FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

OPDP issues untitled letter of 2019 to Vivus over misleading promotion for weight loss drug Qsymia

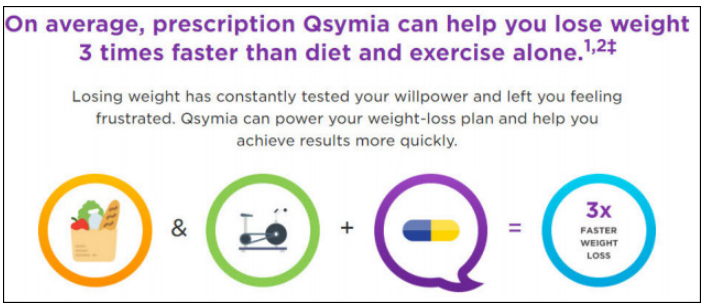
The untitled letter takes issue with claims in marketing materials for Qsymia that create a misleading impression of the drug's effects while downplaying risks and omitting information about the drug's indication. The letter takes issue with the cherry-picking of more favorable data and the failure to display information on contraindications, warnings, precautions and adverse reactions in a prominent way comparable to efficacy information.

The Office of Prescription Drug Promotion (OPDP) sent Vivus an untitled letter—its second enforcement letter in 2019—after determining the webpage for weight loss treatment Qsymia makes false or misleading claims or representations about the drug's efficacy and risks. The website, which was submitted under a Form FDA 2253, allegedly misbrands the drug by creating a misleading impression about the actual benefits patients may expect from the drug, while downplaying its risks and the need for nutritional and lifestyle modifications.

The website includes claims that the drug, on average, can help patients "lose weight 3 times faster than diet and exercise alone," citing references that don't support such claims. The cited studies include calculated ratios of the average absolute amount of weight less for the treatment compared with placebo at weeks 12, 28 and 56, but don't support the rate of weight loss in the claims because they don't describe the amount of weight loss at specific time points. Since the studies were designed specifically to evaluate the amount of weight loss, they cannot support claims regarding the rate of weight

loss. As such, the OPDP suggests that the claims on the webpage are misleading in suggesting the treatment can help patients lose weight three times faster than diet and exercise alone.

The website also omits information about the full indication and effect of diet and exercise. Qsymia is indicated as an adjunct to a reduced-calorie diet and increased physical activity for adult patients who are obese or overweight in the presence of at least one weight-related comorbidity. However, the website fails to properly disclose that a reduced-calorie diet and increased physical activity are needed to achieve benefits. The website includes efficacy claims at 12-, 28- and 56-week milestones for "patients with a body mass index (BMI)* of 30+† or 27 kg/mg2 or greater (overweight) in the presence of at least one weight-related medical condition," along with illustrations of an exercise bike, a bag of groceries and a capsule. The OPDP determined, however, that the illustrations don't properly convey that both exercise and diet are needed to achieve the promoted results. The omissions of contextual



information about the results observed in the placebo group also misleadingly suggest the results can be attributed to the treatment alone.

The untitled letter also takes issue with the selective presentation of more favorable data. The website presents the more favorable absolute amount of weight loss and reduction in waist circumference, which fails to account for baseline measurements and misleadingly implies that all patients, regardless of their baseline weight or waist circumference, may experience results similar to the absolute amounts presented. The data also reflects patient data from distinct points during the trials for only those who remained on the treatment, though a substantial percentage withdrew before the trial ended. As such, the claims may overstate the efficacy of the product and may create a misleading impression that all patients who received Qsymia remained on the treatment.

In addition to issues with the efficacy claims, the OPDP raises concerns with the failure to disclose information related to contraindications, warnings, precautions and adverse reactions "with a prominence and readability reasonably comparable with the presentation of information relating to the benefits." The letter cites factors that may impact prominence and readability, such as typography, layout, contrast, white space and techniques to achieve emphasis. The OPDP notes that risk information for Qsymia is relegated to the bottom of the page and requires viewers to scroll down past the entire benefit presentation to view it. The webpage also fails to provide "any significant signal to alert the viewer that important risk information follows the presentation of benefit information."

The letter calls on Vivus to immediately cease violating the Federal Food, Drug, and Cosmetic Act (FDCA) and to provide a list of all promotional materials that may contain similar violations. It also

requests that Vivus provide a plan for discontinuing the use of violative materials.

OPDP issues untitled letter to Aclaris over interview with paid spokesperson misrepresenting safety, efficacy of seborrheic keratoses treatment

The untitled letter—the third issued by the OPDP so far in 2019—raises concerns about an interview featuring a paid spokesperson, which creates a misleading impression of a seborrheic keratoses treatment by failing to disclose important warnings and precautions, failing to provide information balancing risk information alongside efficacy statement, and disclosing side effects in SUPERs alongside images of efficacy.

The OPDP issued an untitled letter to Aclaris Therapeutics after reviewing a direct-to-consumer interview featuring a paid spokesperson for seborrheic keratoses (SK) treatment Eskata, which was submitted under a Form FDA 2253. The review determined that the interview, which was initially aired on the ABC talk show The View in September 2018 and is available on the company's LinkedIn and Facebook pages, allegedly makes false or misleading claims or representations about the risks and efficacy of the treatment, misbranding the drug under the FDCA. The untitled letter follows advisory comments, provided to Aclaris in March 2018 on draft presentations for the drug, with similarities to the video at issue. At that time, the OPDP recommended proposed presentations be revised to avoid the omission of material information about the risks associated with the drug and to ensure efficacy wasn't overstated.

The video at issue includes a discussion with a physician, who is a paid spokesperson, in which claims and representations about the drug's benefits are made but no "prominent, balancing risk information" is provided. Though the spokesperson directs viewers to the webpage for Eskata for additional information, and though the video features superimposed text (SUPERs) disclosing the drug's most common side effects, the OPDP determined these efforts do not mitigate the failure to reveal serious risks reflected in the warnings and precautions for the drug, including warnings about serious eye disorders and skin reactions. The omission of such warnings and precautions creates a misleading impression about the drug's safety.

Along with the misleading impression of safety, the OPDP determined the video creates a misleading impression about the treatment profile. The letter cites a claim that "typically in one or two treatments the lesions go away, they resolve, and that's the end of it," which is followed by side-by-side visuals of two patients before and after treatment. Though the physician spokesperson refers to the most common adverse reaction (i.e., stinging), other local adverse reactions are not disclosed. The letter takes particular issue with the phrase "that's the end of it," as local adverse reactions to the drug have been observed up to 15 weeks after treatment.

The video includes SUPERs along with the before-and-after images of treatment, but the OPDP cites several issues with the SUPERs, including the fact that the first contains efficacy information unrelated to risks. The OPDP also takes issue with the presentation of SUPERs in conjunction with "compelling and attention-grabbing photographs," which compete for consumer attention and may make it difficult for consumers to adequately understand the common side effects disclosed. The OPDP determined that the information disclosed in the SUPERs isn't sufficient to mitigate the misleading impression created by the video.

The OPDP also raises concerns with the impression of efficacy created by the physician's claims and

side-by-side images, which misleadingly suggest typical patients will experience similar results. Though the letter acknowledges that the images may reflect an accurate experience with the drug for those patients, the personal experience of the patients shown doesn't support the assertion that patients' treatment will typically achieve complete clearance of SK lesions, as clinical studies show only 4% to 8% achieve clearance of all lesions. A SUPER presented alongside the images includes the proportion of patients who achieved clearance of three out of four lesions and states that results may vary. However, the letter raises similar issues with this SUPER as with those disclosing safety, finding that it isn't sufficient to mitigate the misleading impression created by the video. The letter also flags issues with the presentation of images of patients with complete clearance along with the statistic that "18% of patients experienced clearance of 3 out of 4 raised SKs treated with ESKATA vs 0% with vehicle (Day 106 end of study)." Per the letter, the presentation of images with complete clearance alongside data for clearance of two out of four lesions, along with the omission of data on complete clearance, misleadingly suggests the data apply to results displayed in the images.

The letter calls on Aclaris to immediately cease violating the FDCA and to provide a list of all promotional materials that may contain similar violations. Given the prior recommendations and the issues observed in the video, the untitled letter raises concerns that Aclaris is promoting the drug in a way that fails to reflect the serious risks of the drug or to truthfully and non-misleadingly describe its efficacy.

FDA issues draft guidance to enhance diversity in clinical trials for new drugs, biologics

The guidance outlines approaches that sponsors of new drugs or biologics can take to expand eligibility criteria and increase the enrollment of underrepresented populations in clinical trials. It is part of the FDA's effort to encourage drugmakers to enroll populations that more closely reflect the demographics that will take their drugs in the real world.

The FDA issued draft guidance to increase diversity in clinical trial populations by using approaches to broaden eligibility criteria and increase enrollment of underrepresented populations for trials supporting a new drug application (NDA) or a biologics license application (BLA). The guidance is meant to address ongoing challenges to participation in clinical trials and gaps in the representation of certain groups. The guidance, issued as part of a mandate under the FDA Reauthorization Act of 2017, discusses how sponsors can extend eligibility and avoid unnecessary exclusions, and how they can improve trial recruitment to ensure the enrolled population better reflects the population most likely to use the drug. It also offers specific recommendations for extending the eligibility of criteria for trials related to treatments for rare diseases or conditions.

Although eligibility criteria are designed to protect participants by excluding people that may be at unreasonable risk of adverse events relative to the potential benefit, the FDA contends that certain populations are often excluded without strong clinical or scientific justification, which may impede the discovery of important safety information. As such, broadening eligibility criteria, when appropriate, may maximize the generalizability of trial results and enhance the understanding of a drug's benefits profile. The guidance encourages sponsors to use an enrichment strategy, in which there is a targeted inclusion of certain populations to more readily demonstrate the effect of the treatment being tested. However, the FDA advises sponsors to include a reasonable sample of participants who have the disease but don't meet prognostic or predictive enrichment characteristics.

Specific recommendations in the guidance include the following:

- Inclusive trial practices—To help ensure that the clinical trial population reflects the diversity of patients who will use the treatment if it's approved, the FDA recommends approaches to broaden eligibility criteria such as considering whether criteria from phase 2 trials can be eliminated or updated to avoid unnecessary limits; examining each exclusion criterion to ascertain whether it's needed to assure the safety of participants to meet study objectives; and considering the inclusion of children and adolescents in confirmatory trials, when appropriate.
- Trial design and methodological approaches—Clinical design and methodological approaches to enroll a broader population may include using adaptive clinical trials, establishing a pediatric development program early in the development process, or including a broader participant group in the trial as part of a secondary efficacy and safety analysis.

Beyond eligibility criteria, participants may face barriers to enrolling in clinical trials, such as transportation difficulties, onerous financial costs, burdensome clinical trial study visits and a mistrust of clinical research, which may create disincentives to enrolling. The FDA recommends that sponsors consider logistical and other participant-related factors that could limit participation as part of the overall study design. The guidance offers recommendations such as the following:

- Making trial participation less burdensome by taking stock of potential recruitment challenges because of the planned visit schedule and by making participants aware of financial reimbursement for expenses associated with costs incurred during the trial. The guidance makes clear that the FDA doesn't consider reimbursement for reasonable travel expenses to and from clinical trial sites and associated costs, such as airfare and lodging, to raise issues of undue influence.
- Adopting enrollment and retention practices that improve inclusiveness by working with communities to address participants' needs, including involving patients, patient advocates and caregivers in the design of trial protocols; ensuring that clinical trial sites include locations with a higher concentration of racial and ethnic minority patients; incorporating strategies for public outreach and education; holding frequent recruitment events; and exploring agreements to facilitate the exchange of medical records among trial sites.
- Leveraging the expanded access regulations to provide a pathway to potentially offer treatment to patients who don't meet eligibility criteria but who have a serious or immediately life-threatening disease or condition.

FDA finalizes guidance on submissions of promotional materials for drugs, biologics

The guidance outlines types of voluntary and required submissions of promotional labeling and advertising materials for prescription drugs and biologics. It describes the format and content for submissions, including the use of an electronic common technical document.

The FDA issued final guidance describing the electronic and non-electronic format for submissions of promotional materials submitted for prescription drugs or biologics to the OPDP or the Advertising and Promotional Labeling Branch (APLB). The guidance applies to promotional labeling and advertising materials, irrespective of format or medium, including television advertisements, brochures, websites and exhibits.

The guidance uses the FDCA definition of labeling as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article," citing the Supreme Court's determination that language "accompanying such article" should be interpreted broadly to include materials that supplement or explain an article. While the FDCA doesn't define what constitutes an advertisement, the FDA considers advertising to include materials "in published journals, magazines, other periodicals, and newspapers and in advertisements broadcast through media such as radio, television, and telephone communication systems."

The guidance, initially published as a draft in 2015, outlines several general considerations for submissions of promotional materials, regardless of the format in which they are submitted. It directs sponsors to ensure submissions include the appropriate NDA, ANDA or BLA number; use the most specific material type to describe the promotional materials subject to the submission; submit different types of promotional submissions separately; and submit promotional materials directed to health care professionals separately from that directed to consumers. In instances in which promotional materials are directed to both consumers and health care professionals, the guidance directs sponsors to identify the audience type based on the end user for the majority of the information. If an applicant holder collaborated with another company to promote a drug, the FDA directs the applicant holder to send a general correspondence submission to describe the agreement to the OPDP or the APLB.

The guidance indicates that submissions that fall under Section 745A(a) of the FDCA must be submitted in electronic format beginning no earlier than two years after the issuance of guidance specifying electronic submission format. Promotional-materials-related submissions that fall under 745A(a) include postmarketing submissions of promotional materials using a Form FDA 2253 and submissions of promotional materials for accelerated approval products. For submissions that don't fall under 745A(a), the FDA encourages the use of electronic submissions, though paper submissions will be accepted. For postmarketing materials under a Form FDA 2253, the guidance notes that applicants need to submit specimens of mailing pieces and any other labeling or advertising for promotion of the drug at the time of initial dissemination or publication. Each submission must include a completed fillable Form FDA 2235 and a copy of the product's current professional labeling.

For presubmissions of promotional materials for accelerated approval products, the guidance directs sponsors to submit copies of all promotional materials, including promotional labeling and ads, intended for dissemination or publication within 120 days of approval. Submissions should include a clean version of the draft promotional materials; an annotated copy of the proposed promotional materials that clearly identifies the source of support for each claim; the most current FDA-approved prescribing information; and, if applicable, the FDA-approved patient labeling for the medication guide, along with annotations cross-referenced to the proposed promotional materials.

The guidance cautions that while companies may request advisory comments on draft promotional materials, if the FDA learns that the material submitted or substantially similar claims have been disseminated or published, it will not review the materials under the voluntary advisory comment process. The FDA encourages sponsors to request comments on promotional materials prior to launch. Core launch materials may include one comprehensive and one brief promotional labeling piece for health care professionals, one comprehensive and one brief direct-to-consumer (DTC) labeling piece, and a professional or DTC product website. Non-core launch materials are a lower priority than core launch materials. The FDA recommends that sponsors

apply comments on core launch materials to non-core launch materials. The guidance recommends that draft core launch materials be consolidated into a single submission for each intended audience. For comments on proposed DTC television advertisements, the guidance directs sponsors to provide a clean version of the storyboard of the proposed materials, along with an annotated version that clearly identifies the sources of support for each claim.