LOEB & LOEB LLP

FDA Regulatory and Compliance Monthly Recap

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OPDP issues untitled letters to Pfizer, Arog over misleading promotional material

In its second and third untitled letters of 2018, the OPDP took issue with promotional materials that create misleading representations about a product. The letters take issue with material failing to disclose material facts, including risk information and the investigational status of an unapproved drug.

The Office of Prescription Drug Promotion (OPDP) issued separate untitled letters to Pfizer and Arog raising concerns about promotional materials. The letter to Pfizer raises concerns about the omission of risk information and misleading representations about treatment effects, whereas the letter to Arog raises concerns about promotional claims made for an unapproved treatment.

The letter to Pfizer takes issue with a direct-to-consumer video featuring paid spokespersons about its estradiol vaginal ring Estring, as well as corresponding Q&As provided to interview participants submitted under a Form FDA 2253. Inspectors determined the video and material misbrand Estring by making false and misleading representations about the risks and efficacy of the product, which is the subject of a boxed warning concerning several serious, life-threatening risks. The video in question includes a physician and patient – who are both spokespeople – discussing the benefits of the drug. Although the physician refers viewers to a website and directs them to ask their healthcare providers for more information, the video fails to disclose any risk information. As such, it creates a misleading impression about the product's safety.

Inspectors took particular issue with the patient saying she does "not experience any side effects" and "was able to just feel relief." The letter notes that while this may be an accurate reflection of her experience, it misleadingly suggests other patients will have similar experiences, adding to the misleading impression created by the omission of risk

information. In addition, inspectors raised concerns about the patient saying the product provided "pretty much an instant relief," which suggests other patients will experience similar results even though estrogens such as Estring generally require an interval of time to improve symptoms.

The letter to Arog takes issue with a display booth at a medical conference and a webpage that suggested, in a promotional context, that investigational new drug Crenolanib besylate is safe and effective for FLT3-mutated acute myeloid leukemia (AML), though no marketing authorization has been granted. Inspectors noted that the webpage and display booth, featured at the American Society of Hematology's 59th Annual Meeting, described the use of the investigational product in treating FLT3-positive AML, a use that would require the supervision of a physician and adequate directions. The OPDP determined that the investigational treatment doesn't qualify for exemptions from requirements for adequate directions of use because the material makes promotional claims.

The letter cites claims on the conference material suggesting the investigational product is the "future of AML treatment"; can be combined with chemotherapy; is a "potent inhibitor" of FLT3, PDGFRα and PDGFRβ; and can eradicate activating mutations. The letter also raises concerns about the booth appearing in the main exhibit hall of the conference alongside approved products, with no disclosure of its investigational status. It also takes issue with claims on the webpage suggesting the product is "for use" in FLT3-mutated ALM but not disclosing that it is an investigational product, and claims suggesting the product is different from or superior to approved therapies, which suggests it has a role in the AML treatment paradigm.

Perrigo chided for failing to meet postmarketing requirements for testosterone therapy as Gottlieb reinforces FDA's commitment to enforcement

The letter takes issue with Perrigo's decision not to join an industry consortium to complete postmarketing study requirements for testosterone replacement therapy, and with its contention that its product isn't subject to the requirements because it's equivalent to a generic. Commissioner Scott Gottlieb used the letter as an example of the FDA's commitment to enforcing postmarketing requirements.

The FDA sent an untitled letter to Perrigo over a failure to meet milestones in a required postmarketing study for its testosterone replacement therapy (TRT), rendering the therapy misbranded. FDA Commissioner Scott Gottlieb used the letter as an opportunity to warn industry that the agency will continue to enforce compliance with postmarketing requirements. He said the agency is committed to ensuring studies are transparent to the public, and noted that the majority of postmarketing requirements and commitments are progressing toward completion.

According to the letter, the FDA issued letters to all sponsors of TRT products in February 2015 requiring them to conduct postmarketing trials to investigate the risk of major adverse cardiovascular events associated with TRT. Perrigo was encouraged to collaborate with other holders of new drug applications (NDAs) for TRT products to complete the postmarketing trial, but the FDA found out in September 2017 that it had decided not to join a TRT consortium. Perrigo was subsequently notified of its failure to comply with a Final Study Protocol Submission date. In turn, Perrigo asked the FDA to waive its responsibility to conduct the postmarketing trial. The drugmaker argued that the requirements posed an undue financial burden and that its product is AB-rated and equivalent to a generic, and shouldn't be subject to the requirements. Perrigo maintained that it should be responsible only for labeling changes once the postmarketing trials are completed by the consortium.

The letter states that as the holder of an NDA for a TRT product, Perrigo is subject to the requirements until such a time that a formal request to withdraw the NDA has been submitted and a withdrawal

published in the Federal Register. Since the NDA was submitted under section 503(b) of the FDA, it's subject to postmarketing requirements under section 503(o)(3) irrespective of whether it's therapeutically equivalent to another listed drug. Since Perrigo has failed to demonstrate good cause for noncompliance with the requirements, the FDA maintains that the postmarketing trial is in delayed status and the product misbranded.

FDA issues draft guidance on content, format of Indications and Usage section of drug labeling

The draft guidance provides recommendations for clearly conveying the indication in drug labeling and describes instances in which FDA regulations require that additional information be included. The guidance outlines the recommended format and content to ensure the scope of the approved indication is clearly described.

The FDA issued draft guidance providing recommendations on the content and format of the Indications and Usage section of labeling for prescription drug and biological products. The guidance is meant to ensure the labeling clearly communicates the approved indication and provides enough details to ensure a treatment can be used safely and effectively. Per the guidance, the Indications and Usage section needs to accurately reflect the scientific evidence, needs to be written in a concise manner to clearly indicate the use for which the drug has been shown to be safe and effective, and should use clinically relevant and scientifically valid terminology that a healthcare practitioner can understand.

The indication should clearly describe the population for which the determination of safety and effectiveness applies. The guidance notes that in some instances the agency may determine that evidence supports a broader or narrower population than the one studied. For instance, an indication for a broader population than the population studied may be appropriate following an assessment of the generalizability of the evidence, the consistencies in the disease across different groups, and the treatment's overall benefits and risks. Therefore, applicants should discuss the scope of a proposed indication with the agency. Although it may be appropriate in certain cases to consider expanding an indication for an adult population to a broader age group than that of the population studied, the guidance notes that such an approach isn't generally appropriate for pediatric populations. The guidance therefore recommends that indications include age groups and a statement that a drug is approved "in adults" or "in pediatric patients X years of age and older."

Per the guidance, when developing the Indications and Usage section, companies should consider what information is required to clearly communicate the approved indication and whether additional information is needed. Generally, the indication will be adequately communicated by stating the disease or condition being treated and the approved age groups. However, there may be instances in which additional information may be needed, such as when a drug may target different aspects of a disease or when end points are not well standardized. In such cases, it may be necessary to state what benefit the drug has been shown to convey.

The guidance notes that the indication should start with "DRUG-X is indicated" and needs to include the disease or condition being treated along with any information needed to describe the approved indication, such as additional descriptors or qualifiers to identify selected patient subgroups or disease subpopulations for which the treatment is approved. This may include, for instance, language to describe the limitations of usefulness of a treatment, such as "… for older patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy." Generally, limitations of use should be presented separately from the indication and clearly distinguished from contraindications. However,

information that narrows an approved indication and is used to guide appropriate therapy should be directly incorporated into the indication. Instances in which a separate limitation of use may be appropriate include:

- When there is concern or uncertainty about a treatment's effect in certain clinical situations or in certain populations, such as younger patients.
- When a drug is approved without having shown a specific benefit that has been shown with other drugs in the same class.
- When there is uncertainty about the expected benefits, and that uncertainty is pertinent to the recommended dosing, treatment duration or any dose modifications.

Draft guidance outlines new approaches to bolster access to nonprescription drugs

As part of its efforts to increase patient access to treatments and address rising drug costs, the FDA published draft guidance outlining innovative approaches to increase access to nonprescription drug products and to empower patients to self-treat certain conditions. The guidance describes new ways to demonstrate safety and effectiveness in the nonprescription setting.

The FDA published draft guidance outlining two new approaches drug makers may use to demonstrate the safety and effectiveness of nonprescription products when the drug facts labeling (DFL) alone isn't sufficient to ensure safe and effective use. Per the guidance, the approaches may be useful for applicants looking to develop and gain approval for certain nonprescription drugs through the submission of a new drug application. Noting that certain types of drugs may be appropriate for nonprescription use so long as patients have access to resources to help them determine whether the treatment is right for them, FDA Commissioner Scott Gottlieb said the new framework will help sponsors demonstrate that consumers can safely use a treatment without a prescription and associated supervision by a healthcare professional.

The first approach includes developing labeling in addition to the DFL. Per the guidance, the FDA may consider approving additional labeling, such as:

- Information pamphlets or other documents included inside the product carton or container.
- Text or images on a video display, including interactions displays that consumers can review.
- Information on webpages.
- Statements or questions contained in a mobile application.

The second approach includes implementing additional conditions that consumers need to meet to ensure products are used safely and effectively. Additional conditions the FDA may consider to help patients properly self-select and use a treatment may include:

- Completing a self-selection test in a mobile application prior to purchase, which can positively indicate that the consumer is an appropriate candidate for the product.
- Reviewing images or videos that describe the appropriate use of the product before purchasing it.