

Authors

Linda Pissott Reig, Esq.
Principal
lpreib@pbnlaw.com

Jennifer A. Romanski, Esq.
Counsel
jaromanski@pbnlaw.com

Sarina D. Rivera, Esq.
Associate
sdrivera@pbnlaw.com

Managing Editor

Steven P. Benenson, Esq.
Principal
spbenenson@pbnlaw.com

About Porzio

Porzio, Bromberg & Newman P.C. provides a broad array of litigation, corporate, transactional and counseling services to clients and has offices in Morristown and Brick, New Jersey, and New York City. For over 30 years, we have represented pharmaceutical and medical device manufacturers in complex litigations and counseled them on regulatory issues and risk management strategies. Our Pharmaceutical Sales & Marketing Compliance Department counsels clients on PDMA compliance, state sample distribution laws, state marketing disclosure and marketing prohibition laws, federal laws governing promotional materials and product labeling, federal and state anti-kickback laws, and risk management issues.

For more information on Porzio, [click here](#).

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

DDMAC Reasserts Its Oversight of Promotion Directed Not Only to Physicians, But Also to P&T Committees

The FDA's Division of Drug Marketing, Advertising and Communications ("DDMAC") issued four warning letters and two untitled letters from January through April 2007. The six letters address a wall calendar and dry erase board, a journal advertisement, a direct-to-consumer television advertisement, a retail sell sheet, a sales aid, and a physician's presentation and hand-out to the Maryland Department of Health and Mental Hygiene's Pharmacy and Therapeutics Committee.

Themes include (1) omission of and/or minimization of risk information; (2) failure to adequately disclose indication or broadening of indication; (3) unsubstantiated claims, including comparative claims and superiority claims; and (4) patient preference claims. DDMAC also cites an inappropriate reminder advertisement. In addition, DDMAC cites promotion directed to a Pharmaceutical and Therapeutics ("P&T") Committee because it suggests unapproved drug uses. Two letters address the sponsor's failure to submit the promotional item to DDMAC under FDA Form 2253, as required by 21 C.F.R. § 314.81(b)(3).

Omitting or Minimizing Risk Information

All four warning letters discuss promotional pieces that omit or minimize risk information. One warning letter cites a wall calendar and dry erase board that present efficacy claims on the front, but have an adhesive and opaque paper on the back that completely obstructs the risk information. DDMAC notes that the design of the board does not "allow the risk information to be visible or even accessible." Also, DDMAC explains that even if the risk information on the back were accessible (i.e., the items did not completely adhere to the wall and could be lifted), the promotional piece would still misbrand the drug because there is no risk information on the front.

Another warning letter cites a retail sell sheet for topical ear medication because it presents efficacy claims but completely omits all risk information. An advertisement for a topical solution for actinic keratoses of the face or scalp is the subject of a warning letter because it contains several effectiveness claims, but omits risk information about the drug. An efficacy claim that the drug works without weeks of red, raw skin and "skin response usually subsides within a week of treatment ..." contradicts the full prescribing information that states, "erythema and edema

About Porzio Pharmaceutical Services

Porzio Pharmaceutical Services, LLC, (PPS), a wholly owned subsidiary of Porzio, Bromberg & Newman P.C., is dedicated to helping pharmaceutical and medical device manufacturers, wholesale distributors, labelers, and sales and sales support companies master the continually changing regulatory environment that impacts their business. PPS provides the pharmaceutical industry with informational resources, enabling companies to stay compliant with the growing body of federal and state regulations governing pharmaceutical marketing and sales.

For more information on PPS, [click here](#).

About Porzio Pharmaceutical Alerts

Porzio Pharmaceutical Alerts are a free service to our clients, colleagues and friends that provides cutting edge analysis and insight into the various legal and regulatory challenges confronting today's pharmaceutical industry. It provides general information only and is not intended to be comprehensive on the subject addressed or to provide legal advice.

resolved to baseline or improved by **4 weeks** after therapy." Also, DDMAC explains that the reference to the prescribing information in the lower left-hand corner of the ad does not mitigate the misleading presentation.

The handout distributed to the Maryland Department of Health and Mental Hygiene's Pharmacy and Therapeutics Committee discusses a sleep disorder drug. DDMAC views the handout as implying that the drug can prevent driving-related accidents. It notes, however, that the piece omits all risk information, including a statement from the labeling that patients taking the drug should, if appropriate, be advised to avoid driving. Additionally, the full package insert did not accompany the piece as FDA regulations require. (See 21 C.F.R. § 314.81(b)(3)(i)).

Failure to Adequately Disclose Indication or Broadening of Indication

An untitled letter cites a journal advertisement for including efficacy and safety data for a drug wafer that serves as an adjunct to surgery and radiation in certain cancer patients, but failing to present the product's full indication.

Similarly, a retail sell sheet for a topical ear medication was the subject of a warning letter for failing to include the complete indication for the product. The sell sheet claims that the drug is "approved for the treatment of acute otitis media with tympanostomy tubes and acute otitis externa," but does not reveal that the drug is only approved for acute otitis media and acute otitis externa caused by certain microorganisms, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

Another advertisement is the subject of a warning letter because it contains statements broadly promoting the use of the product in patients with actinic keratoses. The product is indicated for the treatment of actinic keratoses, but with specific limitations. Notably, the product was not studied in, and is not indicated for, Grade 3 lesions and is only indicated for the face and scalp.

DDMAC found that a physician presentation and handout to a P&T Committee also impermissibly broadened the drug indication. The handout claims that the drug is safe and effective for the treatment of various disorders associated with fatigue, sleepiness, or inattentiveness and "has utility in" the treatment of "some cases of insomnia" and "other neurologic and psychiatric disorders associated with fatigue, sleepiness or unattentiveness." This claim is followed by a list that includes "Multiple Sclerosis Related Fatigue," "Parkinson's Disease Related Fatigue," "Chronic Fatigue Syndrome [sic] Fibromyalgia & chronic pain conditions," "Attention Deficit Disorder" and "Depression." The drug is not indicated for insomnia, fatigue or any of the listed neurologic and psychiatric disorders.

Also, the handout implies that use of the drug can help avoid motor vehicle accidents and improve social and occupational functioning. It states, "Approximately 25% of night/rotating shift workers meet criteria for **SWSD** [a sleep disorder] resulting in increased risk of motor vehicle accidents, work related accidents and errors, and clinically significant impairments in social and occupational function." DDMAC noted that just because the drug improves wakefulness, it does not necessarily provide these other benefits, particularly since the prescribing information cautions about use of the drug when operating an automobile or other hazardous machinery.

Unsubstantiated Claims, including Comparative and Superiority Claims

One warning letter and one untitled letter address unsubstantiated claims. The warning letter cites a sales aid for presenting unsubstantiated superiority claims regarding a topical ear drop. The reference for some of the claims, including the tagline "All together better," shows no significant difference in cure rates in the two treatment options (87% & 94% versus 84% and 89%). Claims about the product's ability to relieve pain, including the claims "Don't rock the boat: less pain by day 2,"

and "More Patients Report Less Pain," were deemed unsubstantiated because the references do not contain the specific product comparison as a pre-specified endpoint. Also, of the numerous product comparisons presented in the references, only two contain nominal p-values.

As explained by DDMAC, "Any appropriate corrections made for multiple comparisons would show that these comparisons were not statistically significant." The same letter cited the sales aid for superiority claims regarding reduction of inflammation and lower rate of treatment failures. The reduction of inflammation claims are based on a study in which the product does not show a significant difference in reduction of inflammation at three of the four time points analyzed. The claims regarding lower rate of treatment failures is not based on a pre-specified analysis, nor was the result consistent across studies.

Finally, DDMAC notes that the sales aid exaggerated the risks of allergic reactions to neomycin, an active ingredient in the competitor drug. The claim at issue "1 out of 8 patients had an allergic reaction to neomycin ..." is based on a study of patients with chronic eczema of the outer ear canal or recurrent external otitis, and experimental conditions that "do not mimic the clinical usage of topical otic antimicrobials."

An untitled letter involving a journal advertisement is cited for containing unsubstantiated claims for a drug used as adjunct to surgery and radiation for certain malignancies. The claims suggest a clinical benefit because the product is inserted during surgery as compared to radiotherapy alone that cannot begin until after healing from surgery. The clinical study cited in support of this claim, however, revealed that this was done out of necessity and that there was no evidence that this timing presents an advantage. The company also relied on references that were either based on an *in vitro* labeling study or rat and monkey studies, which do not constitute substantial evidence.

Patient Preference Claims

An advertisement for a topical solution for the treatment of actinic keratoses is the subject of a warning letter because it contains the claim that "4 out of 5 patients" prefer the treatment to previous treatments. The claim is based on an open-label study of 27 patients that includes one question about the product based on a 3-point comparability scale asking patients to compare the product to their prior therapies. The study does not directly compare the product with competitor products. Also, as explained by DDMAC, claims about patient preference encompass "multiple aspects of patient experiences with the drugs such as efficacy, side effects, dosing and ease of administration and therefore cannot be adequately measured by one single item." FDA explains that such claims must be based on adequate and well-controlled studies using validated, well-developed instruments to demonstrate patient preference.

Inappropriate Reminder Ad

A direct-to-consumer television ad for a sleep aid was the subject of an untitled letter because the statements and images in the ad suggest that the drug is indicated for use in children. The TV ad includes statements and a tagline about "Back to School," as well as images of school-age children. DDMAC noted that while reminder ads generally do not have to disclose information relating to risks and effectiveness, this reminder ad is unlawful because the statements and images featured in the ad suggest that the drug is indicated for children. DDMAC noted particular concern about the ad because the drug's prescribing information contains a precaution that safety and effectiveness of the drug in pediatric patients has not been established and further study is needed before safety in that population can be assessed. Because the ad is not a reminder ad, DDMAC cites the piece for failure to disclose the drug's indication and major side effects, and failure to make adequate provision for the dissemination of approved labeling.

Promotion of Unapproved Uses

A promotional piece distributed to the Maryland Department of Health and Mental Hygiene's Pharmacy and Therapeutics Committee was the subject of a warning letter because it recommends new unapproved uses for a product, including claims about insomnia and fatigue, for which the drug is not indicated. The piece also contains claims about multiple sclerosis-related fatigue, Parkinson's Disease related fatigue, chronic fatigue syndrome, attention deficit disorder, and depression. DDMAC explained that this unlawful product promotion was "particularly troubling" because the company received a "not approvable" letter for one of the uses being promoted in the piece.

Conclusion

The time spans between violative promotion and FDA action vary. We were able to assess all but one of the letters covered in this alert and the time that elapsed from the date of promotion until FDA action. The time spans were 3.5 months, 6 months (2 letters), 8 months and 9 months.

FDA's targeting of a presentation to a P&T Committee is also particularly noteworthy. It is unclear whether the physician's handout was company-approved. The promotion appears to be an outline of talking points rather than a glossy, commercially produced brochure. P&T Committees often express interest in unapproved uses, and the warning letter reaffirms the need for drug companies to ensure that any discussion of such uses is based on reliable data. Additionally, an unsolicited request for such information should typically precede that discussion. Finally, should your drug company's representative intend to bring a hand-out of talking points to such a Committee, you will want to ensure that the representative obtains your review and approval of that document.

Recent Alerts Are Available on Our Website:

June 18, 2007 - Newly Enacted Nevada Statute Requires Adoption of a "Marketing Code of Conduct." [Click here.](#)

February 26, 2007 - Porzio's Review of DDMAC Untitled and Warning Letters on Rx Drug Promotion [Click here.](#)

January 11, 2007 - FDA to "Redouble" Enforcement Efforts Against Marketed Unapproved Drugs [Click here.](#)

September 18, 2006 - DDMAC Puts Risk Information Front and Center [Click here.](#)

July 20, 2006 - Louisiana Revisits Drug Samples and Lobbying [Click here.](#)

June 26, 2006 - FDA Lifts Stay on PDMA Pedigree Provisions: Is Your Company Prepared? [Click here.](#)

May 9, 2006 - Maine Department of Health and Human Services Issues Proposed Rules to Govern the Disclosure of Clinical Trials and Pharmaceutical Marketing Expenses. [Click here.](#)

May 8, 2006 - DDMAC Launches a Broadbased Attack on a Wide Range of Promotional Materials. [Click here.](#)

February 15, 2006 - Louisiana Weighs in on Drug Sampling and Lobbying. [Click here.](#)

Subscribing and Unsubscribing to Alerts

If you would like to add or change an e-mail address, please send us an e-mail at porziopharmadept@pbnlaw.com.

To unsubscribe from our e-mail list, please reply to this e-mail with "UNSUBSCRIBE" in the subject line.