MARKETING Dietary Supplement/ OTC Drug Combination Products

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With firms endlessly attempting to create innovative products, it was only a matter of time before the marketing of dietary supplement/over-the-counter (OTC) drug combination products began. The Food and Drug Administration has reacted by sending letters to two companies regarding the marketing of such combination products. In the letters, FDA stated it had "serious concerns" about the marketing of dietary supplement/OTC drug combination products and "strongly recommend[ed]" that companies "refrain from marketing products that combine both drug and dietary supplement ingredients."[1] Despite these statements, it appears there are some combination products that present a lower risk of FDA regulatory action than others. An examination of the "low" and "high" risk combination products follows, along with factors to consider before marketing a dietary supplement/OTC drug combination product.

FDA's General Policy

Although the Federal Food, Drug, and Cosmetic Act (FD&C Act) does not prohibit the marketing of a product that is both a food and a drug, FDA generally has expressed a rather inhospitable attitude toward combining food and drug properties into a single product. In the past, however, FDA has not asserted that all such products are inherently improper.

For example, in its rulemaking proceedings on weight control OTC drug products, FDA stated it "agrees ... that it would be reasonable to allow [essential] nutrients to be combined with an active weight control drug."[2] The apparent reason is that persons on diets who take weight control drugs may not be getting sufficient amounts of essential nutrients.

On the other hand, in the preamble to the final FDA regulation on "health claims" for dietary supplements, the agency expressed concern about the marketing of dietary supplement/OTC drug combination products. FDA stated that "multiple use products that are both foods and drugs present a difficult set of competing concerns for the agency. Such products are likely to be both an OTC drug and a dietary supplement."[3] The agency noted OTC

drug products are labeled with instructions to use the "product for a limited period of time" and "to seek medical intervention" if the medical problem persists. However, dietary supplements are labeled with "no instructions for seeking medical intervention or for limiting the duration of consumption of the supplement."[4] FDA stated that "[e]ven though label instructions may identify those directions for food and drug use in separate locations," consumers still may be confused by the labeling and not follow the appropriate instructions for their particular use of the product.[5] FDA added placing nutrient content and health claims on dietary supplement/OTC drug combination products further complicate the use of these products because such claims might cause consumers to focus more on the benefits of consuming the products on a long-term basis, which is inconsistent with the limitation in duration of use in OTC drug labeling.

FDA issued a very similar statement in the preamble of the final rule for health claims for conventional foods, stating a "drug that is labeled with instructions for use that both limit and do not limit consumption would be misbranded ... if it failed to contain a material fact – that is, how to reconcile these conflicting instructions."[6]

As the recent letters indicate, however, FDA is not just concerned about the confusion over dual labeling instructions. In fact, using various asserted premises, FDA issued earlier warnings to companies that added dietary supplement-type ingredients to OTC drug products.[7] FDA's most recent approach, however, is to object to the marketing of these combination products on the ground that they may not be safe or effective.

FDA's May 2000 letter to NTCO[1] referred to an aspirin product with vitamin B-12, while the letter to Ascher[1] referred to an acetaminophen product with melatonin. In both letters FDA stated "the addition of a new ingredient to a legally marketed drug product could affect the safety and efficacy of the drug component." In addition, FDA opined that "[c]onsumers 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."[8]

FDA's Grounds for Objecting to Combination Products

There are several grounds upon which FDA may object to the marketing of combination products. FDA could assert that a dietary supplement/OTC drug combination product is a misbranded food[9] or a misbranded drug[10] if it believes that inconsistent indications or instructions for use are misleading or confusing. FDA also could state that a combination product is an adulterated food[11] or an adulterated[12] or misbranded drug[13] due to the possible interaction of the dietary ingredient and the OTC drug substance.

Further, FDA could evaluate a combination product only as a dietary supplement and state that the inclusion in a dietary supplement of a drug that was never marketed in a food or dietary supplement before approval renders the dietary supplement an unapproved new drug[14] or an adulterated food.[15] Similarly, FDA could evaluate a combination product only as a drug and assert that a structure/function claim for a dietary ingredient that is not the active ingredient of the OTC drug causes the product to be an unapproved new drug.[16] The rationale would be that a structure/function claim is being made for a drug product thus triggering the "structure/function" definition of "drug" in the FD&C Act.[17] If the dietary ingredient is not generally recognized as safe and effective for the "indication" embodied in the structure/function claim, the claim could create an unapproved new drug status for the product.[18]

Low-Risk Versus High-Risk Combination Products

It is not inherently improper for a product to be formulated to include both OTC drug and dietary supplement ingredients and to bear both OTC drug and dietary supplement labeling. Whether FDA will object to this type of product appears to depend on whether the agency feels that the product presents safety concerns.

For example, a popular brand of antacid drug product bears a claim that the product provides calcium (as a nutrient). The product is labeled on its principal display panel as "Antacid/Calcium Supplement." The back label bears the information required by the final monograph for antacid OTC drugs and a

"Supplements Facts" box containing nutrition information. The label also bears the health claim that FDA has approved for foods concerning the relationship between calcium and osteoporosis.[19]

Although this product bears dual labeling instructions – that is, instructions for use of the product as an antacid and as a calcium supplement – FDA does not appear to have taken any regulatory action (at least at the present time) against this product. However, an antacid preparation such as this one, that is labeled or promoted also as a dietary calcium supplement, is the sort of dual product that one would expect FDA to be least likely to challenge for several reasons:

Calcium compounds are approved active ingredients for antacid drug products[20] in addition to being sources of calcium in dietary supplement products. Accordingly, FDA cannot assert that the presence of calcium in the formulation is questionable or that calcium could interfere with the safety or efficacy of the drug since calcium itself acts as both the dietary ingredient and the drug.

The simple statement "calcium supplement" and the FDA-approved health claim for calcium are about the least aggressive type of claims that could be made and, accordingly, are less likely to be offensive to FDA's generally-negative regulatory policy.

Calcium is a nutrient for which there is a well-established scientific (and political) recognition of need. Thus, it would be particularly difficult for FDA to assert that consumers have no legitimate need for or interest in the information that the nutrient calcium is present.

A company can make a credible argument that it has a constitutional right to simply tell the consumer in labeling about the presence of a substance that is properly present in a product.

On the other hand, marketing a dietary supplement product containing a dietary ingredient that is not also the active ingredient of the OTC drug product could present a greater risk of regulatory action even if the dosing and intended use of the product as a dietary supplement and OTC drug are the same.

For example, if the herb echinacea were combined with an OTC cough/cold medication, FDA could assert, as in the recent letters, that the interaction of the herb with the OTC drug ingredient could affect the safety and/or efficacy of the product. Moreover, FDA is likely to be less supportive of these combination products when it believes that the dietary ingredient to be combined with the OTC drug active ingredient is not scientifically recognized as being essential for humans or having a proven beneficial effect.

Furthermore, if a structure/function claim were to appear on the label of an OTC cough/cold product containing echinacea, FDA could assert that the product is an unapproved new drug as a result of the structure/function claim. Although a dietary supplement of echinacea may bear claims describing the supplement's effect on the structure or function of the body, if FDA evaluates the product only as a drug, such a statement could make the herb an "active" ingredient in the OTC drug product that might trigger unapproved new drug status.[21] Similarly, if FDA were to evaluate the echinacea and OTC cold/cough combination product only as a dietary supplement, FDA could assert that the inclusion of the OTC drug active ingredient, which may have never been marketed in a food or dietary supplement, renders the dietary supplement an unapproved new drug[22] or an adulterated food.[23]

Factors to Consider in Marketing a Dietary Supplement/OTC Drug Combination Product

In light of FDA's policy statements and regulatory letters on dietary supplement/OTC drug combination products, and the fact that there are two sets of regulatory requirements to worry about, it might be prudent to consider the following before marketing a combination product:

- Whether FDA would regard the dietary ingredient(s) as presenting safety or efficacy concerns, including any possibility for interaction or interference with the drug substance.[24] If there are safety concerns, then data should be acquired to demonstrate that the combined ingredients are both safe and effective.
- Whether there is any basis for FDA to assert that any of the non-drug ingredients are being used as active drug ingredients, thereby possibly creating unapproved new drug status for the product.
- Whether the FDA-required drug labeling explicitly provides for use of the product only for a limited period of time and, if so, whether this limitation appears to be fundamentally at odds with the dietary use that is provided or promoted by the product.
- Whether the total impression of all of the mandatory drug labeling for the particular product together with all of the dietary supplement labeling is consistent and not confusing.

As a matter of pragmatic reality, it must be recognized that FDA personnel generally do not favor (or are, in truth, hostile toward) these dual status products and can be expected to exercise a generally negative regulatory policy and practice. Any dietary supplement/OTC drug combination product is likely to present a risk of a negative FDA regulatory reaction unless FDA personnel regard the particular combination of ingredients and labeling as rational, useful, and not presenting safety concerns. Thus, it is very important for companies to attempt to anticipate all of FDA's possible objections to the marketing of a combination product and generate data to address all of the agency's concerns.

NOTES:

1. Letters from Margaret Dotzel, Associate Commissioner for Policy, FDA, to David Nolte, NTCO (hereinafter "NTCO letter"); and to James Ascher, Sr., B.F. Ascher & Company, Inc. (hereinafter "Ascher letter"); May 30, 2000.
2. 56 *Federal Register* 37792, 37793-37794; August 8, 1991.
3. 59 *Federal Register* 395, 419; January 4, 1994.
4. Id.
5. Id.
6. 58 *Federal Register* 2478, 2501; January 6, 1993.
7. Letter from Loren Johnson, District Director, Philadelphia District, FDA, to Samuel Lioon, Douglas Laboratories; April 18, 1986; and Regulatory Letter from Joseph Faline, Acting District Director, FDA, to Raj Chopra, Tishcon Corp., September 30, 1986.
8. FDA also noted in its letters that it was uncertain whether the Dietary Supplement Health and Education Act's (DSHEA's) disclaimer could appear on combination products "without furthering consumer confusion." The DSHEA disclaimer must appear on dietary supplements bearing structure/function claims and read: "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." FD&C Act § 403(r)(6)(C).
9. FD&C Act § 403(a)(1).
10. FD&C Act § 502(a), (f)(1).
11. FD&C Act § 402(f)(1)(A), (D).
12. FD&C Act § 501(d).
13. FD&C Act § 502(j).
14. FD&C Act §§ 201(ff)(3)(B), 505(a).
15. FD&C Act § 402(f)(1)(A), (D).
16. FD&C Act § 505(a).
17. FD&C Act § 201(g)(1)(C).
18. FD&C Act § 505(a).
19. 21 CFR §101.72.
20. 21 CFR § 331.11(d).
21. FD&C Act § 201(g)(1)(C).
22. FD&C Act §§ 201(ff)(3)(B), 505(a); see also Pharmanex v. Shalala, No. 99-4087, 2000 US App-LEXIS (10th Cir.; July 21, 2000); (reversing the lower court's decision that the exclusionary clause of 21 USC § 321(ff)(3)(B) is limited to finished drug products).
23. FD&C Act § 402(f)(1)(A)(D).
24. FD&C Act § 501(d).