



May 29, 2008

Jeffrey E. Shuren
Assistant Commissioner for Policy
Food and Drug Administration
via email: jeff.shuren@fda.gov

Re: Marketing of drug-dietary supplement combination products

Dear Mr. Shuren,

On behalf of the American Herbal Products Association (AHPA) and its members, and in light of the recent appearance in the marketplace of Bayer Aspirin With Heart Advantage, a product that combines 81 mg of aspirin with plant phytosterols and that is labeled as an “analgesic phytosterol supplement,” I am writing to request clarification on the current policy of the Food and Drug Administration on marketing of over-the-counter drug-dietary supplement combination products.

AHPA is aware that FDA has in the past recommended that companies refrain from marketing products that combine both OTC drug and dietary supplement ingredients (except for products marketed under an approved new drug application). In a letter dated May 30, 2000 and addressed to attorneys at the firm of Morgan Lewis & Bockius, then Associate Commissioner for Policy, Margaret Dotzel, advised companies considering marketing products that combine or co-package dietary supplements and OTC drug ingredients that:

These types of combination products raise a number of significant public health and policy issues. For example, the addition of a new ingredient to a legally marketed drug product could affect the safety and efficacy of the drug component. In addition, consumers may be confused about the degree of scrutiny FDA gives such combination products. Consumers may believe that both components have been subjected to the more stringent drug regulatory requirements when, in fact, only the drug component may have been reviewed by the agency for safety and effectiveness. Moreover, it is uncertain under what circumstances the disclaimer required by the Dietary Supplement Health and Education Act (DSHEA) (codified in 21 U.S.C. 403(r)(6)(C)) could appear on a combination product without furthering consumer confusion.

The agency must determine under what conditions these combination products can be marketed in accordance with the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by DSHEA. More specifically, the agency must determine what regulatory standards are appropriate, including, but not limited

to, what safety and effectiveness standards will apply and how such products will be labeled. The number of inquiries we have received on this subject has made resolution of these issues a priority at the agency. We will be providing additional information as we develop our policy in this area.

Until the agency has carefully considered these issues, however, FDA strongly recommends that firms refrain from marketing products that combine both drug and dietary supplement ingredients (except for products marketed under an approved new drug application). In this interim period, we intend to take appropriate measures including, if necessary, regulatory action with respect to any such product that violates the FD&C Act or the agency's implementing regulations.

FDA has also previously acted to inform companies that have introduced such combination products that these are unapproved new drugs and misbranded. For example, on October 16, 2001 over the signature of David J. Horowitz, Acting Director, Office of Compliance, Center for Drug Evaluation and Research, the agency issued a warning letter to B.F. Ascher and Company, Inc. in the matter of that company's product identified as Melagesic™ PM Caplets, consisting of 500 mg of acetaminophen and 1.5 mg of melatonin. The warning letter stated:

As formulated and labeled, Melagesic is a 'drug' under section 201(g) (1) (C) of the Federal Food, Drug, and Cosmetic Act (the Act) because it is intended to affect the structure or function of the body (e.g., 'relieves pain,' 'Pain Reliever,' and 'for the temporary relief of minor aches and pains'). ... the presence of the acetaminophen, with its intended use to relieve pain, renders the entire product a drug ... even though the acetaminophen in Melagesic is combined with another ingredient, melatonin, that separately could be marketed as a dietary supplement. When ... a drug and a dietary ingredient are combined into a single product, there is no provision in the Act, as amended by the Dietary Supplement Health and Education Act of 1994, (DSHEA), that exempts any part of that product from the scope of section 201 (g).

... the melatonin used in combination with the acetaminophen is also a drug since it is a component of the finished drug product.... Based on the labeling claims made for it (e.g., 'sleep enhancer'), melatonin is also an 'active' drug ingredient ...

Moreover, based on its formulation and labeling, Melagesic is a 'new drug' ... because Melagesic is not generally recognized as safe and effective for its labeled uses [and] is not subject to the Food and Drug Administration's (FDA's) Over-The-Counter (OTC) Drug Review because no other product formulated with these active ingredients and labeled for these intended uses has ever been commercially marketed, and the agency has never proposed that such a product be included in this Review melatonin is not identified as a monograph nighttime sleep-aid active ingredient and, therefore, may not legally be used as such in any OTC nighttime sleep-aid product.... Thus, Melagesic violates section

505 (a) of the Act because it is a new drug and is not the subject of an approved New Drug Application (NDA).

Melagesic is also misbranded ... because the product lacks adequate directions for use ... because its labeling lacks adequate warnings ... [and] because its labeling fails to identify melatonin as an active drug ingredient.

In a quite similar warning letter issued on the same date and also over the signature of Mr. Horowitz, FDA contacted Omni Nutraceuticals, Inc. about that company's products identified as Inholtra[®] Joint Pain[™] Caplets, consisting of 325 mg of acetaminophen and 375 mg of glucosamine sulfate, and Inholtra[®] Joint Pain Plus[™] Caplets, consisting of 325 mg of acetaminophen, 187.5 mg of glucosamine sulfate, and 150 mg of chondroitin sulfate. This warning letter made many of the same points that were included in its warning letter to B.F. Ascher & Company, and stated, for example, that the products are new drugs under section 201(p) of the Federal Food, Drug and Cosmetic Act; that the glucosamine sulfate and chondroitin sulfate used in combination with acetaminophen in these products "are also drugs since they are components of the finished drug product;" and that the products are misbranded for all of the same reasons articulated in the warning letter to Ascher.

To AHPA's knowledge FDA has not modified the policies described in the May 2000 letter to Morgan Lewis & Bockius, and in the October 2001 warning letters to B.F. Ascher & Company and to Omni Nutraceuticals. If FDA has not, in fact, modified the policies described in these letters, AHPA assumes that FDA should evaluate Bayer Aspirin With Heart Advantage in the same manner that it has evaluated the OTC drug-dietary supplement products previously marketed by Ascher and Omni. If, on the other hand, FDA has now modified the policies it articulated in the above cited correspondence from 2000 and 2001 on OTC drug-dietary supplement combination products, then it may be that none of the concerns described in the previous paragraph are relevant to this Bayer product, and that the marketplace is now open to OTC drug-dietary supplement products.

Against this background, AHPA is asking whether FDA's policy on this subject has or has not been modified. In either case, AHPA is requesting that FDA announce the current policy forthwith so neither the public nor the regulated industry is confused by the introduction of this new product by Bayer HealthCare.

In addition, AHPA notes that in the above cited letter of May 2000, FDA stated that would need to determine "under what conditions these combination products can be marketed" in accordance with current law, as well as "what regulatory

standards are appropriate, including, but not limited to, what safety and effectiveness standards will apply and how such products will be labeled.” FDA also stated that the number of inquiries FDA had received at that time on this subject “has made resolution of these issues a priority at the agency,” and concluded that the agency would “be providing additional information as we develop our policy in this area.” AHPA is also therefore urging FDA, especially if it has concluded that the marketing of OTC drug-dietary supplement combination products is permitted under existing law, to provide the additional information promptly.

AHPA also notes that a significant modification has been made to the regulation of both OTC drugs and dietary supplements since May 2000, in that the Dietary Supplement and Nonprescription Drug Consumer Protection Act was passed in December 2006 and came into effect in December 2007. Under this new law, marketers of dietary supplements and of OTC drugs that are not subject to approval in an application under section 505 of the FD&C Act must, among other requirements, submit to FDA all received reports of serious adverse events and maintain records of all received reports of adverse events. AHPA is concerned that reports of adverse events that may come to be associated with OTC drug-dietary supplement combination products could fail to differentiate between the separate product classes, or that duplicate reporting for individual adverse events may occur. AHPA therefore requests that FDA comment on this topic at such time as the agency issues the aforementioned additional information in this area.

Thank you for your prompt attention to this important matter.

Respectfully submitted,



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Enclosure: Printed copy of website for Bayer Aspirin with Heart Advantage, http://www.bayeraspirin.com/products/ar/ar_bha.htm, accessed May 29, 2008.