Arnall Golden Gregory LLP

Client Alert


Contact Attorney Regarding This Matter:

Alan G. Minsk
404.873.8690 - direct
alan.minsk@agg.com

## FDA Enforcement in the Drug Product Promotional Arena: A Year in Review

The year 2012 was an active one for FDA enforcement in the drug product promotional arena. It started with the rollout of FDA's guidance on responding to off-label requests for information (technically issued in December 2011) and ended with a "what now" scenario after the United States Court of Appeals for the Second Circuit found unconstitutional the criminal prosecution of a drug company's sales representative for off-label promotion.[1] And, with 28 enforcement letters sent by FDA's Office of Prescription Drug Promotion (OPDP) for unlawful promotion, three of which were Warning Letters, the agency enters 2013 with momentum.

This Bulletin summarizes some of the enforcement themes in 2012 and areas of concern that drug companies should consider as they prepare promotional materials for this year. We will not review each enforcement letter or every type of violation in detail, nor will we identify any particular company. Rather, we intend to highlight the scope of enforcement to paraphrase the following saying — if we do not remember the past, we are doomed to repeat these mistakes in the future.

### Overview of OPDP Enforcement

Spoiler Alert: as with previous years, the most common violations cited by OPDP include: omission and minimization of risk information, misleading efficacy claims, misleading superiority claims, and promotion of unapproved uses of a drug/broadening of indication (i.e., off-label promotion). OPDP continues to focus its enforcement resources on the following products: newly-approved, those with significant risks, those cited for violations or in complaints in the past, and those promoted with broad and widespread campaigns.

### Poor Presentation of Risk Information

FDA continues to find problematic the presentation of risk information that is not comparable to benefit claims.

Some examples included:

1 We have prepared Bulletins on both topics, which can be accessed by clicking here and here.

Arnall Golden Gregory LLP
Attorneys at Law

171 17th Street NW
Suite 2100
Atlanta, GA 30363-1031

Two South Biscayne Boulevard
One Biscayne Tower 2690
Miami, FL 33131

1775 Pennsylvania Avenue NW
Suite 1000
Washington DC 20006

www.agg.com


- relegating risk information to "blurry and difficult to read" text in the final 7 seconds of a 3½ minute video, while using video and audio components for benefit claims;

- a 3 minute and 55 second patient assessment video that did not discuss any risk information during its audio-visual presentation;

- a video that discussed drug benefits during its audiovisual presentation, while simultaneously presenting drug risks in rapidly scrolling small text at the bottom of the screen;

- a pitch letter that omitted all product risks, despite an accompanying press release containing Important Safety Information;

- a 12 page patient brochure failing to discuss drug risks until page 8 under the heading "**Side effects**" (emphasis original);

- a brochure presenting efficacy claims in large bolded, colorful text surrounded by significant white space, but discussing risks in block paragraph format, in obscure places, and without headers or other signals to alert readers; and

- a professional phone script that presented efficacy claims but no risks.

**Quality of Life (QOL) Claims**

QOL claims that misleadingly imply a drug will improve other parts of a patient's life remain an FDA concern.

Examples included:

- claims in a website that after the drug treatment, one patient "was the USA Triathlon National Champion" and that another "added Pilates to her exercise regimen;"

- claims in a patient brochure that: "[y]ou may experience renewed interest in attending school, or holding a job" with the drug, and "you may want to join in more social activities with your family and friends;"

- claims in a brand piece that: "I'm cleared, I can take my son to the batting cage. We go sailing on my boat and take nice vacations . . . . I'm loving life;" and

- a video's implication that a drug will allow patients to carry out daily activities, which they may have chosen not to do prior to using the drug.


**Patient Testimonials**

While FDA acknowledges that patient testimonials might be an accurate reflection of personal experiences with a specific drug product, the agency took exception to those claims that suggested the drug could work as well for others as it did for the patient, because the claims lacked "substantial evidence." The extrapolation of benefit from one patient to a larger audience was misleading without proper substantiation. For instance, FDA objected to the following:

- a case highlight that summarized a patient's treatment;
- a branded story describing a patient's diagnosis and subsequent null response to a competitor's treatment, and later success with the promoted drug;
- a video with patient statements such as, "I've been on [the drug] for three months . . . I'm not using my cane as much. I can go across Home Depot . . . . It's great;" and
- a patient video that showed, after treatment with the drug, the patient was able to maintain posture, walk in a straight line, and preserve balance.

**Disclaimers**

A disclaimer or qualifier may attempt to clarify a statement but, if the overriding message in context is unlawful, the disclaimer will not mitigate the risk. FDA found the following disclaimers insufficient to render the material not misleading:

- a professional detail aid's disclaimer, "the contribution of individual components to efficacy has not been evaluated," because FDA found the listing of ingredients and their benefits misleading due to lack of substantial evidence;
- a case highlight's disclaimer, "[t]his case study was adapted from actual case files, and results are not necessarily representative and may vary by patient;" and
- a patient video's qualifier listed on the webpage hosting the video "[t]hese are videos of actual patients being evaluated by their physician. Individual results may vary."

**Oral Statements about Off-Label Uses**

FDA issued enforcement letters to drug companies where representatives verbally suggested their drugs

were safe and effective for unapproved uses. For instance:

- at a peer lunch, a physician spoke on behalf of a drug company and stated that he prescribed the drug for an off-label use, and the drug was as effective as another drug approved for the use; and

- on a sales call to a physician's office, two sales representatives failed to mention the indicated patient population or the drug's limitations (e.g., that it was not a bronchodilator as described in the label).

**Open-Label Studies' Inadequacy to Support Claims**

The agency found open-label studies failed to support long-term claims and, thus, were misleading. Here are two examples:

- claims on exhibit panels (e.g., "**20 years of proven safety**" (emphasis original)) could not be based on open-label extension studies, because patients self-selected to participate and "it is unclear as to why certain patients dropped out or were lost to follow-up;" and

- a consumer webpage's claim, "**8 out of 10** people taking [the drug] had an EDSS score below **3.0 at 10 years**, which means they were still active and able," (emphasis original) could not be based on an open-label, follow-up study.

**Unlawful Promotion of Investigational New Drug**

The agency remained vigilant about employee statements that promoted investigational new drugs as safe and effective, which is unlawful (see 21 C.F.R. § 312.7(a)):

- a CEO's statement on a podcast that the company's investigational new drug "works" for various types of diarrhea and patients (e.g., "cholera patients," and "the most severe, acute, infectious, watery diarrhea"); and

- a senior physician at a research institute's statement on its YouTube channel that its investigational new drug had been demonstrated to "attack cancer cells but protect the other cells, so it's the best of both worlds," and other physicians' observations that they had "seen a lot of success with patients with this particular type of cancer."

**Misleading Comparative Claims**

FDA continued to issue enforcement letters for misleading comparative claims. For example, FDA acted when:

- a website's chart mentioned only certain differences between a drug and its competitor, such as drug approval year and method of administration, but omitted contraindications, serious warnings and precautions, and laboratory test monitoring (the agency considered the latter "highly relevant" to deciding whether to prescribe or take the drug);

- a booth panel's drug superiority claims (e.g., "unsurpassed ischemic efficacy and reduced bleeding vs[sic] heparin") were misleading, because they were based on non-inferiority trials, and FDA considered them inadequate to demonstrate superiority; and

- a press release, based primarily on retrospective, observational research (and the lack of a pre-specified efficacy analysis comparing products), was not properly substantiated.

**Lack of Pre-Specified Endpoints and Efficacy Analysis**

FDA found misleading promotional claims not based on pre-specified endpoints or analysis. Examples of claims that lacked substantial evidence included:

- a webpage's claim that implied treatment would result in reduced opioid use and total parental nutrition need, because both were not pre-specified endpoints in a study supporting the claim;

- a sales aid's efficacy claims regarding "stable disease, stable disease ≥ 6 months, and progressive disease," because they were not pre-specified endpoints in the studies supporting the claims; and

- a pitch letter's claims comparing products based on a study that did not use a pre-specified efficacy analysis.

**Misleading Use of Individual Components of Composite Scores**

The agency determined that demonstrating an effect on a composite score does not demonstrate an effect on its components. FDA found particular claims about these components lacked "substantial evidence or substantial clinical experience" if they were solely based on the composite score. For example, FDA took issue with the following claims:

- effectiveness claims in a phone script and sales aid about nasal congestion, a component of the total nasal symptom score; and

- a patient brochure's statement that a drug can be "highly effective in relieving" symptoms listed as the individual components of a specific rating scale total score.


**AGG Observations**

- OPDP's concerns described in 2012 are not new when compared to previous years. Inadequate presentation of risk information, misleading product comparisons, overstatement of benefit, oral statements, patient testimonials and other selective (i.e., cherry picking) descriptions of data drew the agency's wrath. Companies continue to make the same types of mistakes, although the facts or venues may be different, reminiscent of the refrain, "same song, different pew."

- Much has recently been written (including by AGG) about FDA's enforcement in the off-label promotional area, particularly in light of a December 2012 decision of the United States Court of Appeals for the Second Circuit reversed a conviction of a sales agent for off-label communications. However, as the OPDP letters attest, the dissemination of false or misleading information (e.g., unsubstantiated claims which constitute "misbranding") is more prevalent than action against off-label promotion. As we continuously remind clients, off-label promotion is merely one area of concern, and failure to tell a complete and accurate story is cited more by OPDP as unlawful promotion. Moreover, notwithstanding FDA's loss in the Second Circuit case, the First Amendment does not act as a "get out of jail free" card for all off-label communications. If a sales representative's statement is false or misleading, the statement will not be "protected speech." In fact, FDA has recently stated it will continue to take enforcement action when appropriate.

- OPDP continues to remind industry that its enforcement authority is broad and as FDA will object to violative statements, even in those forums not traditionally a hotbed of activity. For example, press releases, sometimes thought of as off-limits to FDA because they are typically intended for the financial community, were cited by the agency. Companies must remember that the agency views its authority extends to any forum or venue where product information and promotion is disseminated.

- Enforcement letters present industry with a playbook of FDA's enforcement strategy. Companies should review these communications, learn the lessons of others, and continue to review materials internally to ensure compliance.