DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

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VIA FACSIMILE AND U.S. MAIL

Jonathan W. Emord, Esq.
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1050 Seventeenth Street, NW
Suite 600
Washington, DC 20036

Re: Petition for Health Claim: Folic Acid, Vitamin B_6, and Vitamin B_{12} Dietary Supplements and Vascular Disease [Docket No. 99P-3029]

Dear Mr. Emord:

This is in response to your letter of January 22, 2001, regarding a qualified health claim about the relationship between B vitamins and vascular disease.

In our November 28, 2000, letter to you, we advised you that we had re-evaluated the subject claim ("*As part of a well-balanced diet, rich in fresh fruits and vegetables, daily intake of at least 400 µg folic acid, 3 mg vitamin B_6 and 5 µg vitamin B_{12} may reduce the risk of vascular disease*") in response to the court decision directing the Food and Drug Administration (FDA) to consider qualified health claims for dietary supplement labeling (*Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999)) when the evidence in support of the claim does not meet the significant scientific agreement standard. Our conclusion was that FDA would exercise its enforcement discretion, under certain conditions (November 28 letter, at 25-36), for a qualified claim that contained four elements (*id.* at 33-34). The model claim (*id.* at 33) that we gave as an example of an appropriately qualified claim was:

> It is known that diets low in saturated fat and cholesterol may reduce the risk of heart disease. The scientific evidence about whether folic acid, vitamin B_6 and vitamin B_{12} may also reduce the risk of heart disease and other vascular diseases is suggestive, but not conclusive. Studies in the general population have generally found that these vitamins lower homocysteine, an amino acid found in the blood. It is not known whether elevated levels of homocysteine may cause vascular disease or whether high homocysteine levels are caused by other factors. Studies that will directly evaluate whether reducing homocysteine may also reduce the risk of vascular disease are not yet complete.

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In your letter to FDA on December 12, 2000, you stated that this qualified claim omits a material fact that consumers need to know in light of the claim's express reference to the homocysteine-lowering effects of the B-vitamin combination. Specifically, you asserted that the absence of a statement informing consumers that "The U.S. Centers for Disease Control and Prevention has stated that 'elevated plasma homocysteine is an independent risk factor for vascular diseases'" caused the claim to be misleading through material omission. Accordingly, you requested that FDA permit use of the qualified claim as modified to include the statement attributed to the Centers for Disease Control and Prevention (CDC).

In a follow-up letter dated January 22, 2001, you stated that Petitioners would be willing to accept the following modified claim:

> The U.S. Centers for Disease Control and Prevention has stated: "Elevated plasma homocysteine...is an independent risk factor for vascular diseases. It is unknown whether [homocysteine] is a cause of or a marker for atherosclerosis". Studies have generally found that folic acid, vitamin B6 and vitamin B12 lower homocysteine. Studies on whether those vitamins also lower heart or vascular disease risks are suggestive, but not conclusive. Studies on whether reducing homocysteine lessens those risks are not yet complete.

You also asserted that your modified claim includes all material elements of FDA's model claim with the exception of the statement, "It is known that diets low in saturated fat and cholesterol may reduce the risk of heart disease." You characterized this statement as "an FDA public policy pronouncement" and stated that "because Plaintiffs' B-vitamin dietary supplements do not contain saturated fat or cholesterol and would not normally do so, that quoted language is irrelevant to the product."

As discussed below, we believe your attribution of the statements characterizing the relationship between homocysteine, vascular disease and atherosclerosis to CDC, and your omission of the statement regarding diets low in saturated fat and cholesterol result in a claim that is misleading and that fails to meet the general requirements for health claims in 21 C.F.R. §101.14 (see the November 28, 2000 letter at page 39). Specifically, your proposed claim would violate §101.14(d)(2)(iii), which states that a health claim must be complete, truthful and not misleading; and §101.14(d)(2)(v), which states that a health claim must enable the public to comprehend the information provided and to understand the relative significance of such information in the context of a total daily diet.

With regard to the substance of the statement you attribute to CDC ("Elevated plasma homocysteine . . . is an independent risk factor for vascular diseases. It is unknown whether [homcysteine] is a cause of or a marker for atherosclerosis."), FDA advises that it will be necessary for you to submit a supplemental health claim petition to allow the agency to evaluate this modification of the claim. Once the agency has reviewed the evidence you submit, we will be able to make a judgment on whether the addition of this statement to the claim for B vitamins and vascular disease would be misleading.

The attribution of statements from the MMWR article of November 12, 1999 to CDC is misleading.

You stated in your December 12, 2000 letter that the model claim set forth in the November 28, 2000 letter fails to inform consumers that an elevated level of homocysteine has been stated to be an independent risk factor for vascular disease by the U.S. Centers for Disease Control and Prevention (CDC). As evidence of CDC's position, you cite an article from the CDC Morbidity and Mortality Weekly Report (MMWR) of November 12, 1999, entitled "Assessment of laboratory tests for plasma homocysteine – selected laboratories, July - September 1998."

The introductory paragraph of the article contains the following sentence: "*Elevated plasma homocysteine (Hcy), generally defined as fasting plasma Hcy levels greater than 15 μmol/L, is an independent risk factor for vascular diseases (1, 2).*" The notation "(1, 2)" is a citation to two references.[1] You propose to incorporate a portion of this sentence (i.e., "*Elevated plasma homocysteine is an independent risk factor for vascular diseases*") into the qualified claim, and to introduce the statement with "*The U.S. Centers for Disease Control and Prevention has stated:* ".

We reviewed the cited MMWR article and have concluded that your suggested modification to the model claim would be misleading to the extent that it characterizes sentences from the MMWR article as a CDC statement. The article is a report by CDC staff, the purpose of which was to assess the variation (precision and accuracy) in analytical results within and among laboratories that analyze plasma samples for the amino acid homocysteine. The conclusions of the CDC staff who authored the MMWR

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[1] The cited references appear in the MMWR reference list as "1. Boushey CJ, Beresford, SAA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease–probable benefits of increasing folic acid intakes. JAMA 1995; 274:1049-57." and "2. Refsum H, Ueland P, Nygård O, Vollset SE. Homocysteine and cardiovascular disease. Annu Rev Med 1998; 49:31-62." Boushey et al. (1995) combined the results from a number of observational studies (using the mathematical technique of meta-analysis). These authors stated that no studies had investigated the effects of increasing folic acid intake on coronary artery disease (CAD). These authors then drew on two data sets (one with "information link[ing] elevated" homocysteine levels with CAD risk and one with "data associat[ing] higher folic acid intake with reduced" homocysteine levels). From these two data sets, the authors stated that they inferred a relationship between increased folic acid intake and reduced CAD mortality, and used this inferred relationship to estimate the number of preventable CAD deaths that might result from defined increases in folic acid intake. Refsum et al. (1998) performed a general literature review of available studies and suggested that elevated homocysteine is emerging as a risk factor for vascular disease. Refsum et al. (1998) noted, however, that it remains to be shown in randomized placebo-controlled clinical trials that reduction of homocysteine levels has an overall beneficial effect on coronary heart disease. Neither of these reviews included studies whose design would provide definitive information as to whether lowering homocysteine levels would actually result in reduction in risk of vascular disease. Indeed, Refsum et al. (1998) noted that clinical studies are in progress to establish whether vitamin therapy will actually reduce vascular disease risk. It is clear from a review of these two articles that, while the authors drew inferences from the existing literature about an association between plasma homocysteine levels and risk of vascular disease, the authors believe that uncertainties about the nature of the association need to be clarified in controlled clinical trials.

article are that their results "indicate a need to improve analytical precision and to decrease analytical differences among laboratories." The purpose of the MMWR article was neither to provide a review of scientific evidence about the relationship between homocysteine and risk of vascular disease nor to provide a statement of CDC policy relative to this relationship. Consequently, the article cannot be construed as providing the official CDC position on whether homocysteine is an independent risk factor for vascular disease or on any other issue relating to the subject claim.

The statement quoted from the MMWR article ("*Elevated plasma homocysteine (Hcy), generally defined as fasting plasma Hcy levels greater than 15 μmol/L, is an independent risk factor for vascular diseases (1, 2).*") is based on the views expressed by the authors of the cited references (i.e., "1, 2 "). A reading of the MMWR article in its entirety makes clear that the purpose of this statement with its included references is to provide context for the subject of the article, which is an assessment of the accuracy of laboratory testing for homocysteine in blood plasma. It is a statement intended to explain why the topic of the article is of interest, not a conclusion reached by CDC. Scientists commonly cite published literature as background information when writing research reports. Such statements cannot be construed as the official views of organizations for which the scientists work. When statements of official views or policy are included in a report, such statements are generally acknowledged as such. In the MMWR article, the context makes clear that the sentences in question are not intended as the official view or policy of CDC. Moreover, CDC has advised FDA by letter (copy enclosed) that the sentences from the MMWR article are not a CDC statement on whether homocysteine is a risk factor for vascular disease, and that CDC has not taken a position on this issue.

For all these reasons, the introductory wording you propose ("The U.S. Centers for Disease Control and Prevention has stated:") is inherently misleading.[2]

The proposed qualified claim does not meet the general requirements for health claims in 21 C.F.R. §101.14 and is misleading because of the omission of a statement about diets low in saturated fat and cholesterol.

FDA has an obligation to ensure that food labeling is truthful and not misleading. Under the Federal Food, Drug, and Cosmetic Act, a claim can be misleading, and thereby misbrand the food, based on the information that it does not include, as well as the information that it does include. See U.S.C. 343(a)(1) (a food is misbranded if its labeling is false or misleading in any particular); 21 U.S.C. 321(n) ("[I]n determining

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[2] Your January 22, 2001 letter incorrectly characterizes FDA's opposition to the attribution of this statement to CDC as based on application of the criteria for evaluating whether a statement of a scientific body is "authoritative" for purposes of 21 U.S.C. §343(r)(3)(C). FDA has evaluated your proposed changes to the qualified claim in light of the general requirements for health claims and the First Amendment, not in light of the authoritative statement criteria. Those criteria do not apply to your petition because it was submitted under 21 U.S.C. §343(r)(5)(D) and 21 C.F.R. §101.70, not under 21 U.S.C. §343(r)(3)(C). FDA is rejecting the attribution of the statements from the MMWR article to CDC because such an attribution would be misleading, not based on any application of the authoritative statement criteria.

whether the labeling or advertising is misleading there shall be taken into account . . . not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.").

A health claim is a claim that "expressly or by implication . . . characterizes the relationship of any substance to a disease or health-related condition" (21 C.F.R. §101.14(a)(1)). The general health claim requirements state that a health claim must be complete, truthful, and not misleading (21 C.F.R. §101.14(d)(2)(iii)), and that the claim must enable the public to comprehend the information provided and to understand the relative significance of such information in the context of a total daily diet (21 C.F.R. §101.14(d)(2)(v)).

These requirements ensure that consumers will be able to comprehend the significance of the health benefit described in a health claim within the context of the total daily diet so that they may modify their diets to improve their health. As FDA stated in the preamble to the final rule on general requirements for health claims on conventional foods (58 FR 2478 at 2513; January 6, 1993), a wide variety of factors may need to be addressed in a health claim in order to allow consumers to understand the substance-disease relationship in the context of the total daily diet.

By failing to include the first element of the qualified claim outlined in FDA's November 28, 2000 letter (i.e., "It is known that diets low in saturated fat and cholesterol may reduce the risk of heart disease," or language to the same effect), the proposed claim fails to provide a context in which consumers can understand the major factors that affect the risk of vascular disease[3] and thereby modify their diets to reduce their risk of this type of disease. Without this context, the claim is incomplete and is also misleading within the meaning of 21 U.S.C. § 321(n), in that it suggests that increasing intake of B vitamins is an effective substitute for consuming a diet low in saturated fat and cholesterol.

In all of its authorized health claim regulations relating food substances (e.g., lipids, soluble fiber, soy protein, plant sterol/stanol esters) to reduced risk of heart disease, FDA has concluded that information about the total diet must be included as part of the claim. The agency requires all such claims to inform consumers that diets low in saturated fat and cholesterol may reduce the risk of heart disease, or that the substance that is the subject of the health claim should be consumed as part of a diet low in saturated fat and

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[3] Vascular disease is a broad term that includes a number of diseases of the vascular system (i.e., the arteries and veins). Coronary heart disease (i.e., disease of the major coronary arteries) is the most common, most frequently reported, and most serious form of vascular disease.

cholesterol.[4] *See* 21 C.F.R. §§ 101.75(c)(2)(i)(A), 101.77(c)(2)(i)(A) , 101.81(c)(2)(i)(A), 101.82(c)(2)(i)(A), and 101.83(c)(2)(i)(A). The agency determined that such language was necessary for the public to understand fully, in the context of the total daily diet, the significance of consumption of the substance in question on the risk of heart disease.

Thus, the agency has consistently emphasized the need for inclusion of the context of the total daily diet in its authorized health claims. In the case of all authorized health claims relating specific substances to reduced risk of heart disease, this "context of the total daily diet" has taken the form of inclusion of the statement that "diets low in saturated fat and cholesterol may reduce the risk of heart disease." A substance/heart disease claim lacking this context fails to enable the consumer to comprehend the information provided and to understand the relative significance of the information in the context of the total daily diet.

In recent rulemakings authorizing health claims to reduce the risk of heart disease, FDA has continued to emphasize the importance of consuming a low saturated fat, low cholesterol diet. In the preamble to the final rule authorizing a health claim for soy protein, the agency noted that such a diet is "the dietary pattern associated most strongly with reduction of risk from heart disease" (64 FR 57700 at 57719). In the preamble to the final rule authorizing a health claim for oats, FDA expressed concern that consumers would be misled if information about dietary context were omitted, in that the claim would then imply that a diet containing oats could substitute for a diet low in saturated fat and cholesterol (62 FR 3584 at 3594).

FDA's conclusions about the importance of a low saturated fat, low cholesterol diet in reducing the risk of heart disease are supported by the recommendations of other government agencies and respected scientific and medical bodies. For example, the recently distributed Dietary Guidelines for Americans, 2000, a joint publication of the Department of Agriculture and the Department of Health and Human Services, state "Choose a diet that is low in saturated fat and cholesterol and moderate in total fat."[5] The report of the Dietary Guidelines Advisory Committee notes that this recommendation is based on strong scientific evidence of the role of diet in CHD.[6] Likewise, the Dietary Guidelines of the American Heart Association recommend limiting foods high in saturated fat and cholesterol, again based on "continuing evidence that high total and

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[4] This requirement applies regardless of whether the food bearing the health claim contains saturated fat or cholesterol; thus, your argument that your products should not be required to include a statement about low saturated fat, low cholesterol diets because they do not themselves contain saturated fat or cholesterol is irrelevant.

[5] U.S. Department of Agriculture and U.S. Department of Human Services. Nutrition and Your Health: Dietary Guidelines for Americans, 2000, 5th ed. Home and Garden Bulletin No. 232, 2000, p. 28 (http://www.health.gov/dietaryguidelines).

[6] Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 2000, p. 34 (http://www.ars.usda.gov/dgac/dgac_ful.pdf).

LDL cholesterol are strongly related to coronary artery disease risk and that reductions in LDL cholesterol levels are associated with reduced coronary disease risk."[7]

Diets low in saturated fat and cholesterol are considered by expert groups–including the National Academy of Sciences, the National Heart, Lung and Blood Institute, and the Expert Panel of the National Cholesterol Education Program[8]–to be the most effective dietary means of reducing heart disease.[9,10,11] While other dietary factors may contribute to reducing the risk of heart disease, their roles are generally recognized as being of smaller magnitude.[12] In addition, the evidence for the role of a low saturated fat, low cholesterol diet in reducing the risk of heart disease is strong, in that it has been found to meet the significant scientific agreement standard in 21 U.S.C. §343(r)(3) and 21 C.F.R. §101.14(c). In contrast, the evidence for a relationship between B vitamins and reduced risk of heart disease has been found not to meet the significant scientific agreement standard.

For all these reasons, consumers need to be informed about the relationship between low saturated fat, low cholesterol diets and reduced risk of heart disease in order to understand the information provided in your claim and to understand its relative significance in the context of their total daily diets. This information is not a "public policy pronouncement,"

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[7] Krauss, R.M., et al. AHA Dietary Guidelines, Revision 2000: A Statement for Healthcare Professionals from the Nutrition Committee of the American Heart Association. *Circulation* 2000; 102:2284. (http://circ.ahajournals.org/cgi/content/full/102/18/2284).

[8] The Coordinating Committee of the National Cholesterol Education Program (NCEP) includes representatives from numerous federal agencies and expert professional groups. The health care and professional organizations represented include (among others) the American Heart Association, the American Medical Association, the American Academy of Family Physicians, the American Academy of Pediatrics, the American College of Cardiology, the American College of Occupational Medicine, the American Diabetes Association, , the American Nurses Association, the American Pharmaceutical Association, the American Red Cross, the Association of State and Territorial Health Officials, and the Society for Nutrition Education. Federal agencies that are represented on the NCEP coordinating committee include the CDC, the National Heart, Lung and Blood Institute, the National Cancer Institute, the Department of Agriculture, FDA, the Public Health Service's Office of Disease Prevention and Health Promotion, the National Center for Health Statistics, and the Department of Defense.

[9] National Research Council, National Academy of Sciences. Diet and Health: Implications for Reducing Chronic Disease Risk. National Academy Press, Washington, DC, 1989, pp. 537 and 540-541.

[10] U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute, National Cholesterol Education Program. Report of the Expert Panel on Population Strategies for Blood Cholesterol Reduction. NIH Publication No. 93-3046, 1993.

[11] U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute, National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). NIH Publication No. 93-3095, 1993.

[12] National Research Council, *supra* note 9, at 541.

as you say in your January 22, 2001 letter, but rather a vital piece of health-related information supported by the consensus of scientists in the field. The strong relationship between low saturated fat, low cholesterol diets and reduced risk of heart disease is a material fact; without the introductory sentence about this relationship, your claim is misleading because it fails to reveal the most effective dietary means of reducing the risk of heart disease. Without this sentence, the claim suggests that increased intake of B vitamins is the only dietary modification necessary to reduce the risk of heart disease and other vascular diseases.[13]

The agency cannot make a determination on whether the statements you propose to add to the claim for B vitamins and vascular disease would be misleading without a supplemental health claim petition.

In evaluating the health claim you proposed originally, we focused our review on the relationship between the B vitamins folic acid, vitamin B_6, and vitamin B_{12} and risk of vascular disease (see letter of November 28, 2000). In your letter of January 22, 2001, you requested that we review a modification of that claim. The claim that you now propose is focused almost exclusively on the relationship between a biological parameter, homocysteine, and risk of vascular disease. We note that most of the sentences in the claim you proposed on January 22, 2001, focus on homocysteine (e.g., "Elevated plasma homocysteine is an independent risk factor . . ."; "It is unknown whether homocysteine is a cause of or a marker for . . ."; "Studies have generally found that folic acid, vitamin B6 and vitamin B12 lower homocysteine"; "Studies on whether reducing homocysteine lessens . . ."). A statement of the B vitamin/vascular disease relationship that is the subject of the health claim does not appear until the fourth sentence of the five-sentence claim.

Your current proposed claim begins with a statement characterizing homocysteine as an independent risk factor for vascular disease. Risk factors are factors whose presence is associated with an increased probability that disease will develop later.[14] Such factors may be weak or strong; modifiable (e.g., sedentary lifestyles) or unmodifiable (e.g., age, gender, race); dependent upon other factors, or independent of other factors. They may be causally related to a disease or result from the disease or be related to another factor or

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[13] Even if the claim were not misleading without a statement about low saturated fat, low cholesterol diets and reduced risk of heart disease, FDA still has authority to require such a statement. The agency has an interest in promoting the health of American citizens, and that interest is not limited to preventing misleading statements in labeling. *See Rubin v. Coors Brewing Co.*, 514 U.S. 476, 482 (1995) (the prevention of misleading statements "need not be the exclusive government interest " served by [a statutory provision]; promoting and protecting public health also qualify as substantial government interests under First Amendment commercial speech doctrine); *see also 44 Liquormart v. Rhode Island,* 517 U.S. 484, 501 (1996) (the regulation of commercial messages to require the disclosure of beneficial consumer information is a purpose that is consistent with the reasons for according constitutional protection to commercial speech).

[14] Mausner, J.S. and Kramer, S. Epidemiology, An Introductory Text. W.B. Saunders Co., Philadelphia, 1985, p. 6.

factors that is/are associated with the disease. Although FDA did consider the role of homocysteine as a possible intermediate link between B vitamins and reduced risk of vascular disease, our review of your proposed health claim focused on the B vitamin-vascular disease relationship, not on risk factor relationships.

Federal government reports and other reviews prepared by recognized scientific bodies have long noted the multifactorial nature of many chronic diseases (e.g., cancer, coronary heart disease, vascular diseases in general). There are dozens, perhaps hundreds of factors and clinical measurements that are associated with coronary heart disease or vascular disease. They may or may not contribute to overall risk of the disease; if they do contribute, their relative importance may range from insignificant to highly significant.

What is unknown with respect to all but a relatively small number of these factors (e.g., LDL-cholesterol) is their contribution, taken individually, to the overall population risk of the disease in question. As noted above, their contribution may be trivial or significant. It is necessary that the relative role and nature of these factors be placed in an appropriate context to prevent this information from being misleading. Thus, simply identifying a factor as a "risk factor" without providing a context in which the relative significance of the factor can be understood omits information that is material with respect to the representations made for the product and to consequences that may result from its use. Such a statement, without the necessary context, would violate the general health claim requirements in 21 C.F.R. § 101.14(d)(2)(iii) and (d)(2)(v) and would be misleading under 21 U.S.C. § 321(n).

It is clear from the above that an evaluation of the relationship between a biological parameter and a specific disease, and of the relative relationships among potential risk factors for the disease, requires different types of data and/or significantly more complex types of data analyses than those required to evaluate the relationship between a food substance and the risk of a disease. We did not review the data you provided in support of your proposed claim from the point of view of evaluating homocysteine as a risk factor for vascular disease, nor did you provide a literature review or data summaries that focused on this issue.

In an effort to reach agreement with you and end the litigation over your claim, we tried to reach a decision on all aspects of your proposed modification to the claim within the timeframe you requested. We were able to fully consider and reach a decision on your proposed attribution of the MMWR statements to CDC and on the omission of the statement about low saturated fat, low cholesterol diets, as those aspects of your proposed claim did not require the consideration of additional scientific evidence. However, we found that the time was too short to perform the thorough, comprehensive evaluation that would be necessary to evaluate the proposed statements quoted from the MMWR article. Moreover, as discussed above, we did not have the necessary literature review or data summaries on this topic. You are entitled to a decision on the remaining aspects of your proposed claim, but your request must be presented in accordance with the regulatory framework provided for by the statute and regulations to ensure that FDA's evaluation of

your claim takes place in the proper context. For dietary supplement health claims, that context is the petition process prescribed in 21 C.F.R. § 101.70.

For these reasons, we conclude that it will be necessary for you to submit a supplemental health claim petition to allow FDA to evaluate your proposed modifications to your claim within the context of the totality of the relevant scientific evidence. Once FDA has reviewed the literature and data summaries that you submit, the agency can make a decision on whether inclusion in the B vitamin/vascular disease health claim of the statements you propose would be inherently or potentially misleading, and, if potentially misleading, what additional information is necessary to qualify the statements so as to render them non-misleading.

Conclusions

For the reasons explained above, FDA has decided not to exercise enforcement discretion with respect to the use of your proposed claim

> The U.S. Centers for Disease Control and Prevention has stated: "Elevated plasma homocysteine . . . is an independent risk factor for vascular diseases. It is unknown whether [homocysteine] is a cause of or a marker for atherosclerosis." Studies have generally found that folic acid, vitamin B6 and vitamin B12 lower homocysteine. Studies on whether those vitamins also lower heart or vascular disease risks are suggestive, but not conclusive. Studies on whether reducing homocysteine lessens those risks are not yet complete.

In summary, the introductory wording you propose is misleading in that the statements in quotation marks above were not official CDC statements. In addition, your proposed claim does not meet the general requirements for a health claim and is misleading because of the omission of a statement about diets low in saturated fat and cholesterol.

The agency is willing to consider modifying the qualified claim for B vitamins and vascular disease to include the statements in quotation marks above, provided that you submit a supplemental health claim petition that provides us with a summary of relevant scientific data and copies of articles and other publications cited in the petition, as required by 21 C.F.R. § 101.70. FDA has decided not to exercise enforcement discretion with respect to these statements at this time, however, because you have not supplied the information necessary to enable us to evaluate whether these statements are accurate and whether additional information (e.g., on other risk factors) is necessary to prevent the statements from being misleading.

As noted earlier in this letter and in our letter of November 28, 2000, the agency continues to consider the following model claim to be appropriately qualified:

> It is known that diets low in saturated fat and cholesterol may reduce the risk of heart disease. The scientific evidence about whether folic acid, vitamin B_6 and vitamin B_{12} may also reduce the risk of heart and other vascular diseases is

suggestive, but not conclusive. Studies in the general population have generally found that these vitamins lower homocysteine, an amino acid found in the blood. It is not known whether elevated levels of homocysteine may cause vascular disease or whether high homocysteine levels are caused by other factors. Studies that will directly evaluate whether reducing homocysteine may also reduce the risk of vascular disease are not yet complete.

A dietary supplement bearing a claim that is not properly qualified or consistent with the weight of the evidence is subject to regulatory action as a misbranded food under section 403(r)(1)(B) of the Federal Food, Drug, and Cosmetic Act, a misbranded drug under section 502(f)(1), and as an unapproved new drug under section 505(a).

We hope that this letter clarifies FDA's position on the issues raised in your letter of January 22, 2001.

Sincerely,

Virginia Z. Wilbanks

for Christine J. Lewis, Ph.D.
Director
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

Enclosure

Copies to:

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
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Atlanta GA 30333

February 9, 2001

Christine J. Lewis, Ph.D.
Director
Office of Nutritional Products, Labeling and Dietary Supplements
Center for Food Safety and Applied Nutrition
200 C Street S. W.
Washington, D.C. 20204

Dear Dr. Lewis:

This is in response to your inquiry about whether a quotation from a 1999 article in the Morbidity and Mortality Weekly Report (MMWR) is a statement of the Centers for Disease Control and Prevention (CDC) on whether homocysteine is a risk factor for vascular disease. The quotation is as follows: "Elevated plasma homocysteine . . . is an independent risk factor for vascular diseases. It is unknown whether [homocysteine] is a cause of or a marker for atherosclerosis." These sentences appeared in an article entitled "Assessment of Laboratory Tests for Plasma Homocysteine–Selected Laboratories, July-September 1998." MMWR 1999, 48: 1013-1015.

Although the MMWR is a CDC publication, the quoted excerpt from the MMWR article was not intended as a CDC statement on whether homocysteine is a risk factor for vascular disease. The purpose of the MMWR article was to compare laboratory methods for measuring concentrations of homocysteine in human plasma samples. The article was not a discussion of possible risk factors for vascular disease. In addition CDC has not yet made a specific analysis of such risk factors necessary to support such a determination. Any such determination will be made in collaboration with other federal and non-government agencies involved in this area. Accordingly, at this time CDC does not have an official position that plasma homocysteine is an independent risk factor for vascular disease.

Please do not hesitate to contact me if you need additional information.

Sincerely yours,

John Livengood, M.D., M.Phil.
Deputy Associate Director for Science

cc:
Dr. Bowman
Dr. Sinks
Dr. Ward