Boxed Warning Drugs Beware!!

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The Food and Drug Administration's (FDA) Office of Prescription Drug Promotion (OPDP) recently sent three enforcement letters (two Warning Letters and one Untitled Letter) to three prescription drug manufacturers. Both Warning Letters concerned Internet promotion. One Warning Letter and the Untitled Letter were the subject of complaints to OPDP's Bad Ad Program. All three letters addressed the promotion of drugs with **boxed warnings** and focused on minimization of risk information.[1] Despite the low number of total letters issued by OPDP this year, these three letters show that FDA has not gone away, particularly where public health risks are presented, such as with boxed warning products.

Three Recent OPDP Letters

We will briefly describe OPDP's major objections and note our observations.

In the first Warning Letter, OPDP objected to a post on the company's Facebook page for the drug. The Facebook post claimed that the drug would "protect you from health complications" with "no drama." OPDP concluded that these claims suggested that there were no safety concerns associated with the use of this boxed warning drug. The inclusion of a reference and link to the full prescribing information (PI) was not sufficient to mitigate the misleading claims in the post.

In addition, OPDP acknowledged that some of the risk information appeared together with the drug's indication in text format in a separate pop-up box that was visible when hovering a cursor over the drug logo in the corner of the post. However, presenting risk information in this manner did not mitigate the misleading impression from the claims in the post. Finally, neither the post nor the pop-up box included information regarding two of the conditions for which the drug is contraindicated, nor any other warnings and precautions associated with the drug.

The Untitled Letter concerned oral statements made by a company sales representative at a lunch presentation to healthcare professionals. The sales representative's statements were included as part of a report/complaint submitted to OPDP's Bad Ad Program. The Untitled Letter is heavily redacted so the exact nature of the sales representative's statements are not completely clear. However, based on the complaint, OPDP concluded that the sales representative made statements providing evidence that the drug was safe and effective for an unapproved intended use, (use in a certain age group), and for which its labeling did not provide adequate directions for use. Although the product's approved labeling was later updated to include this age group, this labeling was not in effect at the time of the sales representative's statements.

In addition, during the presentation, the sales representative minimized the serious, life-threatening risks described in the boxed warning by: (1) suggesting that healthcare practitioners should not worry about the risk, (2) providing anecdotal claims regarding the age of patients who experienced

1 www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM623557.pdf
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesby FDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM623636.pdf
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serious adverse reactions, and (3) noting that other treatment centers have the drug on formulary and were not concerned about the boxed warning.

In the most recent letter, a Warning Letter, OPDP cited a company for an Internet webpage that discussed two of its drug products, one of which contains a boxed warning. The letter concluded that the webpage was false or misleading because it presented information about the uses and/or benefits of both drugs, but failed to include **any** risk information about either product. As we have seen in other enforcement letters, OPDP acknowledged that the webpage included references to the full PIs for both drugs on other websites. However, this did not mitigate the omission of risk information from the webpage.

AGG Observations

- OPDP is still very much engaged in enforcement activities related to promotional materials, with a particular focus on violations where safety concerns might be implicated (e.g., drugs with boxed warnings, how companies characterize risk information, minimization of risk).
- OPDP's Bad Ad Program is alive and well!
- In general, the agency is treading lightly when it comes to enforcement of off-label promotion in light of First Amendment concerns. However, the Untitled Letter described above was based on oral statements by a sales representative that provided evidence of an unapproved use. It is worth noting that FDA issued the letter despite the fact that the new use was added to the labeling a short time later. Although the sales representative's statements sounded particularly egregious, firms should ensure that their sales training programs address the dangers of off-label promotion and minimization of risk.
- OPDP continues to pay particular attention to Internet promotion. Two of the letters described above remind us that: (1) Internet webpages that discuss the benefits of a drug product must also describe the product's risks (a link to the PI or reference to another website is not acceptable), and (2) firms are responsible for product promotional communications on Internet sites (e.g., Facebook) that are owned, controlled, created, influenced, or operated by, or on behalf of, the firm, and these communications must comply with applicable regulatory requirements.
- In September, Janet Woodcock, M.D., Director of the Center for Drug Evaluation and Research, told the Alliance for a Stronger FDA that the agency is treading lightly in its enforcement of advertising regulations because of First Amendment concerns; one reason the number of OPDP enforcement letters has plummeted in recent years. However, Dr. Woodcock went on to say that FDA is looking primarily for advertising violations, "Where we really think there might be a threat to human safety, where they really are doing something egregious." In issuing these three letters regarding the promotion of drugs with boxed warnings, OPDP has taken Dr. Woodcock's directive to heart. Companies with boxed warning drugs should re-double their efforts to ensure that their promotion complies with FDA regulations and policies.

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