods. These other foods are primarily other beverages, such as tea blends and tea-juice blends, but can also include certain desserts, such as ice creams and cakes. FDA intends to consider the exercise of its enforcement discretion for qualified health claims for green tea and breast cancer and for green tea and prostate cancer to be used on the label or in the labeling of green tea-containing foods when the food does not exceed any of the disqualifying nutrient levels for fat, saturated fat, cholesterol, and sodium.

B. 10% Minimum Nutrient Content Requirement

Under the general requirements for health claims, a food may not bear a health claim unless it contains, prior to any nutrient addition, at least 10 percent of the Daily Value for vitamin A, vitamin C, iron, calcium, protein, or dietary fiber per RACC (see 21 CFR 101.14(e)(6)). The purpose of this provision is to prevent the use of health claims on foods of minimal nutritional value.

FDA has previously exempted certain foods from the 10% minimum nutrient content when it has been determined that such exemptions could assist consumers in maintaining healthy dietary practices. For example, the agency exempted spreads and dressings for salads from this requirement in the plant sterol/stanol esters and CHD health claim interim final rule (65 FR 54686 at 54711). More recently, FDA considered a qualified health claim for walnuts and a reduced risk of CHD, even though walnuts did not meet the minimum 10% nutrient requirement (Walnuts and Heart Disease Enforcement Discretion Letter, http://www.cfsan.fda.gov/~dms/qhcnuts3.html).

Green tea is composed of 99.7% water and contains no vitamin A, vitamin C, calcium, protein or fiber. It does contain 0.05 mg iron per RACC, which is well short of the 1.8mg required for the 10% minimum nutrient requirement for iron. Therefore, green tea does not meet the 10% minimum nutrient content requirement of 21 CFR 101.14(e)(6). However, as an essentially non-caloric food composed mostly of water, inclusion of green tea in the diet does not negatively affect the caloric balance of the diet and does not impede in any significant way the ability of consumers to maintain healthy dietary practices. Therefore, FDA intends to consider the exercise of its enforcement discretion for green tea that does not meet the 10% minimum nutrient content requirement in 21 CFR 101.14(e)(6). However, green tea-containing foods may not share this unique non-caloric attribute with brewed green tea. Therefore, FDA does not intend to consider the exercise of its enforcement discretion for green tea-containing foods that do not meet the requirements of § 101.14(e)(6).

The general requirements for health claims provide that, if the claim is about the effects of consuming the substance at other than decreased dietary levels, the level of the substance must be sufficiently high and in an appropriate form to justify the claim. Where no definition for

"high" has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect (see 21 CFR 101.14(d)(2)(vii)). However, the agency finds that this provision cannot be applied to either the qualified health claim for green tea and reduced risk of breast or the qualified health claim for green tea and reduced risk of prostate cancer because the scientific evidence for these relationships is not conclusive, and does not support the establishment of a recommended daily dietary intake level, or even a possible level of effect for the general U.S. population. Therefore, the agency continues to consider any label or labeling suggesting a level of green tea to be useful in achieving a reduction in the risk of breast or of prostate cancer for the general healthy population to be false and misleading under Section 403(a) of the Act.

V. Agency's Consideration of Disclaimers or Qualifying Language

We considered but rejected use of a disclaimer or qualifying language to accompany the proposed claims for green tea and cancers other than breast cancer and prostate cancer. 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 claims. 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 false 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."). 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 decisive connotation for which 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).

VI. 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

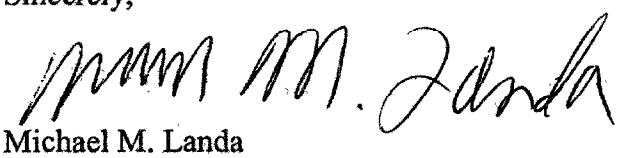
is no credible evidence to support qualified health claims for green tea consumption and a reduced risk of gastric, lung, colon/rectal, esophageal, pancreatic, ovarian, and combined cancers. Thus, FDA is denying these claims. However, FDA concludes that there is very limited credible evidence for qualified health claims specifically for green tea and breast cancer and for green tea and prostate cancer, provided that the qualified claims are appropriately worded so as to not mislead consumers. Thus, FDA intends to consider exercising enforcement discretion for the following qualified health claims:

1. "Two studies do not show that drinking green tea reduces the risk of breast cancer in women, but one weaker, more limited study suggests that drinking green tea may reduce this risk. Based on these studies, FDA concludes that it is highly unlikely that green tea reduces the risk of breast cancer."

2. "One weak and limited study does not show that drinking green tea reduces the risk of prostate cancer, but another weak and limited study suggests that drinking green tea may reduce this risk. Based on these studies, FDA concludes that it is highly unlikely that green tea reduces the risk of prostate cancer."

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 significant scientific agreement, that will support a qualified health claim for the claims that have been denied, that will no longer support the use of the above qualified health claims, or that raises safety concerns about the substance that is the subject of the claims.

Sincerely,



Michael M. Landa
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