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DEC 23 2003

Steven Shapiro, Esq.
Seth A. Flaum, Esq.
Ullman, Shapiro & Ullman, LLP
299 Broadway
Suite 1700
New York, New York 10007

Dear Mr. Shapiro and Mr. Flaum:

This is in response to your letter of April 14, 2003 on behalf of your client Metagenics, Inc. of San Clemente, California. Your letter responded to our March 19, 2003 letter to Metagenics concerning claims for Metagenics' dietary supplement product called Perimine. These claims were the subject of a notification to FDA under 21 U.S.C. 343(r)(6) and 21 CFR 101.93.

In our March 19, 2003 letter, we stated that the claims "...promotes a healthy immune response in people who may be sensitive to environmental substances," "Modulates IgE-mediate responses," "Promotes healthy histamine levels," and "Promotes balanced leukotriene synthesis through the inhibition of 5- and 12-lipoxygenase (LOX)" suggested that the product is intended to treat, prevent, or mitigate a disease, namely allergies, and that the product that was the subject of the claims, Perimine, appeared to be subject to regulation under the drug provisions of the Federal Food, Drug, and Cosmetic Act (the Act).

In your letter, you assert that allergies, "particularly when due to environmental substances," are not diseases or health-related conditions and that the four claims cited above are proper structure/function claims. In the alternative, you propose various modifications to the claims quoted above to bring them within the scope of claims that may be made in the labeling of dietary supplements pursuant to 21 U.S.C. 343(r)(6) (section 403(r)(6) of the Act).

We disagree with your assertion that allergy is not a disease as that term is defined in 21 CFR 101.93(g)(1). You state that an allergy is not a disease in the sense that it is not a consequence of 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. Rather, your position is that allergies are merely a physiological response to an allergen that results in "temporary exaggerations of the body's natural immune defenses" and that allergy symptoms can be properly viewed as "an indication that the human body is functioning properly as it tries to combat allergens." We disagree.

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An allergic response is, in fact, unambiguously a consequence of damage to a system (the immune system) such that it does not function properly in that it is hypersensitive to allergens. An allergy is a “hypersensitivity caused by exposure to a particular antigen (allergen) resulting in a marked increase in reactivity to that antigen upon subsequent exposure sometimes resulting in harmful immunologic consequences”.¹ An allergic reaction is a cascade of processes that produces a spectrum of signs and symptoms. Although each sign and symptom may not necessarily be a disease in itself, together these signs and symptoms make up a characteristic syndrome that evidences that the body is having an exaggerated response to an antigen (allergen). Factors such as the severity of the hypersensitivity (mild or serious), the nature of the antigen (natural, man-made, etc.), or the frequency of occurrence (occasional or frequent) are no more relevant to reaching a determination as to whether allergies are or are not diseases than they would be in reaching a conclusion that common, mild conditions caused by pathogens, such as the common cold, are in fact also always diseases. What is relevant to reaching a conclusion that an allergic response is a disease is the fact that it is an exaggerated, over-reaction of the immune system to an antigen. It is not, as you assert, simply a reflection of a “normal” immune response to an antigen. Therefore, an allergy is a condition that fits squarely within the scope of the term disease as defined in 21 CFR 101.93(a).

You asked whether modifying the scope of your claims to refer to “minor” or “occasional allergy” would remove FDA’s objection to these claims. You asserted that such modified claims would be consistent with FDA’s position with regard to claims about conditions such as constipation, sleeplessness, or overweight. As you point out, in FDA’s final rule on structure/function claims for dietary supplements, the agency stated that claims to relieve “occasional” constipation or sleeplessness could be acceptable structure/function claims, depending on context. See 65 Fed. Reg. 1000, 1015, 1022 (2000).

We do not believe that claims about allergies can be qualified such that they are not disease claims. As stated above, allergies are hypersensitivities to antigens or allergens that are diseases, regardless of whether they are mild, occasional, or in response to “natural” allergens. Thus, modifying a claim to state that a product is intended to treat, mitigate, cure, or prevent only “minor” or “occasional” allergies does not result in the allergies no longer being a disease; rather, such a claim simply adds context describing the severity of the disease that the product is intended to treat, cure, prevent, or mitigate.

In contrast, the conditions you used in your letter as examples (e.g., constipation or sleeplessness) describe a spectrum of conditions that may have similar signs or symptoms, but which have different underlying causes, some of which are diseases and some of which are not. Consequently, a claim containing context that makes clear that a product is intended only for use in responding to those conditions that are not the result of a disease may fall within the scope of a structure/function claim. This is not the case, however, with allergy claims because, as described above, all allergies are diseases.

¹Stedman’s Medical Dictionary, 26th edition.

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In your letter, you also noted that FDA had not objected to notifications submitted for other products that contained single claims similar to one or more of your client's claims. The claims that your client notified us about explicitly stated that its product was intended to promote "a healthy immune response in people who may be sensitive to environmental substances." The other claims for your product included claimed effects of the product on IgE-mediated responses, histamine levels, and inhibition of 5- and 12-lipoxygenase, all of which are characteristic immunophysiological consequences associated with an allergic reaction. In contrast to the claims made by other firms, which were ambiguous and general in nature and did not evidence that the product was intended for use by persons with allergies, your client described a series of characteristic physiologic consequences of a hypersensitivity reaction and limited the intended use of the product to persons with that disease. As such, the claims included in your notification described a specific population of persons with a disease and described actions of the product on a characteristic set of physiologic responses to that disease.

In summary, we continue to believe that the position set forth in our March 19, 2003 letter to Metagenics, Inc. is correct. For the reasons set forth above, allergies are diseases within the meaning of the Act. Consequently, a product that implicitly or explicitly is represented to treat, cure, prevent, mitigate, or cure allergies or a characteristic set of signs or symptoms of an allergic reaction is subject to regulation as a drug.

Please contact us if we may be of further assistance.

Sincerely yours,



Susan J. Walker, M.D.
Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

Copies:

FDA, Center for Drug Evaluation and Research, Office of Compliance, HFD-300
FDA, Office of the Associate Commissioner for Regulatory Affairs, Office of
Enforcement, HFC-200
FDA, San Francisco District Office, Office of Compliance, HFR-PA140

Page 4 - Steven Shapiro, Esq. and Seth A. Flaum, Esq.

cc:

all w/copy of incoming

HFA-224

HFA-305 (docket 97S-0163)

HFS-800 (file)

HFS-810 (file)

HFS-811 (Moore, w/original incoming)

HFD-40 (Behrman)

HFD-310

HFD-314

HFS-607

HFV-228 (Benz)

GCF-1 (Nickerson)

r/d:HFS-811:RMoore:3/13/03

Revised:HFD-40:RBehrman:6/2/03

Revised:GCF-1:LNickerson:10/15/03

f/t:HFS-811:rjm:10/15/03:docname:84178.adv:disc79

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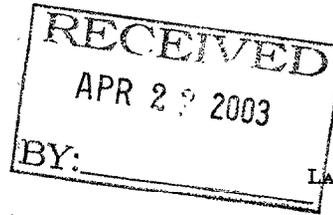
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OF COUNSEL
IRVING L. WIESEN

* ADMITTED IN NY & NJ
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^o ADMITTED IN FL
[†] CEA



April 14, 2003

VIA CERTIFIED MAIL – RETURN RECEIPT REQUESTED

Susan J. Walker, M.D.
Acting Director
Division of Dietary Supplement Programs (HFS-800)
Office of Nutritional Products, Labeling and Dietary Supplements [ONPLDS]
Center for Food Safety and Applied Nutrition [CFSAN]
Food and Drug Administration [FDA]
5100 Paint Branch Parkway
College Park, MD 20740

RE: FDA "courtesy" letter dated March 19, 2003 about Perimine

Dear Dr. Walker:

We are counsel for Metagenics, Inc. ("Metagenics") of San Clemente, California and have been asked by them to respond in writing to FDA's courtesy letter dated March 19, 2003 that was signed by you and involved claims submitted to FDA on February 27, 2003 pursuant to Section 403 (r)(6) of the Federal Food Drug and Cosmetic Act (FDCA) and Food and Drug Administration (FDA) regulation at 21 CFR 101.93 for its dietary supplement product called **Perimine**. In that letter, your office advised Metagenics that it considered the following claims:

- "... promotes a healthy immune response in people who may be sensitive to environmental substances;" ("Claim #1")
- "Modulates IgE-mediate responses;" ("Claim #2")
- "Promotes healthy histamine levels;" ("Claim #3")
- "Promotes balanced leukotriene synthesis through the inhibition of 5- and 12- lipogenase (LOX)." ("Claim #4")

improper for a product marketed as a dietary supplement, in that they "identify a population of consumers and a characteristic set of physiological responses that they would have to 'environmental substances' (i.e. allergens [*sic*]), and they suggest that the product is intended to treat, prevent, or mitigate a disease, namely allergies."

We disagree with FDA's position that "allergies," particularly when due to environmental substances, are a disease or even a health-related condition. We respectfully submit that each of the

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Division of Dietary Supplement Programs
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four claims are proper structure/function claims. People have reactions to various types of allergens everyday, none of which rise to the level of a disease or health related condition. As such, we request that FDA provide a further and more detailed explanation of its basis for objecting to each of Perimine's claims, specifically the Agency's claim that allergies are a disease.

Allergies are not a Disease

A disease is defined as 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.¹ An allergy is not a disease in this sense. There are many types of allergies each of varying severity. The type of allergy a person has depends on the allergen provoking the symptoms and the area of the body affected by allergy symptoms. The process by which environmental allergens work is as follows, when allergens enter the body, they are recognized by IgE (immunoglobulin E) antibodies. The antibodies activate mast cells that release histamines. Histamines cause inflammation, local swelling, itchiness, sneezing and mucus production inside the nose. It is our understanding that allergies are more appropriately described as temporary exaggerations of the body's natural immune defenses. In a sense, allergies and allergy symptoms are an indication that the human body is functioning properly as it tries to combat allergens. The reason why some persons have allergies and others do not relates to the natural level of IgE that each person possesses: the higher the level of IgE, the greater the allergic response. Therefore, claims relating to promoting or supporting any part of this normal human immune response (function) are proper structure/function claims. Moreover, allergies are self-limiting, can be mild in nature, and generally subside when the person is no longer exposed to the allergen (*e.g.* pet dander, or mold).

Allergy Structure/Function Claims

Regardless of whether allergies are properly considered a disease by FDA, a conclusion to which we strongly contest, Metagenics' label claims for Perimine, as submitted, and as further proposed herein are proper structure/function claims and entirely consistent with the intention of DSHEA. In order to compromise with the Agency, Metagenics may be willing to modify the scope of its claims so that they specifically only relate to "minor" or "occasional" conditions. This modification would be entirely consistent with FDA's present position with regard to such conditions as constipation, sleeplessness and overweight, which it originally stated in its January 6, 2000 final rule on Statements Made for Dietary Supplements Concerning the Effect of a Product on the Structure or Function of the Body. FDA agreed that certain conditions, which it had previously considered diseases, such as constipation, insomnia and obesity, actually have a variety of causes and varying levels of severity and as such certain claims regarding minor or occasional aspects of those conditions (*e.g.* "occasional constipation," "occasional sleeplessness" or "overweight") are consistent with the intent of DSHEA and are actually valid structure/function claims. FDA recognized that constipation has a variety of causes, many of them unrelated to disease. For example, constipation can be caused by changes in diet and schedule, and by travel. Constipation

¹ 21 C.F.R. 101.14 (a)(5).

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can also, however, be a symptom of such serious diseases as bowel obstruction and irritable bowel syndrome. Allergies also have a variety of causes such as mold, pet dander, or pollen. The difference is, however, unlike constipation, none of the causes of environmental allergies appear to be related to disease, nor are allergies a symptom of serious disease. Although a strong argument exists that the Agency is wrong to treat allergies as a disease, an even stronger argument can be made in support of claims similar in concept to the constipation structure/function claims accepted by FDA. Just as "For relief of occasional constipation" is not considered a disease claim under the rule, "For the relief of occasional allergies" should not be considered a disease claim either. In any event, Metagenics makes no mention of "allergies" on its label.

Furthermore, just as FDA suggested that the labeling of a product that claimed to treat occasional constipation should make clear that the product is not intended to be used to treat chronic constipation, which may be a symptom of a serious disease, Metagenics proposes a label statement that the product is not intended to treat chronic allergies. So long as the allergy claims are properly substantiated and are not directed at individuals actually suffering from a disease condition, none of which have been established, we believe that Metagenics' proposed label constitute proper structure/function claims.

We note that there are many other products on the market making claims similar to those objected to herein. Many of which have submitted "30 day" letters pursuant to Section 403 (r)(6) of the FDCA and FDA regulation at 21 CFR 101.93 and do not appear to have received FDA "courtesy" responses. These claims include:

- "To Maintain Healthy Levels of Immunoglobulin E (IgE);"
- "Yakriton can help balance histamine production;"
- "Supports normal & stable mast cell function and normal levels of Cox-2 and lipoxigenase enzymes."

Copies of the notification letters in which these statements appear are enclosed for your consideration.

In light of the fact that the Agency has allowed claims similar to those it objected to in its courtesy letter to Metagenics, and that allergies, as explained herein, do not appear to be a disease or health related condition, we would greatly appreciate your advising us of the propriety of Metagenics original claims on Perimine (Claims #1-4), including, the legal and scientific basis upon which you based those decisions.

Does the Agency's objection have anything to do with the aggregation of all four claims? If so, which of the claims does the Agency have a specific issue with? What if Claim #1 were modified to

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read "...promotes a healthy immune response in people who may be sensitive to *minor* environmental substances;" why wouldn't this statement be a valid structure/function claim?

Would the Agency change its position if Metagenics added the following warning statement to its original proposed label? "This product is only intended to treat minor and occasional allergies. For the treatment of chronic allergies or severe symptoms of hay fever, consult a licensed health care professional."

What if Claim #1 were modified to appear in the same manner as claims regarding constipation. For example, "for the relief of occasional allergies." Why wouldn't this statement be a valid structure/function claim?

What if Claim #1 were modified to read "...promotes a healthy immune response in people who suffer from *occasional* allergies from environmental substances;" why wouldn't this statement be a valid structure/function claim?

What if Claim #1 were modified to read "...promotes a healthy immune response in people who suffer from occasional allergies from foods or common household allergens;" why wouldn't this statement be a valid structure/function claim?

Doesn't the Agency agree that Claims #2-4 are valid structure/function statements, whether used together or individually, as they are nearly identical to claims that have appeared, apparently without objection, before the Agency in past "30 day" letters? If not, to which parts of those claims do FDA specifically object?

Unless we hear otherwise from you, we plan to proceed with marketing Perimine in conformity with the above listed claims. Thank you for your assistance in this matter. We look forward to hearing from you.

Yours truly,

ULLMAN, SHAPIRO & ULLMAN, LLP



Steven Shapiro

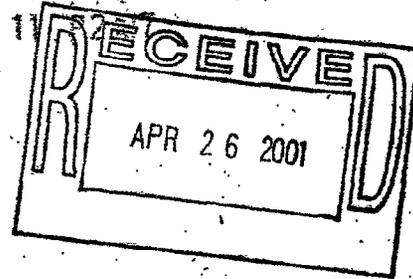


Seth A. Flaum

Enclosure

cc: Metagenics, Inc.

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April 24, 2001

The Office of Special Nutritionals (HFS-450)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C. Street S.W.
Washington, DC 20204

Dear Sir/Madam:

This is a notification pursuant to 21 U.S.C. 343(r)(6) that Standard Process Inc., Palmyra, Wisconsin 53156-0904, is making the following statements:

1. Yakriton supports healthy liver function by enhancing blood-filtering activities, thereby promoting the liver's natural detoxifying efforts.
2. Yakriton can help balance histamine production.

These statements are made for a dietary supplement containing calcium lactate, calcium stearate, arabic gum, and mixed tocopherols. The name of the product is Antronex®.

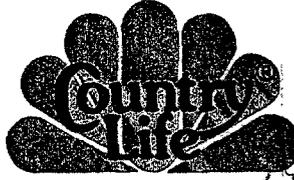
The information contained herein is accurate and Standard Process Inc. has substantiation that the statements are truthful and not misleading.

Sincerely yours,

Ann Holden
Standard Process Inc.

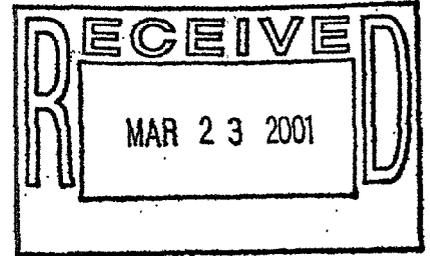
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Partners in Health and Beauty



Office of Special Nutritionals (HFS-450)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, SW
Washington, D.C. 20204

March 19, 2001

This letter serves as a 30 day notification pursuant to Section 6 of the Dietary Supplement Health and Education Act of 1994 (DSHEA), that Country Life@ is using the following statement on the label of ICE FACTORS™ Tablets (dietary ingredients: vitamin C, calcium, magnesium, taxifolin (dihydroquercetin), bromelain, turmeric extract, papain, ginger extract, green tea extract, grape seed extract (*Vitis vinifera*) & perilla seed extract (*Perilla frutescens*)). This statement is accompanied by the required disclaimer. To the best of my knowledge, the information contained in this notice is complete and accurate.

Supports normal & stable mast cell function and normal levels of Cox-2 and lipoxygenase enzymes.

Sincerely,

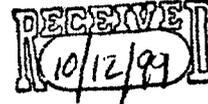
Kenneth Israel
New Product Development Coordinator

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Allergy Limited, LLC
22855 Savi Ranch Pky, Ste. G
Yorba Linda, CA 92877

Office of Nutrition

Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 "C" Street, SW
Washington, D.C. 20204



Re: 30-Day Dietary Supplement Notification

October 5, 1999

Dear Office of Nutrition:

Pursuant to 21 CFR Part 101.93(a)(2), the following is a notification to FDA that we have begun to market a dietary supplement in the U.S.

(i) Name and Address of the manufacturer:

Natural Alternatives International, Inc.
1185 Linda Vista Drive
San Marcos, CA 92069 USA

(ii) The text of the statement is:

To Maintain Healthy Levels of Immunoglobulin E (IgE)*

*This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

(iii) The names of the dietary supplements:

Vitamin C (as ascorbic acid),
Thiamin (as thiamine mononitrate),
Riboflavin,
Niacin (as niacinamide),
Vitamin B6 (as pyridoxine HCL),
Vitamin B12 (as cyanocobalamin), and
Manganese (as manganese citrate).

(iv) The brand name is:

Immun-Eeze

I, Hepburn T. Armstrong, am the responsible individual and hereby certify that the information presented in this notice is complete, accurate and, as the notifying firm, we have substantiation that the statement is truthful and not misleading.

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A handwritten signature in black ink that reads "Hepburn Armstrong".

Hepburn T. Armstrong

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