

Calwood Nutritionals, LLC
1288 Hay Meadow Lane
Sykesville, Md 21784
February 17, 2016

Evelyn Bonnin
Baltimore District Director
Food and Drug Administration
Baltimore District Office
6000 Metro Drive, Suite 101
Baltimore, MD 21201-2199

February 2, 2016
Re: WARNING LETTER, CMS # 482185 FEI 3003103962

Dear Ms Bonnin,

We take strong exception in regard to your first complaint that Calwood Nutritionals products are “drugs under section 201(g)(1)(B) of the Act [21 U.S.C. 321(g)(1)(B)] because they are intended for use in the cure, mitigation, treatment, or prevention of disease.” This is not true as all of our advertising indicates their use is for protein nutrition, wherever needed.

For instance the American Cancer Society (ACS) states in its **Nutrition for the Person With Cancer During Treatment:** A Guide for Patients and Families: Proteins: “We need protein for growth, to repair body tissue, and to keep our immune systems healthy. When your body doesn’t get enough protein, it might break down muscle for the fuel it needs. This makes it take longer to recover from illness and can lower resistance to infection. People with cancer often need more protein than usual. After surgery, chemotherapy, or radiation therapy, extra protein is usually needed to heal tissues and help fight infection.”

[<http://www.cancer.org/acs/groups/cid/documents/webcontent/002903-pdf.pdf> accessed 2/17/16]

Oral consumption of the essential amino acids has been shown to fulfill the need for protein nutrition for nearly 70 years (see Appendix 3) “Consequently, there appears to have been little appreciation of the fact that the nutritive value of a protein depends upon the kind and quantities of its components. Under the circumstances, it is not surprising that emphasis should have been placed upon the amount of protein ingested without much reference to possible differences in nutritive quality.” [The Amino Acids in Nutrition. Rose WC. Yale J Biol Med. 1932 Mar;4(4):519-36.] (see Appendix 4 for Dr. Rose’s papers on defining the essential amino acids)

More recently, Dr. RR Wolfe and colleagues have shown that the oral consumption of the essential amino acids for protein formation is anabolic while the non-essential amino acids are catabolic (see ref. 55-57, Appendix 3). Clearly, the essential amino acids have been known to be necessary for protein nutrition for many years, regardless of whether they are obtained through eating proteins or a balanced formula of the essential amino acids.

It is hoped that neither you, nor your Compliance Officer would make the argument that the ACS is advocating proteins as a new and unapproved drug which “are intended for use in the

cure, mitigation, treatment, or prevention of disease.” And yet, your letter to Calwood Nutritionals makes that exact argument! Your claims are clearly unwarranted.

On the National Cancer Institute’s own government website, under About Cancer, Nutrition in Cancer Care (PDQ®), the advice given is: “Cancer and cancer treatments may affect taste, smell, appetite, and the ability to eat enough food or absorb the nutrients from food. This can cause malnutrition (a condition caused by a lack of key nutrients). Malnutrition can cause the patient to be weak, tired, and unable to fight infections or get through cancer treatment. Malnutrition may be made worse if the cancer grows or spreads. Eating too little protein and calories is a very common problem for cancer patients. Having enough protein and calories is important for healing, fighting infection, and having enough energy.”

[<http://www.cancer.gov/about-cancer/treatment/side-effects/appetite-loss/nutrition-pdq> accessed 2/17/16] Do either you or your Compliance Officer say that this is an unapproved drug claim? The NCI official position is that “Eating too little protein ... is a very common problem for cancer patients.” Please copy us on the letter when your Compliance Officer finds that the NCI advocating protein for the treatment of cancer. Such a letter would be absurd as you are well aware. The NCI’s position is that protein is helpful. Our statement that the “The Calwood formulas of essential amino acids provide a pleasant tasting way to obtain the nutrition you need while your doctors are fighting your disease...” is in no way different from the position of the ACS and the NCI.

We have been offering these same formulas since 2000 and have had numerous FDA inspections. None of your previous inspections suggested problems with this wording. As a result of our discussions, in the previous 3 inspections, your Compliance Officer agreed, as did your office, that our products were “foods” and not dietary supplements. Indeed, your office was advised that “New labels are being prepared to indicate that Nutrasentials, Nutramine and Nutramine AminoBites are foods meant to sustain normal nutritional status rather than dietary supplements” (which labels were supplied to your office on December 8, 2012). Your office accepted these determinations with no response.

The FDA’s current actions have resulted in great harm to Calwood Nutritionals, as we are now threatened with a class action law suit in the state of New Jersey which cites every unfounded accusation made by your office. We have been further damaged as your warning letter has been posted on social media with derogatory remarks and customer questions as a result.

At no time have we ever indicated that the essential amino acid formulations are for the treatment of any disease and that includes kidney disease. We maintain now as we always have, that the essential amino acids are an aid to proper nutrition while following the diet Dr. Walser and others have shown to be effective in avoiding dialysis. To my knowledge, no one in the medical literature has ever indicated that the essential amino acids have any effect on kidney disease. However, there can be no doubt that the essential amino acids are beneficial in maintaining proper nutritional health wherever such health is lacking.

To wit:

William Rose, beginning in 1949 and continuing through 1955, published a series of studies which defined the essential amino acids needed to be present in the diet of humans for proper muscle production. (Beginning at “Amino acid requirements of man. ROSE WC, Fed Proc. 1949 Jun;8(2):546-52” to “The amino acid requirements of man. XV. The valine requirement;

summary and final observations. Rose WC, Wixom RL, Lockhart HB, Lambert GF. J Biol Chem. 1955 Dec;217(2):987-95.”)

As to whether the essential amino acids are safe nutritionally in maintaining protein nutritional health, and especially in kidney patients when on a modified or low protein diet, our own government funded the 840 patient MDRD study which used the exact formula of essential amino acids in our products and showed that the formula provided a nutritionally sound basis for maintaining all nutritional protein indices while treating kidney disease with a very-low protein diet. [no authors cited. Effects of dietary protein restriction on the progression of moderate renal disease in the Modification of Diet in Renal Disease Study. J Am Soc Nephrol. 1996 Dec;7(12):2616-26].

Dr. William Mitch writes “Subsequent analyses of MDRD results indicate that protein restriction can slow progression of CRF. ... In patients with uremia or progression despite other measures, dietary therapy should be started along with monitoring for dietary compliance and nutritional adequacy.” (Abstract of “Dietary therapy in uremia: the impact on nutrition and progressive renal failure.” Mitch WE. Kidney Int Suppl. 2000 Apr;75:S38-43.) As Dr. Mitch said, and we have always maintained with your inspectors, **the diet is the therapy. The essential amino acids are given for “nutritional adequacy.”** That is what foods are for – **“nutritional adequacy.”**

As a food, our tested balanced formula of essential amino acids has been shown to be of value in the nutritional support of protein synthesis.

In reply to the quotations from our website www.calwoodnutritionals.com

#1 Your inspector selected a passage stating, “The Calwood formulas of essential amino acids provide a pleasant tasting way to obtain the nutrition you need while your doctors are fighting your disease...” Please notice that there is no intimation that the Calwood formulas fight the disease, as the “doctors” do that – they are a pleasant tasting way to obtain the nutrition needed. Virtually every paper in the medical literature on nutrition in the cancer patient points out the need to encourage the patient to eat a nutritionally sound diet (see above for the American Cancer Society and NCI positions on this statement). While a poor diet is known to cause a number of diseases (see e.g., Wikipedia on “Nutrition”), none of the diseases in our list is caused by “poor nutrition.” Again, Wikipedia states: “The most important aspect and defining characteristic of protein from a nutritional standpoint is its amino acid composition.” Hopefully, you and your Compliance Officer are sufficiently trained in nutrition to realize that plant proteins are low in certain essential amino acids, lysine, methionine and threonine, and that animal feeds are fortified with these for the proven nutritional benefit of increased lean body mass. The essential amino acids have no extraneous materials and the balanced formula developed by Rose represents the best way to provide protein nutrition. What Calwood Nutritionals did for nephrologists in general, and Dr. Walser in particular, was “to provide a pleasant tasting way to obtain the nutrition you need while your doctors are fighting your disease.”

Let us be clear, the essential amino acids are the basis of sound protein nutrition and our product accomplishes that in a “pleasant tasting way.” However, it does not and we have nowhere claimed nor implied, that the essential amino acids are responsible, in any way, for treating or improving kidney function or other diseases where protein nutrition may be needed.

Your position that no disease may be mentioned on our website is simply untenable. Your office has taken a position directly contradicting the NCI which states additional protein may be necessary, not for the treatment of cancer, but “for healing, fighting infection, and having enough energy.” (See referenced statement of NCI on Cancer and Protein above).

It is possible that your Compliance Officer may have been questioning whether the use of the essential amino acids to promote muscle synthesis was a disease claim, however, none of the diseases mentioned on our web where we suggest that protein nutrition is important are caused or treated by protein (see the positions of the American Cancer Society and the National Cancer Institute above).

If you and your Compliance Officer question whether the essential amino acids do indeed promote muscle synthesis, we are aware of *Pom Wonderful v. FTC* and the recent ruling by the US Court of Appeals for the District of Columbia Circuit [[https://www.cadc.uscourts.gov/internet/opinions.nsf/CF44C4FA22F615C585257DDD00549353/\\$file/13-1060-1535012.pdf](https://www.cadc.uscourts.gov/internet/opinions.nsf/CF44C4FA22F615C585257DDD00549353/$file/13-1060-1535012.pdf), accessed 2/18/16] in which the summary clearly states that a randomized, controlled, clinical trial is required before claiming a causal relationship between consumption of our products and the treatment or prevention of any disease. We claim as does the ACS, the NCI and all nutritional textbooks which deal with protein nutrition in human or animal nutrition, that routine protein production is not a disease state even though a disease state may be present at the time of said protein production by the body. We have claimed that the essential amino acids are valuable for protein synthesis and that is firmly established by literally hundreds of scientific studies. For your benefit, I include an abbreviated list from prominent researchers of over 200 recent clinical trials in which the essential amino acids were used to promote muscle synthesis. (See Appendices 1, 2 and 3)

#2 Your letter made no mention of the antecedent “result” in previous paragraphs to which the selected “result” referred and those paragraphs fully discuss the efforts Calwood Nutritionals made to make the essential amino acids palatable. These results **do not** refer to the treatment of a disease nor do they indicate that taking them will in any way ameliorate any disease. The first clause objected to when taken as a whole is not improper in this regard; “We are convinced that many other disease states can be helped by our available products. Proper nutrition is especially important in cancer, and even for AIDS patients” That is exactly the stand of the National Cancer Institute and the American Cancer Society cited above. Nevertheless we will rearrange the statement to clarify further as; “We are convinced that our available products can help maintain proper protein nutrition with many other disease states. Proper protein nutrition is especially important in all disease states, especially in those where the therapy may reduce appetite, such as cancer and AIDS.”

#3 We will insert “proper protein nutrition” after “useful for” to specify the products’ use.

#4 We will insert “proper protein nutrition” after “useful for” to specify the products’ use.

#5 We will insert “proper protein nutrition” after “essential amino acids” to specify the products’ use. Please note that the use of the essential amino acids in the referenced paper (1) was a clinical trial of 76 patients, while reference (2) was a clinical trial of 26 patients and

reference (3) was a retrospective review of 16 patients placed on this regimen. Notice that we specify “the diet was as effective in people with diabetes as in those without it,” and make no claims for the use of the essential amino acids in the effectiveness of the treatment.

#6 We will insert “while maintaining proper protein nutrition” after “low protein diet” to specify the products’ use.

#7 The sentence after the one selected for your letter states the purpose of the balanced formula: “There are only beneficial effects from the diet while maintaining your nutritional status with a balanced formula of essential amino acids for the kidney patient.” The treatment is the diet and the beneficial effects of a vegetarian diet can be seen in a number of clinical studies by Dr. Dean Ornish as shown briefly in the following papers selected from among his 94 studies in medical journals.

1. ...And the only side-effects are good ones. Ornish D. *Lancet Oncol.* 2011 Sep;12(10):924-5. doi: 10.1016/S1470-2045(11)70227-3.
2. Lifestyle changes are related to reductions in depression in persons with elevated coronary risk factors. Pischke CR, Frenda S, Ornish D, Weidner G. *Psychol Health.* 2010 Nov;25(9):1077-100. (997 persons)
3. Comparison of coronary risk factors and quality of life in coronary artery disease patients with versus without diabetes mellitus. Pischke CR, ...Ornish D. *Am J Cardiol.* 2006 May 1;97(9):1267-73 (440 persons)
4. Improvement in medical risk factors and quality of life in women and men with coronary artery disease in the Multicenter Lifestyle Demonstration Project. Koertge J, ... Ornish D. *Am J Cardiol.* 2003 Jun 1;91(11):1316-22. (440 patients)
5. Intensive lifestyle changes may affect the progression of prostate cancer. Ornish D, ... Carroll PR. *J Urol.* 2005 Sep;174(3):1065-9 (93 patients)

Your Compliance Officer should have made mention of the fact that all the points following this are excerpted from Dr. Walser’s book “Coping with Kidney Disease A 12-Step Treatment Program to Help You Avoid Dialysis” – Mackenzie Walser, M.D.with Betsy Thorpe and contributions by Nga Hong Brereron, M.S., RD., J.B.C.L.C. At the time of writing this book, Dr. Walser was Professor of Pharmacology, Experimental Therapeutics and Medicine. Dr. Walser did invent a new drug which is widely used throughout Europe, Asia, and the Middle East under the name KetoSteril and is referred to in his book as the “ketoanalogs” of certain of the essential amino acids.

Dr. Walser selected the case histories on the use of the very low protein diet we excerpted from 46 of his papers published in peer reviewed medical journals on the effect of the diet with the essential amino acids and their analogs (see Appendix 1). He was joined in efforts to investigate

the very low protein diet by many colleagues in the US and around the world.

Low Protein Diet and Kidney Failure in PubMed:

47 papers by M Apparicio, Service de Néphrologie et Hémodialyse, Hôpital Pellegrin, 1 rue Jean Burguet, F-33075 Bordeaux Cedex, France prior to his work with Dr. Chauveau

28 papers by Dr. P Chauveau, Service de Néphrologie et Hémodialyse, Hôpital Pellegrin, 1 rue Jean Burguet, F-33075 Bordeaux Cedex, France

23 papers by Dr. Denis Fouque, Department of Nephrology, Hôpital Edouard Herriot, JE 2411-University Claude Bernard Lyon 1, Lyon Cedex 03, France

21 papers by Dr. Jonas Bergstrom, Division of Renal Medicine, Department of Clinical Science, Karolinska Hospital, Karolinska Institutet, S-141 86 Stockholm, Sweden.

55 papers by Dr. Gino Barsotti, Nephrology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

11 papers by Dr. Teplan, Clinic of Nephrology, Institute for Clinical and Experimental Medicine and Institute for Postgraduate Education, Prague, Czech Republic.

Concerning the comments on the shop.calwoodnutritionals.com website, Nutramine Product page, your reviewer has clearly copied what we maintain – "Nutramine is USP grade amino acids formulated for nutrition in kidney disease patients and those with the early signs of kidney disease. Research shows protein restriction slows the progression of kidney failure..." This paragraph clearly states that "protein restriction slows the progression of kidney failure." The problem is the progression of kidney failure. The essential amino acids are not stated to affect the progression, but the protein restriction does. The first paragraph of Dr. Walser's review, Should protein intake be restricted in predialysis patients? Walser M, Mitch WE, Maroni BJ, Kopple JD. *Kidney Int.* 1999 Mar;55(3):771-7 states, "It has been known for at least 100 years that protein reduction reduces symptoms in chronic renal failure (CRF) [1]. Because most of these symptoms are caused by accumulation of the products of protein metabolism, this is to be expected. The history of the use of protein-restricted diets in renal disease has been reviewed elsewhere [2, 3]."

It should be obvious to anyone reading these statements that Calwood Nutritionals does not advocate the use of the essential amino acids to treat a disease!

We find the same to reasoning to be true of our brochures on Nutramine Amino-Bites, Nutramine, and Nutrasentials Drink Mix. Each one of these brochures specifically states the diet is used for the treatment of pre-dialysis patients.

The brochure for Nutrasentials Drink Mix is quoted "Nutrasentials Drink Mix is useful to maintain nutrition in individuals needed additional muscle synthesis." This has been shown to be the function of the essential amino acids and we would point to multiple clinical trials showing that this formula functions in this manner, especially the NIH sponsored study of 1756 patients [Effect of a ketoacid-aminoacid-supplemented very low protein diet on the progression of advanced renal disease: a reanalysis of the MDRD feasibility study. Teschan PE, Beck GJ, Dwyer JT, Greene T, Klahr S, Levy AS, Mitch WE, Snetelaar LG, Steinman TI, Walser M. *Clin Nephrol.* 1998 Nov;50(5):273-83.]. For smaller trials see all of the papers by Dr. Wolfe, which deal extensively with muscle production by the essential amino acids and review extensive clinical and scientific data from more than 800 patients.

Your office classified our products as a food, which should only require 2 studies and we

have presented a specific list of 167 trials and undefined lists of more than 185 more that are easily identified. It is incredible to me that a reviewer from your office would even question the maxim taught to every student of animal and human nutrition which is that the essential amino acids are the precursors of muscle synthesis. In addition to which, proper nutrition is not a disease state.

Your reviewer's claim, "Your Amino Acid products Nutramine, DialysAid, Nutramine-Amino Bites, and Nutrasentials Drink Mix are intended for treatment of one or more diseases that are not amenable to self- diagnosis or treatment without the supervision of a licensed practitioner" is absurd on the face as virtually anyone can tell whether they are getting weaker by the very action of how long it takes them to get out of a chair. That our customers need proper nutrition is emphasized in virtually every publication dealing with the subject put out for public information, whether from the FDA or the USDA or the many scientific societies that are asked about nutrition.

It is hard for a person educated in nutrition to believe that an FDA Compliance Officer would make a statement concerning a balanced formula of essential amino acids (such as our products), such as, "Therefore, it is impossible to write adequate directions for a layperson to use your products safely for their intended purposes." There simply are no safety concerns for an individual consuming these products as directed for protein nutrition, regardless of what disease they might have concurrently. The "essential amino acids" are just that – "essential." This has been treated as a basic scientific fact in nutrition for over 70 years. If you don't have the essential amino acids as a food, you will die!

Stating that "It is impossible to write adequate directions for a layperson to use your products safely" is similar to saying a layperson cannot safely determine how much steak they can eat. As pointed out in the NCI and ACS website, just such instructions are given to the general public ("Having enough protein and calories is important for healing, fighting infection, and having enough energy.") without giving a quantity of protein to eat. In a study of 24 elderly men the maximum amount of essential amino acids given was 40 g (equivalent to about 1 pound of lean beef), but the rate of protein synthesis continued its upward trend at that level for the elderly (Appendix 2, Study 4, Cuthbertson, et al.). A much larger study of the low protein diet used the 10.5 g/day of the essential amino acids recommended on our website (Appendix 2, Study 5, no authors).

Anyone can get the essential amino acids in a variety of foods, but if a patient's treatment restricts the foods available (protein restriction in kidney disease), or the patient no longer finds foods palatable (as in cancer), they must get their protein (or its building blocks, the essential amino acids) elsewhere. Literally 100's of papers in the medical literature substantiate this basic fact.

We ask that you retract the assertion that our products are an "Unapproved New Drug" and that your office of the FDA perform additional training in nutrition and science for your Compliance Officers.

Concerning Adulteration

We appreciate your inspector catching these typographical errors. We have never had Yellow #3 and #40 in any of our facilities. Our products contain FD&C Yellow #5 and FD&C

Green #3. This has been corrected on our labels.

Misbranding

1. After obtaining new software, the labels for DialysAid Orange Drink Mix, Nutramine AminoBites Essential Amino Acid Chewable Bites, and Nutrasentials Orange Essential Amino Acid Drink Mix have been corrected (see attached labels and Nutrition Panels).
 - a. the panels now contain protein and sodium;
 - b. the nutrition panel for Nutramine AminoBites Essential Amino Acid Chewable Bites now contains protein, sodium, potassium and phosphorous;
 - c. the nutrition panel for Nutrasentials Orange Essential Amino Acid Drink Mix now contains protein, sodium, potassium and phosphorous;
 - d. the size of the serving for DialysAid Drink Mix and Nutrasentials Drink Mix has been changed to be consistent at 1 scoop;
 - e. the % daily value for trans fat has been removed;
 - f. the “Essential Amino Acids” and “Amino Acids/serving” have been removed from the label;
 - g. the labels now include the units of measure; (see attached labels)
 - h. the label has been changed to include the gram weight;
 - i. the panel now contains proper headings, hairlines, bars, holding, and rounding of nutrients;
 - j. the heading for the panel has been changed to Nutrition Facts;
 - k. the footnote has been removed.
2. DialysAid Orange Drink Mix and Nutramine Essential Amino Acid Chewable Bites now contain the common name of each of the essential amino acids.
 - a. each amino acid is now listed and the term “essential amino acids” has been removed;
 - b. the term “EAA” has been removed from the ingredient list;
 - c. the ingredient list has been changed to remove the indefinite statements;
 - d. the typographical error has been corrected.
3. DialysAid Orange and Nutrasentials Orange Essential Amino Acid Drink product labels have been changed to the term “Drink Mix”.

The term “take” has been removed from the label so that your Compliance Officer will realize that the Calwood Nutritional products are foods .

The reason for the explanation of the USP grade identification is the worry our customers have about the quality of our products. Unfortunately many providers of single or incomplete mixtures of essential amino acids use amino acids that are not believed by the consumer to meet these requirements.

As noted above in the numbered points, these items have been corrected as specified.

We believe we now conform to all the FDA regulations and have corrected the deficiencies your Compliance Officer noted.

Sincerely,

Gary Calton, PhD
Managing Member

Attachments:

Appendix 1 A list of 46 papers by Dr. MacKenzie Walser (and his associates) and 9 reviews.

Appendix 2 A list of 4 reviews and 7 studies of muscle formation by essential amino acid mixtures by researchers other than Wolfe

Appendix 3 A list of 118 studies and 11 reviews published in journals indexed by the National Library of Medicine (PubMed), which were selected from the laboratory of Dr. RR Wolfe

Appendix 4 A listing of 23 papers by Dr. WC Rose in establishing the essentiality of certain amino acids for protein nutrition in man.

Nutrition Facts panels for Nutrasential Amino Bites Peach, Nutrasential Amino Bites Pineapple, Nutrasential Amino Bites Chocolate, Nutrasential Amino Bites Mango, Nutrasential Amino Bites Banana, Nutrasential Amino Bites Apple

Revised labels for Nutrasential Amino Bites Peach, Nutrasential Amino Bites Pineapple, Nutrasential Amino Bites Chocolate, Nutrasential Amino Bites Mango, Nutrasential Amino Bites Banana, Nutrasential Amino Bites Apple

Revised labels for Nutrasentials Lemonade Essential Amino Acid Drink Mix, Nutrasentials Orange Essential Amino Acid Drink Mix, Nutrasential Lemon Tea Essential Amino Acid Drink Mix, Nutrasential Cherry Essential Amino Acid Drink Mix, Nutrasential Grape Essential Amino Acid Drink Mix, and DialysAid Orange Essential Amino Acid Drink Mix