

Porzio Pharmaceutical Alert

Porzio's Quarterly Review of DDMAC Untitled & Warning Letters on Rx Drug Promotion

DDMAC Launches a Broadbased Attack on a Wide Range of Promotional Materials

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In the first calendar quarter of 2006, the FDA's Division of Drug Marketing, Advertising, and Communications ("DDMAC") issued three untitled and four warning letters. Among the promotional pieces at issue were four patient-directed pieces (one patient brochure and three websites), seven pieces on display or distributed at scientific conferences, two professional journal ads, one sales aid and one promotional mailer. Remarkably, one letter addressed violations involving a drug that is no longer sold due to safety concerns. Two letters found insufficient underlying references to "data on file" citations. Two letters addressed the failure to submit websites under the 2253 form, and one untitled letter included a reference to a promotional violation involving the same drug that had occurred nearly six years ago.

In general, the violations cited this quarter can be grouped into five categories: omission/minimization of risk information, unsubstantiated effectiveness claims, unsubstantiated superiority/comparative claims, broadening of indication, and misleading graphic material. As in past quarters, DDMAC cited omission of risk information more than any other violation.

The following is our review of the claims that the FDA found violative in the first calendar quarter of 2006.

Omitting/Minimizing Risk Information

DDMAC cited the omission or minimization of risk information more than any other violation, an issue it raised in all seven letters. Numerous deficiencies existed in one journal ad, including omitting contraindications, and claiming that the drug "may" increase the risk of a certain kind of cancer, although the package insert revealed an actual two to twelve fold risk

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increase. Likewise, omission of the boxed warning, as well as a statement that the drug does not prevent dementia (but failing to disclose that the drug actually increases the risk of dementia), were also discussed. Opting for general rather than specific terms to define side effects (e.g. disclosing cardiovascular risks, but not specifying that myocardial infarctions have been associated with the product) was deemed unacceptable, as was the lack of prominence and readability with respect to the few risks that were disclosed.

DDMAC also found risk information to be minimized in a thirteen page sales aid, in which the boxed warning appeared on page 2, the phrase “see package insert” was found on numerous pages and the only other risk information was relegated to page 11 under the heading “Favorable Safety and Tolerability.” The most common adverse events were included, but serious risk information was excluded, and the prominent heading of “Favorable Safety and Tolerability” was found misleading because it suggested that the risks were minimal in nature.

Another journal ad was cited in an untitled letter for failing to include important warnings regarding the drug’s administration to patients with a prior history of heart disease. DDMAC also noted that, although the ad contained a boxed warning highlighting the types of risks associated with the drug, including fatal or life-threatening neuropsychiatric disorders, the ad failed to warn about the specific types of psychiatric adverse events listed in the warning section of the package insert.

A product brochure for a varicose vein treatment, which was also featured on the company’s website, did not include any risk information. Nonetheless, the brochure publicized that the product was “Approved by the FDA” and “guarantees safety compared to compounded forms that may not meet FDA standards and are not guaranteed.” DDMAC objected to the use of the phrase “guarantees safety,” noting that FDA approval does not guarantee the total safety of a product and that other factors, such as appropriate patient selection and proper drug preparation and administration, play a role.

A warning letter also described the omission of important risk information in a promotional mailer, including that the product contained aluminum that may be toxic with prolonged administration. As it had done in the past, DDMAC deemed insufficient a reference to the full prescribing information in small type at the bottom of the piece. DDMAC noted that risk information is needed to qualify safety or effectiveness claims that appear in each part of the promotional piece. Also, inclusion of a black box in the mailer was not alone sufficient when other important warnings (for example, the need for caution with particular patients) warranted discussion in the piece.

DDMAC cited digital billboard panels, exhibit panels, and a video for a diagnostic radiopharmaceutical in an untitled letter for repeatedly featuring the claims, “Rapid, Safe, and

Simple,” but completely omitting the most frequent and serious risks. It determined that the support for “rapid” was insufficient because it was not defined in the submitted references, nor specifically evaluated in the definitive clinical studies involving the product. Likewise, “simple” and “it’s easy to do” and no “big learning curve” were not substantiated in light of the 9 step reconstitution process, 7 step radiochemical purity test and 90 minutes needed for image collection.

Unsupported Effectiveness Claims

DDMAC discussed overstatement of efficacy in one warning letter and two untitled letters. In the warning letter, DDMAC cited a sales aid for presenting numerous claims regarding the effectiveness of a hypertension drug in a clinical trial. According to DDMAC, these claims were misleading due to the inadequacy of the studies relied upon. For example, one study was an open-label, uncontrolled trial, without a concurrent placebo control. DDMAC also criticized the sales aid for containing numerous claims regarding the “goal attainment” of patients taking the drug. For example, “Nearly 7 out of 10 patients . . . reached the aggressive goal . . .” and “Other trials demonstrate excellent monotherapy goal attainment vs other antihypertensives.” The study data upon which these claims relied was derived from a secondary analysis of the inadequate study.

A journal ad was the subject of DDMAC’s scrutiny in an untitled letter for its claim that “Only [Drug Name] offers a proven treatment option for the significant and growing number of nonresponders and relapsers.” The claim was derived from information in the package insert and studies that related to failure with older regimens, which were no longer the standard of care. DDMAC concluded that the claim misleadingly implied that the drug was effective with patients who failed treatment with a newer drug regimen. DDMAC observed that the ad did not contain contextual statements that might have corrected the misleading implication.

Unsupported Superiority/Comparative Claims

DDMAC examined unsupported superiority claims in three warning letters. In one letter, DDMAC critiqued a sales aid that claimed superiority to a vast array of competitor products, all without substantiation. In some instances, the studies relied upon were deemed inadequate because they were open-label and uncontrolled. In other instances, the studies did not show statistical significance, or showed only equivalent effects. Additionally, a pooled meta-analysis of 43 double-blind, randomized, controlled trials with patients only on a starting dose of a competitor’s drug, rather than the maximum approved dose, was deemed insufficient. The meta-analysis was not a concurrently controlled study (but rather a historically or externally controlled trial), which can introduce bias because the results are known before the comparisons are made. Likewise, different patient populations can vary greatly in their response to a drug.

Along the same lines, DDMAC also cited a journal ad for suggesting superiority by implying that the drug provided targeted treatment. For example, one claim stated, “[The drug] helps you treat them as individuals” and included the statement: “*Because all menopausal women are not alike . . .*” juxtaposed with a graphic of a female-shaped cookie cutter. DDMAC determined that such claims implied that the drug provided unique therapeutic benefits without adequate substantiation.

Another problematic claim highlighted in the same letter was that the drug provided a “distinct patient benefit,” but neither of the supposed bases withstood scrutiny. First, the ad stated the product was plant-derived. Although initially derived from a plant, the drug was in fact a synthetic estrogen. In either event, however, whether plant-derived or synthetic, there was no support that this provides a “distinct patient benefit.” Likewise, the drug was touted as being available in low .45 mg. doses, but the ad failed to disclose that another product was offered in a lower starting dose of .3 mg.

Similarly, a product brochure was cited in a warning letter for containing such phrases as “preferred therapy,” “right treatment,” “and “safer” to suggest a comparison between the drug and other sclerotherapy treatments without providing evidence of the drug’s superiority.

Broadening of Indication

Broadening of indication was a violation addressed in one warning letter and two untitled letters. In one letter, DDMAC addressed a patient brochure containing numerous claims concerning the long-term effectiveness of the product, despite the fact that the company had received a non-approvable letter for use of the product as chronic treatment. For example, the statement “without regular treatment, seborrheic dermatitis can reappear without warning” appeared next to a graphic of a prescription for a 120 ml bottle of the product with six refills. In addition, the brochure contained claims such as, “Make [the drug] a simple part of your weekly routine” and “[the condition] can be effectively managed with ongoing treatment.” The piece also contained 8 weekly diaries for patients to track their treatment schedule. In DDMAC’s view, the brochure thus misleadingly suggested using the drug for long-term treatment.

Additionally, DDMAC objected to a statement in the patient brochure that created a misleading impression about the use of the product in pediatric populations. Clarification that the drug was not indicated for infants appeared on the next page, but DDMAC deemed this insufficient to correct the misleading impression that the drug was so approved.

DDMAC also cited a product exhibit panel and product video of a company for misleadingly suggesting its effectiveness in a broader range of patients than the clinical evidence

supported. In the same letter, DDMAC also criticized the product video because it created the impression that the product was indicated for all cases and was 100% accurate in diagnosing appendicitis. Among the product claims made in the video were, “Our surgeons 2 to 1 said, ‘I don’t need another study to diagnose appendicitis’. . . It was that valuable to them.”

Likewise, DDMAC criticized a brochure in a warning letter for promoting a product for all patients with “small uncomplicated varicose veins of the lower extremities”, despite the fact that the product should only be used on dilated veins and that the “benefit to risk ratio should be considered in selected patients who are great surgical risks.”

Misleading Graphic Matter

DDMAC analyzed one warning letter for presenting misleading graphic material. The product brochure in question contained several graphics of clear, varicose vein-free skin. One page of the brochure contained the claim, “Life quality improved.” DDMAC stated that the graphic and statement were misleading because the product had not been shown to provide *total* cosmetic correction of varicose veins or improved quality of life. In fact, a range of outcomes was possible based on, for example, the severity of the disease and depth of skin tone. Likewise, the adverse reactions section of the package insert revealed the product’s potential to cause permanent discoloration along the vein.

Conclusion

In the first quarter of 2006, DDMAC has shown that it will continue its aggressive surveillance of a vast range of promotional pieces. As in previous quarters, the omission of risk information remains a primary concern, along with claims based on unreliable medical studies and the use of misleading text or graphics. While basic principles seem to inform DDMAC’s judgment, its review is undeniably specific to the product, the underlying science, and the promotional piece at issue. More than ever, companies must engage in a rigorous, interdepartmental medical, regulatory and legal review of their promotional pieces to avoid becoming the next DDMAC target.