A Review of Summer FDA Enforcement Against Unlawful Drug Product Promotion

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The summer season hasn't slowed down the Food and Drug Administration's Office of Prescription Drug Promotion (OPDP) from taking enforcement actions against perceived unlawful product promotion. A review of these enforcement letters, without identifying any particular company or product, offers insight into some of OPDP's concerns, which companies should consider as they promote their products. We will not review each enforcement letter or every type of violation in detail. Instead, we emphasize the key trends that these letters reveal, and also discuss other relevant non-OPDP related enforcement.

Summary of OPDP Enforcement

The most frequent violations cited by OPDP continue to focus on minimization and omission of risk information and material facts, misleading comparative claims, unsubstantiated claims, and overstatement of efficacy claims. In addition, whether the promotional materials are distributed online or by physical means, OPDP will take enforcement action if it has objections.

Minimization and Omission of Risk Information

The agency continues to find problematic the presentation of risk information that is not comparable to benefit claims. Examples included:

- a print ad that discussed drug benefits in large, bolded or colorful text with graphics, while presenting risk information on the adjacent page without a color scheme, borders, or graphics; OPDP stated the risk information "appears unconnected to the efficacy claims and is therefore not likely to draw readers' attention;"[1]
- a sales aid that discussed the most important risks on its back cover in black font in single-spaced bullets, while the effectiveness claims appeared in large, bolded headlines with colorful graphics;[2] and
- a website that presented drug benefits at the top of the page accompanied by colorful graphics and large bolded headers, but discussed risks at the bottom of the site under the product logo, a tagline, footnotes, and citations; OPDP expressed concern that viewers might think information beneath this content was not important or related to the main message.[3]

In other enforcement letters, FDA objected to promotional materials that included the name and indication but failed to disclose any risk information, such as:

- two online banners that discussed the drug's indication and efficacy claims, e.g., "Twice as

1 Untitled Letter to Johnson & Johnson International, Inc. on behalf of Janssen Pharmaceuticals, Inc. (June 6, 2013), at 2, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitesbyFDA/UntitledLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM357833.pdf.

2 Untitled Letter to Sigma-tau Pharmaceuticals (May 22, 2013), at 4, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/UntitledLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM355260.pdf.

3 Untitled Letter to Validus Pharmaceuticals, LLC (May 6, 2013), at 3, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/UntitledLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM355263.pdf.

Strong Half as Long;"[4]

- a print ad that included the company logo, drug name, indication, and a question with the disease identified (and which also was not submitted to OPDP on a Form 2253 at the time of initial distribution);[5] and
- a promotional email sent to healthcare professionals implying the product's safety and efficacy, (e.g., "**Eliminate Your Concerns**" (emphasis in original) and "**Remove the Variables**" (emphasis in original) with the word "Dosing" near the claim) without including the drug's full approved indication or information that administration of the drug required additional steps related to reconstitution.[6]

Omission of Material Facts and Risks Listed in the Prescribing Information

In several instances, OPDP used a product's prescribing information to identify missing information from the promotional material. For instance, OPDP cited violations when:

- a sales aid's headers stated "hematological side effects . . . can be **predicable and manageable**," (emphasis in original) even though the [product labeling] disclosed that the most common adverse reactions of the drugs were "[c]ytopenias with delayed onset and prolonged duration, some complicated by hemorrhage and severe infection;"[7]
- a sale's aid claim that patients taking the drug experienced a certain median time to progression compared to other patients, but omitted stating that this information was "not significantly different between study arms," as the product labeling noted;[8]
- a sales aid's imagery and claims suggested that a drug can target lymphoma cells without targeting health cells, (e.g., the drug can deliver "**radiation precisely** where it's needed" (emphasis in original)), but the [product labeling] stated that the drug can cause damage in both target and nearby cells;[9]
- a print ad's claim that a drug did not require "**dosage adjustments**," (emphasis in original) but the product labeling mentioned that dosage should be reduced for certain patients with renal impairment;[10] and
- a webpage contained graphics and claims about a drug's mechanism of action (e.g., raising "the levels of all three of the neurotransmitters in the brain responsible for mood elevation . . ."), despite the product labeling disclosing that the drug's mechanism by which its "inhibitors act as antidepressants is not fully understood." (emphasis in original).[11]

Unsubstantiated Misleading Comparative Claims

OPDP considered certain comparative claims misleading, because they were not supported by head-to-head comparison trials. For example, OPDP took exception to the following claims:

- two website banners' drug superiority claims (i.e, "Twice as Strong Half as Long . . . Once a day for 2 weeks");[12] and
- a sales aid from a booth at an oncology conference that claimed a drug "enhanced patient benefits," resulting in

4 Untitled Letter to Merz Pharmaceuticals, LLC (July 31, 2013), at 2, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/UntitledLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM364070.pdf.

5 Warning Letter to Acorda Therapeutics, Inc. (July 25, 2013), at 2-3, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM363213.pdf.

6 Untitled Letter to Mobius Therapeutics, LLC, (May 2, 2013), at 2, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM356235.pdf.

7 Untitled Letter to Spectrum Pharmaceuticals (July 23, 2013), at 3, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM363215.pdf.

8 Id. at 5.

9 Id. at 2-3.

10 Untitled Letter to Johnson & Johnson International, Inc. on behalf of Janssen Pharmaceuticals, Inc. (June 6, 2013), at 2.

11 Untitled Letter to Validus Pharmaceuticals, LLC (May 6, 2013), at 6.

12 Untitled Letter to Merz Pharmaceuticals, LLC (July 31, 2013), at 3-4.

"fewer patient visits."[13]

Lack of Substantial Evidence in Efficacy Claims Due to Variance Among Treatment Groups

OPDP found misleading certain efficacy claims that were not supported by substantial evidence or substantial clinical experience, because the studies cited to support them did not control for differences among groups appropriately:

- a webpage's claims that implied treatment would result in "clinical success," but where the references did not control for "multiplicity;"[14]
- a sales aid's claims regarding enhanced efficacy if patients received earlier treatment of the drug, because the study in support of the claims did not compare patients at the same point in the course of the disease and, instead, retrospectively, compared outcomes between different patient populations;[15] and
- a webpage's statement about efficacy rates drawn from meta-analyses completed in "diverse patient populations, with different doses of the drug, and under varying clinical conditions."[16]

FDA does not find meta-analyses or retrospective studies constitute sufficient evidence to support efficacy claims.

Lack of Pre-Specified Endpoints in Efficacy Claims

OPDP found misleading efficacy claims based on studies that lacked pre-specified endpoints in the following situations:

- a website's claim that "[i]mprovement in results **continues** 2-4 weeks after treatment" (emphasis in original), which misleadingly implied that the drug is effective at points that were not pre-specified endpoints in the studies;[17]
- a website's claim that patients were able to follow "**the full course of treatment**," (emphasis in original) but the references cited to support the claim did not include pre-specified endpoints designed to evaluate patient adherence and lacked documentation supporting that they were "well-defined and reliable assessments of patient adherence;"[18]
- statements in a sales aid about overall survival (e.g., "[d]ata from this study suggest a strong correlation between response quality after first-line treatment (complete response) and survival"), but the study supporting the claims lacked data evaluating the drug on any efficacy endpoint;[19]
- pie charts in a sales aid that demonstrated an improvement in patient response rates, but the references cited in support of the chart were based on a post-hoc, exploratory subgroup analysis;[20] and
- claims suggesting that levels of a biomarker were associated with clinical responses to the drug, when the references supporting the claims were based on retrospective studies and institutional chart reviews.[21]

Non-OPDP-Related Enforcement

In a non-OPDP related enforcement action, taken by an FDA district office, FDA held a dietary supplement company responsible for testimonials posted on the company's Facebook page that rendered its dietary supplement product an unapproved new drug.[22] One of the posts was "I took Life Glow Plus for two months, 20 capsules a day, and my foot

13 Untitled Letter to Sigma-tau Pharmaceuticals (May 22, 2013).
14 Untitled Letter to Merz Pharmaceuticals, LLC (July 31, 2013), at 2-3.
15 Untitled Letter to Spectrum Pharmaceuticals (July 23, 2013), at 4-5.
16 Untitled Letter to Validus Pharmaceuticals, LLC (May 6, 2013), at 4.
17 Untitled Letter to Merz Pharmaceuticals, LLC (July 31, 2013), at 4.
18 Id.
19 Untitled Letter to Spectrum Pharmaceuticals (July 23, 2013), at 3-4.
20 Id. at 5.
21 Untitled Letter to Johnson & Johnson International, Inc., on behalf of Janssen Biotech Products, L.P., (May 22, 2013), at 2, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM355605.pdf.
22 Warning Letter to Vibrant Life Vitamins, (Aug. 7, 2013), available at: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm364664.htm.

started to get well and the swelling went down."[23]

Also in the same Warning Letter, FDA cited specific instances of metatags (e.g., "heart disease, heart attack, fight heart disease") which it determined to be disease treatment claims.[24]

AGG Comments and Recommendations

- Industry must pay careful attention to all promotional materials (e.g., banner ads, emails, and other non-traditional materials) to ensure every claim is substantiated.
- While it seems obvious, promotional materials must not conflict with the product's labeling or omit relevant information from the product labeling.
- Risk information must be presented in a truthful, balanced, and prominent manner compared to the positive, promotional statements. Of course, where the indication or claims are mentioned, risk information cannot be ignored.

23 Id.
24 Id.

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