FDA Regulatory and Compliance Monthly Recap

OCTOBER 2019

KEY FINDINGS

OPDP issues enforcement letters to Galt, Kowa Pharmaceuticals for misleading promotional matters

The OPDP sent a warning letter to Galt Pharmaceuticals citing repeat issues in promotional material for an insomnia drug and issued an untitled letter to Kowa Pharmaceuticals over misleading patient testimonials for a cholesterol treatment. The letters bring the OPDP's total enforcement actions so far in 2019 to seven, with five untitled letters and two warning letters.

The Office of Prescription Drug Promotion (OPDP) issued its second warning letter of 2019 to Galt Pharmaceuticals after a review of a professional email for insomnia treatment Doral, submitted under a Form FDA 2253, revealed issues in the presentation of risk and efficacy information. The warning letter cites previous communications in which the OPDP flagged potential issues with promotional material for the drug, including an untitled letter issued to Sciecure Pharma, the former application holder, in 2014. The former letter cited omitted risk information, unsubstantiated superiority claims and a lack of disclosure of material facts. In the warning letter to Galt, the OPDP raises concerns about Galt promoting the drug in a similarly violative manner.

The warning letter takes issue with the professional email making claims and representations about the benefits of the drug without disclosing warnings or precautions and omitting material facts about risks. For instance, no information is disclosed regarding the potential for benzodiazepine withdrawal syndrome, nor is information provided about precautions against driving or engaging in hazardous activities and concerns about the use of Doral with other sedative-hypnotics.

Though the email includes a statement directing readers to a "full list of warnings and precautions" in the prescribing information, the letter indicates that such a statement doesn't mitigate the omission of risk information.

The OPDP also found that the claims and presentations about Doral misleadingly downplay the risks of abuse and dependence while suggesting the drug, which is a C-IV scheduled substance, is safer than other prescription and OTC products. The reference cited to support such claims used an algorithm that the FDA determined "lacks actual abuse data in human subjects and has not been validated." Though Galt included a statement indicating that a comparison chart that is part of the presentation is "not intended for efficacy comparison" and indicating that the algorithm has "not been validated in subsequent research," the OPDP said such disclosure doesn't mitigate the "overwhelming impression that Doral is superior in safety to other prescription and OTC products." The warning letter also takes issue with a phrase suggesting Doral is the only marketed insomnia treatment that addresses difficulty sleeping, staying asleep and awakening in the morning, as there are other marketed medications indicated for all those components of sleep.

Separately, the OPDP issued its fifth untitled letter of 2019 to Kowa Pharmaceuticals after determining that a video montage on YouTube featuring patient testimonials made false or misleading claims about the risks associated with cholesterol treatment LIVALO. The letter cites concerns that the testimonials may misleadingly suggest that the drug is safer than competitors' because they suggest that patients switching to the drug will experience fewer side effects than with other statins, or no side effects at all. Though the OPDP acknowledges that the testimonials may reflect the real experience of the patients in the video, the letter cautions that testimonials don't adequately support the suggestion that other patients will have similar experiences. The video includes a SUPER indicating that "individual results may vary," but the OPDP determined that such a statement doesn't mitigate the misleading impression created. The letter also cites a failure to disclose information related to contraindications, warnings, precautions and adverse reactions "with a prominence and readability reasonably comparable to the presentation of efficacy information," as the risk information is presented only as scrolling text at the bottom of the video.

The letters direct the companies to immediately stop distributing the violative materials and to provide the FDA with a list of any promotional materials that may include similar violations and a plan to stop using them. The warning letter to Galt directs the company to issue corrective messaging.

FDA issues draft guidance on encouraging patient engagement in medical device trial design

The guidance provides recommendations on how device makers can engage patients in different aspects of medical device clinical investigation design. The guidance aligns with ongoing FDA efforts to engage patients in regulatory processes and follows the first meeting of the agency's Patient Engagement Advisory Committee.

The FDA published draft guidance offering recommendations on how device makers can engage patients in the design of clinical studies for medical devices, following efforts by the Patient Engagement Advisory Committee (PEAC) to develop ways in which patient input can be gathered throughout the device life cycle. The guidance is meant to facilitate the use of patient engagement to improve the design and conduct of clinical studies. It

discusses the benefits of engaging patient advisers early in the development process, delineates which patient engagement activities aren't subject to FDA regulation, and addresses misconceptions about submitting patient engagement information to the FDA regarding the design and conduct of trials.

The PEAC, which is composed of patients, caregivers and those who represent their needs, has worked with the Center for Devices and Radiological Healthand patient organizations to provide recommendations to the FDA about patient engagement in medical device trials. In a consensus recommendation, the PEAC urged the agency to work with industry to develop a framework to make clear how patient advisors can engage in the clinical investigation process. As part of that recommendation, the FDA is undertaking efforts to encourage patient engagement in clinical investigations. The draft guidance reflects part of that effort and is based on public discussion and feedback on the potential impact of patient engagement on medical device investigations. Per the guidance, the FDA believes that, done effectively, patient engagement may help overcome the challenges of clinical investigations, including those related to patient enrollment and retention, while accelerating the investigation process.

The guidance defines patient engagement as "intentional, meaningful interactions with patients that provide opportunities for mutual learning, and effective collaborations." It applies to engagement in the design and conduct of clinical investigations, but doesn't address participant reimbursement, promotion of devices or dissemination of trial results. For the purposes of engagement, patients are defined as "individuals with or at risk of a specific disease or health condition, whether or not they currently receive any therapy to prevent or treat that disease/condition," and those "who directly experience the benefits and harms associated with medical products."

The guidance describes two distinct roles for patients who interact with researchers, sponsors or the agency: 1) study or research participants are those who are or become a participant in research, either as a control or as a recipient of the test article; 2) patient advisors are those who have experience living with a disease or condition and may serve in an advisory or consultative role to improve trial design and conduct, but who are not themselves involved in the research. The FDA recommends that sponsors identify patient advisors and clearly define their role early in the planning process, while soliciting their input on protocol development. The guidance recommends that sponsors consider using existing educational materials or working with organizations to provide training to patient advisors to help them more effectively contribute to the process.

The guidance indicates that since patient advisers' engagement is typically in a consultative or advisory capacity, such activities, on their own, will generally not be considered to constitute research or an activity subject to FDA regulations. As such, research regulations, including requirements for institutional review boards, will not typically apply. However, interactions between study or research participants and investigators often include collecting information as part of a research plan and generally fall within the context of a "clinical investigation" subject to FDA regulations. As such, they must meet applicable requirements, including those for investigational device exemptions and protection of human subjects. The guidance encourages sponsors to engage with the FDA about patient engagement approaches through an informational meeting through the Q-Submission Program.

FDA publishes second in string of guidance documents encouraging patient-focused drug development

The FDA issued draft guidance discussing methods to identify what matters most to patients as it relates to burden of disease and burden of treatment in order to inform medical product development. The guidance is the second in a series of guidance documents the FDA is developing on the use of patient experience data in product development and regulatory decision-making.

The FDA published the second draft guidance in its four-part series of patient-focused drug development guidances being developed to outline, in a stepwise manner, how stakeholders can leverage patient experience data in medical product development and regulatory decision-making. The present guidance, dubbed Guidance 2, outlines approaches to identifying what is most important to patients as it relates to burden of disease and burden of treatment. Guidance 1 addressed methods of collecting accurate and representative data, and upcoming guidance documents will address approaches to identifying and developing methods to measure impacts in clinical trials (Guidance 3), and methods, standards and technologies to collect and analyze clinical outcome assessment (COA) data for regulatory decision-making (Guidance 4).

Guidance 2 describes methods for collecting patient experience data but doesn't provide specific instructions on how to use particular methods. As such, the FDA cautions that it should not be viewed as a substitute for engaging subject matter experts. The guidance addresses methods to determine what is important to patients, which may subsequently be used to inform the development or selection of COAs and the generation and use of patient preference information. The guidance directs stakeholders to conduct background research, such as literature reviews, and engage with subject matter experts when developing research questions and selecting appropriate methods for identifying what is important to patients.

For qualitative methods, the guidance cautions that how questions are framed is "critical to collecting unbiased patient input," and leading questions that imply the desired answer should be avoided. In terms of quantitative methods, the guidance notes that survey instruments and items should align with the research objectives, be specific to the concept of interest (such as disease symptoms or treatment side effects), be tested for usability and be assessed for potential social desirability bias. Stakeholders should avoid incomplete, poorly worded and leading questions, as well as "double-barreled" questions, which are those that ask about two or more concepts at once.

The guidance includes recommendations for data collected prospectively using social media, noting that sources should be carefully selected with the research question in mind as "findings across social platforms may be distinctly different." The FDA recommends that social media research explore an array of networks and communities to solicit data that can be generalized to the population of interest. The FDA notes that while it's ideal to examine data from communities that provide personal information, in order to allow verification of personal characteristics, it may be appropriate in certain cases to explore communities that allow for anonymity. When using social media data analysis, methods should address potential limitations and how such limitations impact data integrity and interpretation.

Draft guidance addresses how industry may interact with FDA on complex innovative clinical trial designs for drugs, biologics

As part of its mandate under the Cures Act, the FDA issued draft guidance to describe how applicants and sponsors may interact with the agency on complex innovative clinical trial design proposals for drug or biological products. The guidance focuses on FDA and sponsor interactions for CID proposals for trials intended to provide substantial evidence of effectiveness.

The FDA issued draft guidance on interactions between the agency and sponsors or applicants on complex innovative trial design (CID) proposals. In line with requirements under Section 3021 of the Cures Act, the guidance addresses the use of novel trial designs in the development and regulatory review of drugs and biologics, the types of information that should be submitted for review, and how sponsors may solicit agency feedback on technical issues pertaining to modeling and simulation.

Per the guidance, there is no "fixed definition" of CID because what is considered innovative or novel can change over time. The guidance considers CID to include "trial designs that have rarely or never been used to date to provide substantial evidence of effectiveness in new drug applications or biologics license applications." However, the guidance does not indicate whether specific novel designs are or are not appropriate for regulatory use, as such determinations are made on a case-by-case basis depending on the reasons the design is being proposed, its validity in a particular setting and other factors unique to a specific development program. The guidance centers primarily on FDA and sponsor interactions for CID proposals for trials meant to provide substantial evidence of effectiveness. Typically, interactions for such CID proposals will take place in the context of investigational new drug applications (INDs) or pre-IND meetings. Novel trial designs require clear communication between sponsors and the FDA on aspects of the design and how the trial data will be analyzed and presented.

The guidance encourages sponsors to engage with the FDA early to discuss their CID plans, using existing pathways for FDA interactions such as Type A, Type B, Type B end-of-phase and Type C meetings; IND amendment review; and potentially pre-IND meetings for early-phase trials with novel elements. The guidance cautions that since reviews of CID proposals typically involve challenging assessments of design characteristics, it may be difficult for the agency to sufficiently review designs under short timelines. The FDA notes that sponsors may consider the pilot program for complex innovative trial designs (CID Pilot Program) to obtain additional meetings on proposed CID. The pilot offers additional opportunities to meet with the agency about CID proposals and to secure detailed feedback from review teams and senior regulatory decision-makers.

Since detailed documentation is needed for the agency to properly review novel design proposals and offer feedback, the guidance directs sponsors to document novel features they expect to incorporate, along with timing and details of the planned implementation and how the design will address underlying scientific objectives. Elements that should be submitted for review may include:

- Information on the choice of trial design and how it fits into the drug development plan, with explanations of how the novel design offers advantages over conventional designs
- A description of key aspects of the design, along with plans for possible adaptations,

implementation details for interim analyses, and any unique or novel decision criteria

- An evaluation of the operating characteristics of the design, including the chance of generating incorrect conclusions and the reliability of treatment effect estimates
- A comprehensive data access plan outlining how trial integrity will be maintained

The guidance offers specific recommendations for Phase 3 trials that leverage control data from Phase 2 trials and for Sequential Multiple Assignment Randomized Trials, which are designed to inform the development of adaptive interventions.

Related Professionals

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