FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

OPDP issues first warning letter of 2019 over DTC advertisements making false, misleading claims about erectile dysfunction drug

The warning letter — the fifth enforcement action issued by the OPDP so far in 2019 — raises concerns about print ads and banners for ED treatment Stendra making efficacy claims without disclosing risk information and suggesting the treatment may be used for an unapproved use. The letter also calls into question claims suggesting the drug is more effective than its competitors.

The FDA's Office of Prescription Drug Promotion (OPDP) sent a warning letter to Metuchen Pharmaceuticals after a review determined a direct-to-consumer print ad and several display banners promoting erectile dysfunction (ED) treatment Stendra make false or misleading claims or representations about the drug. The warning letter, which is the OPDP's first of 2019, calls into question the representation of efficacy claims without sufficient disclosure of risk information. It also cites concerns about claims promoting the drug for an unapproved use.

The letter raises particular concerns about claims in the print ad suggesting that Stendra can reduce the risk of heart failure, as the drug lacks approval for such use and the labeling doesn't include adequate directions for such use. The OPDP takes issue with the claim because Metuchen has provided no evidence to support it and the existing prescribing information for Stendra includes a warning and precaution about cardiovascular risks associated with the drug and use in certain patients with congestive heart failure. The OPDP also raises concerns with the print ad's use of the term "next-generation," which suggests that Stendra is safer and more effective than competitors. The print ad provides no references to support

the claim, nor is the FDA aware of any evidence to support the assertion.

The warning letter also raises concerns about the prominence of the efficacy claims in the print ad. Per OPDP, "[F]actors impacting prominence and readability include typography, layout, contrast, headlines, paragraphing, white space, and other techniques apt to achieve emphasis." In this case, the efficacy claims are presented in large bolded font and colorful text and graphics, whereas risk information is presented in a smaller font size in single-spaced format at the bottom. Since the risk information isn't displayed in a "reasonably comparable" prominence and readability, the ad minimizes the risk associated with the drug.

Apart from the print ad, one banner ad includes the claims "Get Hard & Stay Hard" and "Indulge in life's sweetest pleasures whenever you want," but fails to communicate any risk information, including a precaution about prolonged erection. The letter takes particular issue with the phrase "whenever you want" in the efficacy claim. The OPDP contends the claim suggests Stendra can be safely dosed to provide efficacy at any time, though the prescribing information clearly states that the maximum recommended dose is once per day. The ad is also misleading because it fails to disclose material information about the indication for Stendra, as it doesn't clearly state that the drug is indicated for the treatment of ED, misleadingly suggesting people without the condition can safely use the drug to achieve and maintain an erection.

A second banner ad includes claims such as "the ED pill for your lifestyle" and "the fast-acting ED prescription." The ad provides a list of common side effects but fails to provide information about contraindications, warnings or precautions for the drug, creating a misleading impression about its safety. The letter raises concern about a claim in the banner ad that the drug can be taken with or without food and alcohol, without communicating the risk that excessive alcohol consumption while taking the drug can increase the risk of headache, dizziness, increased heart rate and decreased blood pressure.

In all, the OPDP determined that the advertisements create a misleading impression about the drug's safety. The letter explains that a statement directing viewers to ask their doctors for more information doesn't mitigate the misleading impression created by the omission of risk information. The letter directs Metuchen to provide a plan for disseminating truthful, non-misleading and complete corrective messages addressing the issues raised by the OPDP.

FDA issues draft guidance outlining Accreditation Scheme for Conformity Assessment pilot for premarket reviews of medical devices

The voluntary conformity assessment initiative is meant to promote predictability and consistency in the premarket review process for medical devices while improving regulatory efficiency. Under the pilot, the FDA would recognize and grant ASCA Accreditation to qualified testing laboratories, which medical device makers can work with in support of premarket submissions.

The FDA published draft guidance proposing a pilot Accreditation Scheme for Conformity Assessment Program (ASCA), which it was mandated to establish under the 2017 reauthorization of the Medical Device User Fee Act. The draft guidance delineates the goals, scope, procedures and framework for the voluntary program, under which testing laboratories may be accredited by accreditation bodies adhering to criteria specified by the FDA to assess the conformance of a device within certain FDA-recognized standards. The guidance follows a

public workshop in which the FDA solicited input from stakeholders on the pilot.

Although evidence of conformity to FDA-recognized consensus standards often provides an efficient means for a device maker to address certain issues of safety and effectiveness, the FDA needs to have confidence in the declaration of conformity. The pilot is meant to help address some of the existing limitations to declarations of conformity, particularly variability in the reliability of conformance determinations, to ensure they are sufficient to fully address questions about safety and effectiveness or premarket authorizations. It is also designed to encourage international harmonization by incorporating elements from well-established international conformity assessment practices and standards.

The guidance explains that under the pilot's assessment scheme, recognized accreditation bodies can accredit testing laboratories using ASCA program specifications associated with each eligible standard. Once a testing laboratory is accredited, it may carry out testing to determine whether a device conforms with at least one of the standards eligible for inclusion in the ASCA pilot. When an accredited lab completes such testing, a test report will be given to a device maker, which may then include a declaration of conformity with supplemental documentation as part of a premarket submission to the FDA.

Per the guidance, the FDA will generally accept determinations from ASCA-accredited testing labs that a medical device is in conformity with the specified testing to a particular standard. The agency doesn't plan to review complete test reports in support of a declaration of conformity from ASCA-accredited testing laboratories unless it is done as part of a periodic audit, the summary test report indicates an issue with the testing, or the agency becomes aware of information "materially bearing on the safety or effectiveness of the device." The agency plans to periodically audit accreditation bodies and testing laboratories to ensure they are adequately meeting program expectations.

Per the guidance, the FDA will consider several factors in deciding whether to recognize an accreditation body or testing laboratory for participation in the pilot, including whether an accreditation body has a scope of "signatory status" to the International Laboratory Accreditation Cooperation (ILAC) Mutual Recognition Arrangement and whether it is based in the U.S. Device makers may voluntarily choose to use a testing laboratory participating in the pilot to complete testing for premarket submissions. However, the pilot doesn't alter the device maker's responsibility to address pertinent information in the premarket submission, including the onus to document how testing supports approval or clearance.

FDA outlines plans for STeP program to medical devices ineligible for Breakthrough Device program

The FDA published draft guidance detailing a voluntary program for devices targeting diseases or conditions that are less serious than those eligible for the Breakthrough Devices Program but may still pose serious or life-threatening risks. The program will include features to expedite feedback and reduce the time needed to achieve marketing authorization for a device.

The FDA issued draft guidance describing a new, voluntary program for certain medical devices and device-led combination products that are "reasonably expected to significantly improve the safety" of existing treatments or diagnostics for diseases or conditions less serious than those eligible for the Breakthrough Devices Program. Known as the Safer Technologies Program (STeP), the program was

initially proposed under the 2018 Medical Device and Safety Action Plan and will include features to accelerate feedback and reduce the time for marketing authorization. The guidance cautions, however, that the FDA plans to prioritize resources for the Breakthrough Devices Program over STeP because the former is statutorily mandated.

STeP is modeled on the Breakthrough Devices Program and will include two phases. In the first phase, interested sponsors will formally ask for inclusion in the program through a Q-submission; in the second phase, actions will be undertaken to accelerate the development of the device and prioritized review will be granted to the subsequent regulatory submissions. The program is based on communication and collaboration between the FDA and sponsors. As such, the guidance indicates that "the commitment on behalf of the sponsor to resolve all scientific and regulatory issues in a timely manner should match that of FDA."

Devices and device-led combinations are eligible for the program if they are subject to review under a premarket approval application, *de novo* classification request or premarket notification. Per the draft guidance, eligibility factors include:

- The device is ineligible for the Breakthrough Devices Program because of the less serious nature of the disease or condition being addressed; and
- The device is reasonably expected to significantly improve the benefit-risk profile of a device through substantial safety innovations that reduce the occurrence of known serious adverse events, device failure modes, or use-related hazards or errors, or by improving the safety of another device or intervention.

The guidance describes the program principles as:

- Interactive and timely communication – For devices accepted into the program, the FDA will provide interactive and timely communication throughout the development and review process.
- Review team support – Regulatory submissions for devices accepted into the program will receive review team support and engagement from senior management.
- Review of regulatory submissions – The FDA will prioritize the reviews of regulatory submissions for STeP devices. However, the agency cautions that "review times of the marketing submission may take longer for devices accepted into STeP than for other devices because their anticipated technological or design innovations may raise novel scientific issues."
- Benefit-risk assessments and premarket/postmarket balance of data collection – For devices in the STeP program, the agency plans to use "timely postmarket data collection" to accelerate the development and review of devices, as appropriate for certain submissions types.
- Efficient and flexible clinical study design – For STeP devices, the FDA will consider proposals for "efficient and flexible clinical study designs," which may include the use of real-world data sources to support a proposed indication or labeling.
- Manufacturing considerations for PMAs – For devices that require a preapproval inspection, the FDA plans to accelerate the review of manufacturing and quality system compliance for devices in the program that are consistent with those established under the Breakthrough Devices Program.

FDA accelerates efforts to modernize medical device program with several guidance documents

The FDA published several final guidance documents addressing the 510(k) Program, de novo classification requests, uncertainty in benefit-risk assessments and the humanitarian device exemption program. The agency has been undertaking efforts to modernize its medical device program.

As it continues to take steps to modernize the 510(k) Program, the FDA finalized an array of guidance documents it has been working on over the past couple of years. The agency also started operationalizing the new Safety and Performance Based Pathway for medical devices with several draft guidance documents detailing the recommended premarket performance criteria and testing methodologies for four specific types of devices. Among the guidance documents published are:

- Finalized guidance on the Special 510(k) Program – The guidance details a shift in focus for the Special 510(k) Program, which offers an optional pathway for manufacturers to modify marketed devices. Per the guidance, while the program was previously "limited to review of changes that did not affect the device's intended use nor alter the device's fundamental scientific technology," it will now focus on "whether the method(s) to evaluate the change(s) are well-established, and whether the results can be sufficiently reviewed in a summary or risk analysis format." The guidance follows the kickoff of a pilot program in October 2018 to expand the program.
- Finalized guidance on the Abbreviated 510(k) Program – Following efforts to expand the Abbreviated 510(k) Program, the final guidance provides recommendations on the best approach to demonstrate substantial equivalence in premarket notifications. The program is meant to facilitate the use of an efficient submission preparation and review process by leveraging guidance documents, special controls and voluntary consensus standards. Per the guidance, the use of guidance documents may facilitate review through reliance on "summary reports" that briefly outline the testing conducted to support the submission. Summary reports include the device description, device design requirements, risk management information, and a description of test methods used to address performance characteristics.
- Final guidance on formatting for abbreviated 510(k) submissions – The guidance outlines and describes the 20 sections for traditional and special 510(k)s, such as information on animal and clinical performance testing, biocompatibility, proposed labeling, and software.
- Final guidance on the FDA's Refuse to Accept (RTA) policy for 510(k)s – The guidance lays outs the procedures and criteria used in assessing whether a 510(k) submission can be accepted for review. The FDA's current 510(k) RTA policy includes an early review of criteria. The FDA says it will notify the applicant within 15 days of receiving the submission if it is administratively complete or whether there are missing element(s).
- Finalized guidance on uncertainty in benefit-risk assessments – The guidance explains when FDA review staff may be able to accept greater premarket uncertainty about a device's benefit-risk profile. It describes the FDA's process for considering acceptable levels of uncertainty about a device when making benefit-risk determinations for premarket applications, humanitarian device exemption (HDE) applications or *de novo* classification requests. In response to industry feedback, the guidance reduced the use of the term "appropriate" and instead makes additional

use of the term "reasonable." The guidance also lays out an approach for devices for small patient populations applied on a case-by-case basis.

- Finalized guidance on the HDE Program – Incorporating changes under the Cures Act and FDA Reauthorization Act, the final guidance describes the HDE Program's current review practices, including what criteria are considered to determine whether a device has shown "probable benefit." Per the guidance, the types of evidence that may be used to support an HDE application include "investigations using laboratory animals, investigations involving human subjects, nonclinical investigations, and analytical studies for in vitro diagnostics." The guidance makes clear that applicants may have little or no clinical experience with a device before they apply for an exemption.
- **Three final guidance documents on *de novo* requests** – The FDA published three guidance documents clarifying aspects of the *de novo* classification process for devices for which there is no predicate, including:
  - Final guidance on acceptance review for classification requests – The guidance delineates the criteria the FDA will use when assessing whether a request for an evaluation of automatic class III designation should be accepted for a full review.
  - Final guidance on user fees and refunds for classification requests – The guidance describes what types of requests are subject to user fees, what exceptions to user fees exist and which actions may lead to refunds of user fees already paid.
  - Final guidance on FDA and industry actions on *de novo* requests – The guidance details which actions the agency and industry may take and the actions' impact on performance goals under MDUFA IV for *de novo* requests received between FY2018 and FY2022. Per the guidance, when a request has been accepted for substantive review, the agency may issue an order either granting or declining the request for classification or may ask for additional information.

Related Professionals

For more information, please contact:

Scott S. Liebman	sliebman@loeb.com
Eve Costopoulos	ecostopoulos@loeb.com

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