



AUG 19 2008

Sin Hang Lee, MD  
Fleminger, Inc.  
160 Hawley Lane, Suite 205  
Trumbull, CT 06611

RE: Petition for Reconsideration: Letter Responding to Health Claim Petition  
Dated January 27, 2004: Green Tea and Reduced Risk of Cancer Health Claim  
(Docket No. 2004Q-0083)

Dear Dr. Lee:

This letter responds to your petition for administrative reconsideration of the decision by the Food and Drug Administration (FDA or the agency) regarding the health claim petition dated January 27, 2004, and supplemented May 21, 2004, for qualified health claims for green tea and reduced risk of certain cancers (Docket No. 2004Q-0083). Your petition for administrative reconsideration, dated August 5, 2005, and supported by your letters to the agency, dated July 1, 5, and 6, 2005, was submitted to the agency, on behalf of Fleminger, Inc., pursuant to 21 C.F.R. § 10.33. You requested that the agency reconsider its decision issued in a letter to you, dated June 30, 2005 (herein referred to as "the June 30<sup>th</sup> letter"). That letter was a response to the health claim petition filed by you, on behalf of Fleminger, Inc., requesting that the agency authorize a qualified health claim characterizing the relationship between the consumption of green tea and a reduced risk of cancer.

The June 30<sup>th</sup> letter set out the agency's determination that there was no credible evidence to support qualified health claims for the relationship between green tea consumption and a reduced risk of gastric, lung, colon/rectal, esophageal, pancreatic, ovarian, and combined cancers. Thus, FDA denied these claims. However, FDA did conclude that there was very limited credible evidence for qualified health claims specifically for the consumption of green tea and breast cancer and for the consumption of green tea and prostate cancer, provided that the qualified claims were appropriately worded so as to not mislead consumers. Thus, the June 30<sup>th</sup> letter sets out FDA's intent to consider exercising enforcement discretion for the following two qualified health claims:

*"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."*

FDA-2004-Q-0427

PDN

*“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.”*

#### Agency Decision on Your Request for Reconsideration

Under 21 C.F.R. § 10.33, interested persons may request that the Commissioner reconsider a decision rendered on a petition. 21 C.F.R. § 10.33 provides that a request for reconsideration shall be granted if the Commissioner determines that all the following apply: (1) the petition demonstrates that relevant information or views contained in the administrative record were not previously or not adequately considered; (2) the petitioner's position is not frivolous and is being pursued in good faith; (3) the petitioner has demonstrated sound public policy grounds supporting reconsideration; and (4) reconsideration is not outweighed by public health or other public interests. A petition for reconsideration may not be based on information or views not contained in the administrative record on which the decision was made. See 21 C.F.R. § 10.33(e).

An interested person who wishes to rely on information or views not included in the administrative record must submit them with a new health claim petition. If a request for reconsideration is granted, under 21 C.F.R. § 10.33(i), the Commissioner shall review and rule on the merits of the matter. As discussed below, you set out several arguments in support of your request for reconsideration of the June 30<sup>th</sup> letter. However, none of your arguments demonstrates that the agency failed to consider or adequately consider relevant information or views contained in the administrative record for the decisions in the June 30<sup>th</sup> letter. Therefore, we have determined that your request for reconsideration does not meet the criteria in 21 C.F.R. § 10.33(d)(1). Therefore, the agency denies your request for reconsideration of the June 30<sup>th</sup> agency letter.<sup>1</sup> Your arguments in support of your request for reconsideration are addressed below.

- 1. In section I of your August 5, 2005 petition for reconsideration, you argue that the claims contain confusing language. In support of your argument, you cite a number of media and industry reports and opinions of FDA's determination in the June 30th letter.**

The intent of a qualified health claim is to be truthful and not misleading by accurately describing the state of the science supporting the claim. FDA's determinations must be guided by the state of the science supporting a given health claim.

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<sup>1</sup> 21 C.F.R. § 10.33(d) requires that all four criteria be met for a request for reconsideration to be granted. Because we have determined that your request does not meet 21 C.F.R. § 10.33(d)(1), it is not necessary for us to address the other criteria in 21 C.F.R. § 10.33(d).

After an extensive scientific review of all the publicly available evidence, the agency believes that the two aforementioned claims most accurately describe the very limited credible evidence supporting the relationships between the consumption of green tea and reduced risk of breast and prostate cancer. To avoid confusion or mischaracterization of FDA's conclusions, the agency published the June 30<sup>th</sup> letter on the Internet at <http://www.cfsan.fda.gov/~dms/qhc-gtea.html>. By publishing the letter, FDA provided the public with unfiltered access to the agency's reasoning in evaluating the petition, as well as to the precise language of the two claims determined by the agency to be truthful and not misleading.

Your argument does not demonstrate that the agency failed to consider or adequately consider relevant information or views contained in the administrative record as required in 21 C.F.R. § 10.33(d)(1) to grant a request for reconsideration. Furthermore, the information you use to support your arguments, the media and industry reports and opinions issued after the June 30<sup>th</sup> letter, are not relevant here. Such reports and opinions are not part of the administrative record for the June 30<sup>th</sup> letter. As previously stated, a petition for reconsideration cannot be based on information and views not contained in the administrative record for the June 30<sup>th</sup> letter.

- 2. In section II of your August 5, 2005 petition for reconsideration, you argue that two studies (Suzuki et al., 2004; Sonoda et al., 2004) included in FDA's review of your qualified health petition should not have been considered by FDA because they were published after the submission of your petition and were not included in your original petition.<sup>2</sup>**

FDA's scientific review of a petition is not limited to information included in the original petition. As described in sections I and II(G) of FDA's guidance on qualified health claims, the *Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements*, claims will be based on the extent to which the totality of the publicly available evidence supports the claims. As further specified in the guidance, in addition to information and views included in the petition, the agency receives comments during the official comment period.

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<sup>2</sup> We note that your petition for reconsideration incorrectly refers to FDA's July 28, 2005 letter as a "ruling." You contend that the "ruling" in the letter dictates that FDA should not have considered the Suzuki et al., 2004 and Sonoda et al., 2004 studies because they were not made public until after the date of your submission. FDA's July 28, 2005 letter was correspondence intended to provide clarification on the reconsideration process under 21 C.F.R. § 10.33 and does not constitute an agency ruling on any matter. The letter suggests that you review FDA's regulations at 21 C.F.R. § 10.33 if you wish to submit a request for reconsideration and states that "if you wish to rely on information or views not previously included in the record of your January 17, 2004 petition ... you would need to submit a new petition, rather than seeking only reconsideration." This statement correctly states the requirement in 21 C.F.R. § 10.33(e) that a petition for reconsideration may only be based on information contained in the administrative record on which the decision was made. The studies in question were appropriately included in the administrative record for the June 30<sup>th</sup> letter.

Furthermore, in its evaluation of every health claim or qualified health claim petition, the agency conducts a literature search for additional publicly available evidence relevant to its scientific review that is not included in either the petition or comments to ensure that any claims are based on the totality of publicly available evidence. The studies you contend should not have been considered, Suzuki et al. (2004) and Sonoda et al. (2004) were obtained by the agency in the literature search conducted as part of the scientific review of your petition. This detail is described on page six, in Section II, of the June 30<sup>th</sup> letter. All the studies considered by the agency are included in the administrative record.

The fact that the agency identified two studies through its literature search that were not included in your original qualified health claim petition does not demonstrate that the agency failed to consider or adequately consider relevant information or views contained in the administrative record as required in 21 C.F.R. § 10.33(d)(1) to grant a request for reconsideration.

**3. In section III and IV of your August 5, 2005 request for administrative reconsideration and in sections I, II, III, and IV of your July 5, 2005 letter, you question the agency's scientific review of the studies about the green tea and breast or prostate cancer qualified health claim. You outlined the following concerns:**

a) You assert that Suzuki et al. (2004) is a short communication.

Agency's Response:

The short communication by Suzuki et al. (2004) provided sufficient information about the two studies for the agency to evaluate them individually based on the scientific review process described in section I of the June 30<sup>th</sup> letter. Therefore, the fact that the communication is short does not demonstrate that the agency failed to consider or adequately consider relevant information or views contained in the administrative record of the June 30<sup>th</sup> letter.

b) You assert that Suzuki et al. (2004) consists of two cohort studies that are flawed because "*...in Japan at the time of the survey, the majority of patients with cancer were not told the true diagnosis...and that the diagnosis of adenocarcinoma had been histologically confirmed in 80 percent of the cases.*" You cite to Tsubono et al. (2001) as the basis for your assertion.

Agency's Response:

Tsubono et al. (2001) used the same cohort as Suzuki et al. (2004) but evaluated gastric cancer whereas Suzuki et al. (2004) evaluated breast cancer. The Suzuki et al. (2004) article states "*through population based cancer registries, 103 incident cases of breast cancer were identified in cohort 1 and 119 in cohort 2.*" Suzuki et al. (2004) does not mention using questionnaires to assess cancer status or that only 80% of the breast cancer cases were histologically confirmed. The author in Tsubono et al. (2001) states, "*[w]e ascertained the incidence of cancer by means of computerized linkage with the records in the Miyagi Prefectural Cancer Registry, one of the earliest and most accurate population-based cancer registries in Japan.*" The article also states that "*we did not inquire about a history of cancer in the questionnaire, because in Japan at the time of the survey, the majority of patients with cancer were not told the true diagnosis, and hence the accuracy of self-reports was thought to be low.*" Tsubono et al. (2001) further states that "*the diagnosis of adenocarcinoma had been histologically confirmed in 80% of the cases.*" This quote, however, refers to gastric cancer cases described in the prior sentence. Tsubono et al. (2001) does not refer to the number of breast cancer cases histologically confirmed and was not used for the breast cancer claim. Your arguments regarding the Suzuki et al. study do not demonstrate that the agency did not consider or adequately consider relevant information or views in the administrative record of the June 30<sup>th</sup> letter.

- c) You note that the number of breast cancer cases in cohort II cited in Suzuki et al. (2004) does not match the number of breast cancer cases discussed in another article (Nakaya et al., 2003) using the same cohort.

Agency's Response:

There are several legitimate reasons why the number of cancer cases evaluated in two separate studies using the same data could vary. Research articles evaluating different exposure factors (e.g., green tea or personality traits) may have different inclusion/exclusion criteria which could change the number of cancer cases. For example, if a subject did not answer the question regarding green tea intake, the subject could not be used in the analysis for green tea but may be used in the analysis for personality characteristics and cancer. Your argument regarding the different number of breast cancer cases in the cohorts in the two studies does not demonstrate that the agency failed to consider or adequately consider relevant information or views in the administrative record of the June 30<sup>th</sup> letter.

- d) You question why the agency characterized the Wu et al. (2003) study as weak in the claim language even though it received a high methodological quality rating.

Agency's Response:

The methodological quality rating only concerns whether the methods used were appropriate for the particular study design type. By contrast, the study design type rating addresses the fact that some design types provide stronger evidence than others. For example, a randomized, controlled intervention trial can establish a causal relationship between a substance and a disease, whereas case-control studies can only show an association and cannot prove causality.

Suzuki et al. (2004) reported on two cohort studies, whereas Wu et al. (2003) was a case-control study. As we stated in the June 30<sup>th</sup> letter, "*prospectively designed studies provide stronger evidence for an association than case-control studies since there are fewer forms of bias.*" Hence, case-control studies provide weaker, more limited evidence for a substance and disease relationship than cohort studies. A weaker (e.g., less reliable) study can be of high methodological quality, but because of its limited reliability, provides weaker evidence than a prospective cohort study. FDA clearly considered this issue in the June 30<sup>th</sup> letter and your questions do not demonstrate that the agency failed to consider or adequately consider relevant information or views in the administrative record.

- e) You note that the Wu et al. (2003) study has more cancer cases and used in-person interviewers to collect data compared to the Suzuki et al. (2004) studies which had fewer cancer cases and used a self-administered questionnaire.

Agency's Response:

As discussed above in the response to (3)(d), case-control studies, like Wu et al. (2003), are inherently weaker (e.g., less reliable) as a result of study design than prospective cohort studies, such as Suzuki et al. (2004). The number of cases and controls included in each study is relevant to weighing the total strength of the evidence, but cannot overcome the limitations of the weaker case-control study design type where, as here, both studies are of high methodological quality. Again, this argument does not demonstrate that we failed to consider or adequately consider relevant information in the administrative record.

- f) You argue that in-person interviews used by Wu et al. (2003) are superior to mailed self-administered questionnaires used in the Suzuki et al. (2004) cohort studies.

Agency's Response:

We incorporate by reference the response above to (3)(d), setting out that case-control studies are inherently of weaker study design type than prospective cohort studies. Both the Wu et al. (2003) and Suzuki et al. (2004) studies received high methodological quality ratings. Both studies used validated questionnaires to assess green tea consumption and the agency considered both in-person interviewer and self-administered questionnaires equal in ascertaining exposure status of the subjects. The methodological difference you note cannot overcome the limitations of the weaker case-control study design type where, as here, both studies are of high methodological quality. This argument also does not demonstrate that the agency failed to consider or adequately consider relevant information in the administrative record.

g) You claim that some studies are more relevant than others in considering the total body of evidence in support of a relationship between green tea and cancer because some study populations had access to higher quality green tea than others. Your assertions along this line include the following.

- The articles by Suzuki et al. (2004) and Sonoda et al. (2004) should not have been used by the FDA because they were conducted in northern rural Japan where the quality of green tea consumed is of poor quality.
- Green tea consumers in Los Angeles know where to get quality green teas because they are descended from the Middle Kingdom of China, which values quality green tea, as opposed to the residents of Miyagi, Japan who filled out the Suzuki et al. (2004) questionnaire.
- The Sonoda et al. study finding no relationship between consumption of green tea and reduced risk of prostate cancer is flawed because the cases came from two regions of Japan that consume green tea of very different quality because of different access to quality green tea - one region borders a famous tea producing region, the other does not produce tea.
- Jian et al. should have received more consideration because it was conducted in a region of China that has access to high-grade green tea with more EGCG by weight than lower quality green tea.

In support of your arguments, you reference a picture of a tea peddler in Hangzhou, China and a map of tea producing regions of Japan and two studies (Fujiki et al. 2002; Fujiki 2005) which you claim are relevant to the question of quality of green tea consumed in different locations of Japan and its effects on cancer prevention.

Agency's Response:

The agency evaluates qualified health claim petitions based on the publicly available science in the administrative record. None of the studies from which scientific conclusions can be drawn provided the nutrient composition or other characteristics, such as quality, of the green tea consumed in their particular study. Hence, it is not possible to assess the "quality" of green tea in any of the studies. We also note that the picture and map you reference in support of your assertions were not included in your original petition and cannot be considered in connection with this request for reconsideration. See 21 C.F.R. § 10.33(e). Your assertions do not demonstrate that the agency failed to consider or adequately consider relevant information or views in the administrative record of the June 30<sup>th</sup> letter.

- 4. In your letters to the agency, dated July 1, 2005 and July 6, 2005, you propose revisions to the claim language considered by FDA for enforcement discretion to include reference to the content level of epigallocatechin gallate (EGCG) in the green tea.**

In support of your proposal, you reference the National Cancer Institute's (NCI) Chemopreventive Branch and Agent Development Committee's recommendation on the quality and quantity of green tea to be consumed for potential anticancer benefits entitled "Clinical development plan: tea extracts, green tea polyphenols, epigallocatechin gallate." and published in the Journal of Cellular Biochemistry 26S:236-257 (1996) ("NCI Article"). The article was included with your original health claim petition.

Agency Response:

As stated in the June 30<sup>th</sup> letter, "*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.*" The Clinical Development Plan developed by NCI summarizes the status of promising chemopreventive agents regarding evidence for safety and chemopreventive efficacy in preclinical and clinical studies. The NCI article references an article by Yang et al. (1993) which documented the contents of typical green tea. The NCI article (Chemopreventive Branch and Agent Development Committee, 1996) states "*There are a number of different types of green and black tea. They differ in genetic variety and production methods to yield, for example those with high theaflavin content or strong aroma.*" Therefore, the agency does not believe that the 1996 NCI article represents a standard for green tea set by the NCI. Your argument regarding the NCI article also does not demonstrate that we failed to consider or adequately consider all relevant information or views in the administrative records of the June 30<sup>th</sup> letter.

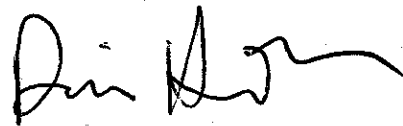
Agency Conclusions

For all the reasons set out above, FDA denies your petition for reconsideration. The agency concludes that your petition does not satisfy the requirements for reconsideration because none of the issues raised in your petition demonstrates that the agency failed to consider or adequately consider relevant information or views contained in the administrative record, as required by 21 CFR § 10.33(d)(1).

Although 21 C.F.R. § 10.33(d) gives the Commissioner the discretion to grant a request for reconsideration when the Commissioner determines that it is in the public interest and in the interest of justice, the agency believes that granting the request on this basis is not warranted here in light of the extensive scientific review that underlies the June 30<sup>th</sup> letter. Moreover, even if your request for reconsideration were granted, reconsideration of the decision set out in the June 30<sup>th</sup> letter would result in the same decision. The scientific evidence is clear that there was no credible evidence to support qualified health claims for a relationship between consumption of green tea and a reduced risk of gastric, lung, colon/rectal, esophageal, pancreatic, ovarian, and combined cancers and very limited credible evidence for the qualified health claims for consumption of green tea and reduced risk of prostate and breast cancer.

As noted in the June 30<sup>th</sup> letter, 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. Until such time that FDA evaluates new information, you may continue to rely on FDA's June 30<sup>th</sup> letter for the agency's current evaluation of the state of the total body of evidence in support of a relationship between consumption of green tea and reduced risk of different cancers. At this time, FDA intends to continue its consideration of the exercise of enforcement discretion only for the two claims set out in the June 30<sup>th</sup> letter.

Sincerely,

A handwritten signature in black ink, appearing to read "David J. Horowitz". The signature is fluid and cursive, with a long horizontal stroke at the end.

David J. Horowitz, Esq.  
Assistant Commissioner for Policy  
Food and Drug Administration