KING & SPALDING

Client Alert

FDA & Life Sciences Practice Group

February 5, 2013

2012 Year in Review: FDA OPDP Warning Letters and Untitled Letters

In 2012, the Center for Drug Evaluation and Research's (CDER) Office of Prescription Drug Promotion (OPDP) issued a total of 28 enforcement letters to pharmaceutical manufacturers, two fewer than in 2011. Of the 28 letters, three were Warning Letters and 25 were Untitled Letters. Roughly 68 percent (19 letters) of the promotional materials reviewed in the enforcement letters were directed at healthcare professionals, and 5 of OPDP's enforcement letters were issued regarding drugs with boxed warnings, including one Warning Letter. Only three enforcement letters (11% of all enforcement letters issued) were the result of complaints received through the Bad Ad Program, one of which was a Warning Letter and two of which cited oral statements by sales representatives. Two enforcement letters were issued regarding emerging media—an iPad sales aid and a podcast interview.

Notable Trends in 2012:

The most frequent allegations cited by OPDP in 2012 were:

Allegation	2012	2011
Omission and Minimization of Risk Information	64%	77%
Overstatement of Efficacy	43%	37%
Unsubstantiated or Misleading Comparative or Superiority Claim	32%	23%
Unsubstantiated Claims	29%	37%
Omission of Material Facts	18%	17%
Broadening, Omission, or Misleading Indication	14%	27%

Rather than focusing on the truthfulness of individual statements that appear in promotional items, FDA is increasingly digging into the balance of information provided in a promotional piece and on the overall context in which a particular claim appears. This nuanced approach was signaled by the rise of "Omission of Material Facts" as one of the most frequent allegations in OPDP's letters in 2012.

Notable trends observed in 2012 included:

- FDA is closely scrutinizing claims that concern individual components of composite scores to determine if the tests that

For more information, contact:

Nikki Reeves
+1 202 661 7850
nreeves@kslaw.com

Marian J. Lee
+1 202 661 7955
mlee@kslaw.com

Christina M. Markus
+1 202 626 2926
cmarkus@kslaw.com

Elaine Tseng
+1 415 318 1240
etseng@kslaw.com

Joanne H. Chan
+1 202 626 2914
jchan@kslaw.com

King & Spalding
Washington, D.C.
1700 Pennsylvania Avenue, NW
Washington, D.C. 20006-4707
Tel: +1 202 737 0500
Fax: +1 202 626 3737

www.kslaw.com

measure the composite scores were adequately designed to measure the individual components of the score.

- FDA is objecting broadly to patient testimonials and case studies because the outcomes portrayed, while truthful, are not representative of the typical patient experience and are misleading and not supported by substantial evidence.

- FDA is narrowing the extrapolations that can be made from known facts so that manufacturers are largely limited to the exact data that are presented in data sources.

Observations and Lessons Learned from 2012 OPDP Letters:

- ***Be careful with breakdowns of composite scores.*** In 2012, FDA issued a total of 5 enforcement letters, one of which was a Warning Letter, that cited claims based on individual components of composite scores. In most cases, promotional materials contained claims of improvement with regard to specific symptoms of the FDA-approved indication for the drug. In each case, FDA objected to the claims because the scales or tests were designed to generate a total or overall composite score that incorporated scores for improvement of individual symptoms, not to evaluate the individual symptoms on their own. For example, in a September 18, 2012 Warning Letter, FDA objected to claims that the drug, FazaClo, was effective in relieving "distressing symptoms such as agitation, unusual thoughts, hearing voices, . . . lack of motivation, and lack of interest in social activities" that were based on "a clinical trial studying [the drug's] effect on the Brief Psychiatric Rating Scale (BPRS) total score, the cluster of four key BPRS items (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought criteria), and the Clinical Global Impression (CGI) scale." FDA explained that "[d]emonstrating an effect on the composite total scores of these scales does not demonstrate an effect on an individual component of these scales," so the clinical study was not considered substantial evidence to support claims about individual symptoms of schizophrenia. We recommend that manufacturers exercise caution when breaking down composite measures to support claims if the underlying study design did not specifically contemplate analyzing the individual components of the measure.

- ***Avoid the common pitfalls associated with the use of patient testimonials and case studies.*** OPDP issued a total of 3 letters that cited testimonials or case studies. FDA's objection to these types of materials was two-fold. First, while acknowledging that the stories may be accurate reflections of patient experiences, FDA found that the testimonials or case studies misled consumers into believing that most or all patients would respond in the same, atypical way to treatment. Second, FDA objected on an evidentiary basis, stating that "one patient's treatment response does not constitute substantial evidence for [a] claim." As is usually the Agency's position, FDA found that disclaimers stating that "individual results may vary" were not sufficient to correct the misleading impression of the testimonials and case studies. FDA's sensitivity to testimonials and case studies has been observed both in the drug and device space, signaling a need for manufacturers to ensure that the stories reflected in these materials reflect the typical patient experience and outcomes that are supported by clinical trial data.

- ***Stick to what your sources say and avoid extrapolating too far beyond stated, known facts.*** In several 2012 letters, FDA denied claims that made inferences beyond the exact data presented in the sources used to support the claims, even if the claims could potentially be viewed as logical inferences or implications of the data.

- In a June 19, 2012 Untitled Letter, FDA objected to claims that the antibiotic, Zmax, had a clinical effect that lasted 10 days following administration. FDA "acknowledge[d] that in the clinical trials for Zmax, clinical and microbiologic evaluations for both approved indications were conducted at the Test of Cure visit, 7 to 14 days post treatment," but "Zmax is only administered one time as a single dose, [so] it is unclear exactly how long the extent of the therapeutic benefit would be maintained."

- In a Warning Letter issued on September 18, 2012 regarding promotion of the drug, FazaClo, FDA objected to a claim suggesting that clozapine is more effective than other schizophrenia treatments, despite the fact that "clozapine has been demonstrated to be more effective than chlorpromazine and is the only product currently approved to treat severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia," because FDA was not aware of substantial evidence demonstrating that "clozapine is more effective than all other products for treatment-resistant schizophrenia."

- ***FDA continues to scrutinize clinical study design and data analysis plans for data cited in support of claims and statements.*** As in previous years, FDA's enforcement letters found promotional materials to be false or misleading based on the analyses used to examine data in support of promotional claims. In 2012, FDA continued to closely examine data, often objecting to exploratory analyses, secondary endpoints, and retrospective analyses. These objections highlight the importance of study design and the need to determine the ultimate use or goal for study data when designing clinical trials to ensure that necessary analyses are pre-specified in the study plan and proper endpoints are identified.

For your reference, we have prepared a chart that provides: (1) a list of 2012 OPDP Warning and Untitled Letters, and (2) highlights of promotional violations alleged in each letter. The chart is available online in a searchable PDF document at: http://www.kslaw.com/library/publication/ca020513_chart.pdf.