FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

OPDP issues fifth untitled letter of the year to Supernus for misrepresenting Oxtellar XR in KOL video

In its fifth untitled letter in 2016, the OPDP raised concerns about a Spanish KOL video suggesting Supernus' treatment for partial seizures can be used for all seizure types, while downplaying the risks associated with the drug.

The FDA's Office of Prescription Drug Promotion (OPDP) sent an untitled letter to Rockville, Maryland-based Supernus Pharmaceuticals on Oct. 31, 2016, after a key opinion leader Spanish video was flagged for making false and misleading representations about Oxtellar XR, an adjunct therapy approved for partial seizures.

The OPDP found the video misbrands the drug and provides a misleading impression about its safety and efficacy, making its distribution a violation of the Federal Food, Drug, and Cosmetic Act. The video also provides evidence that the drug is intended for an unapproved use for which labeling does not provide proper directions for use.

The office took issue with a doctor in the video stating that he often used the medication in combination with other treatments when epilepsy is not controlled and suggesting that the drug has helped improve the level of convulsive control. According to officials, using the general terms "epilepsy" and "convulsive" leaves an impression the drug is intended for use in treating epilepsy, including seizures not defined as partial. Although the proper indication is included in scrolling text following the doctor's presentation, the OPDP said this doesn't negate the doctor's statements. Officials also raised concerns about the doctor's testimonials representing the drug as safe and effective for the treatment of all seizure types, though no evidence has been provided to support such a claim.

Officials also flagged the video's failure to properly represent risk. In the opening segment, the doctor makes claims related to the drug's

benefits, but fails to disclose risks associated with the drug. While the risks are described in rolling text with a voiceover at the end of the video, the overall presentation is misleading because it fails to convey risks with a prominence comparable to that of the efficacy statements. Given the drug's association with several serious, possibly life-threatening risks, the OPDP said the video's representation is particularly problematic from a public health perspective.

The warning letter calls on Supernus to provide a list of all promotional materials for the drug that contain such violations, along with a plan for discontinuing the use of the materials.

FDA publishes guidance outlining device reporting requirements for manufacturers under MDR regulation

The guidance outlines the FDA's interpretation of regulatory requirements under MDR regulation and provides input on what types of reports manufacturers need to file in relation to medical device adverse events. It requires manufacturers to submit reports within 30 days, or five days in certain circumstances, of any adverse events reasonably linked to death or serious injury.

The FDA issued guidance detailing reporting and record-keeping requirements for device-related adverse events and certain medical device malfunctions, per the Medical Device Reporting (MDR) regulation. The MDR regulation provides a mechanism for identifying and monitoring adverse events and requires medical device makers to adhere to certain reporting and record-keeping requirements, including:

- Submitting MDR reportable events to the FDA;
- Establishing and implementing procedures to identify and assess medical device events to determine whether the event is MDR reportable; and
- Establishing and maintaining complete files for all complaints regarding medical device events.

MDR reportable events are defined as events a device maker becomes aware of that reasonably indicate a marketed device may have caused or contributed to death or serious injury, or may have malfunctioned and, as a result, contributed to death or serious injury. The guidance also calls on medical device makers to report user errors, whether they are the sole cause of or a factor contributing to an MDR reportable event, as these often signal underlying issues with device labeling, the user interface or other aspects of device design.

MDR reportable events need to be reported to the FDA within 30 calendar days of the manufacturer becoming aware of the event. However, there are some instances in which a medical device report needs to be submitted within five days, including:

- Cases that require remedial action to prevent an unreasonable risk of substantial harm to public health; or
- Cases in which the FDA makes a written request for a five-day report.

Reports of MDR events must contain all the information in the device maker's possession or that has been obtained from a user facility, importer or other initial reporter, as well as information obtained by analyzing or testing the device. Separate reports should be submitted for each device involved in a reportable event, even if an adverse event involves multiple suspect devices. Supplemental reports must also be submitted when information not available at the time of the initial report becomes available and would alter any information or conclusions in the original report.

Per the guidance, manufacturers must maintain and implement internal systems that allow for:

- Timely and effective identification, communication and assessment of events that may be MDR reportable;
- A standardized review process for ascertaining whether an event is MDR reportable; and
- Timely transmission of complete reports to the FDA.

The guidance applies to any person who:

- Repackages or changes the container, wrapper or labeling of a device as part of the device distribution;
- Initiates specifications for devices made by a second party for subsequent distribution; and
- Makes components or accessories that are medical devices and are ready to be used and intended to be commercially distributed and used as is, or that are processed by a licensed practitioner or other qualified person to meet the needs of a specific patient.

FDA finalizes rule on citizen petitions delaying generic approvals; declines PhRMA requests

The final rule makes clear that the FDA will not delay the approval of pending ANDA, 505(b)(2) or 351(k) applications because of citizen petitions unless a delay is needed to protect the public health. The rule serves as a response to an uptick in petitions filed late that raise no valid issues and are designed only to prevent approval of a generic application. The FDA rejected several requested changes by PhRMA.

The FDA issued a final rule updating its regulation regarding citizen petitions and petitions for stay of action (PSAs) requesting that the agency delay action on pending abbreviated new drug applications (ANDAs), 505(b)(2) applications or certain applications submitted under the Public Health Service Act (PHS Act). The final rule follows an uptick in petitions requesting the agency not approve certain applications unless certain requirements are met. Often these petitions raise scientific or legal issues related to the standards for approval, such as a particular method for demonstrating bioequivalence. Although these petitions may contribute to the FDA's evaluation of an application when submitted early, petitions that are submitted late in the review process and do not raise valid issues may result in approval of an application being wrongly delayed.

The updated rule implements certain provisions of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as enacted by the Food and Drug Administration Amendments Act of 2007 (FDAAA) and the Food and Drug Administration Safety and Innovation Act (FDASIA). By enacting this provision, the FDA says Congress indicated its desire to ensure petitions are not used to wrongly delay approval of applications. Per section 505(q) of the FD&C Act, the FDA is not permitted to delay approval of a pending application because of any request, unless a request is in a citizen petition or PSA and it's determined that a delay is required to protect public health.

The rule also clarifies that the FDA plans to respond to petitions within 150 days of receipt. It also makes clear that the FDA can dismiss a petition if changes in law, facts or circumstances since receipt render the petition null. This 150-day period is not to be extended for any reason, the FDA states. The FDA reserves the right to deny a petition at any time if it determines the petition was submitted with the goal of delaying the approval of an application without raising any valid issues. The FDA will be considered to have taken final action on a petition if it makes a final decision during the 150-day period or if the period expires without a final decision.

PhRMA had asked the FDA to revise the proposed rule to limit its application to cases in which there is evidence a relevant ANDA or 505(b)(2) application is pending, but the FDA declined to do so, saying

the existence of a pending application is not made public by the agency and petitions could be therefore used to uncover the existence of such application. PhRMA also requested that the FDA put in place a method of notifying a petitioner if it's determined that a delay of approval of an ANDA or a 505(b)(2) application is not required to protect public health. The FDA, however, said it wouldn't do so, because section 505(q) of the FD&C Act doesn't mandate such a notification. Additionally, PhRMA asked the agency to issue a regulation making clear that a delay in an approval of an application can be extended beyond the 150-day review period for a petition. The FDA said it wouldn't do so, because uncertainty in predicting the time required to resolve a certain issue makes it impractical to establish an expectation of the length of delay. The FDA also declined to oblige PhRMA's request that it abandon its practice of not providing a substantive response to every 505(q) petition, saying it is outside the scope of the rulemaking.

The FDA estimates the rule will result in one-time costs to industry of approximately $613,800, with annual costs of roughly $1,700. These equate to a total annualized cost of approximately $89,100. The total annualized costs include the administrative cost to review the rule, estimated at $87,400, as well as the cost for additional efforts to prepare certifications for petitions and verifications of both responses to petitions and supplements to petitions, pegged at $1,700.

FDA releases updated guidance for collection of race and ethnicity data in clinical trials for drugs, biologics and medical devices

The guidance, intended to promote more consistent demographic subgroup data collection practices, reflects a standardized approach to collecting race and ethnicity data in accordance with Affordable Care Act (ACA) and Food and Drug Administration Safety and Innovation Act (FDASIA) requirements.

The FDA published updated guidance, replacing a 2005 version, to provide input on how clinical trial sponsors can meet the requirements regarding presentation of demographic data on investigational new drug (IND) applications and new drug applications (NDAs) and the collection of race and ethnicity data in biologics license applications (BLAs) and medical device applications.

After an FDASIA-mandated report revealed diversity gaps in race and ethnicity data in clinical trial applications for FDA□regulated medical products, the agency held a public hearing in 2014 soliciting industry feedback on the challenges associated with the collection, analysis and availability of demographic subgroup data. The updated guidance reflects the concerns and recommendations generated in public workshops by a variety of experts and stakeholders, which the FDA incorporated into an action plan intended to improve the completeness and quality of such data. The guidance supports the action plan by detailing the FDA's standardized approach for the collection and availability of demographic subgroup data and the analysis of race and ethnicity data.

To maintain consistency with the current Office of Management and Budget directive and the National Institutes of Health guidance for collecting racial and ethnic data, the FDA recommends sponsors use a two-question approach to request race and ethnicity information from clinical trial participants:

- **Question 1 (answer first):** Do you consider yourself Hispanic/Latino or not Hispanic/Latino?
- **Question 2 (answer second):** Which of the following five racial designations (American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White) best describes you? More than one choice is acceptable.

The guidance also provides the following FDA recommendations:

- **Self-reporting:** The FDA recommends that trial participants self-report race and ethnicity information and be permitted to designate a multiracial identity. Race and ethnicity should not be assigned by the study team conducting the trial.
- **Ethnicity:** The agency outlines the minimum recommended choices that should be offered to trial participants.
- **Race:** The FDA recommends a list of minimum choices that should be offered to trial participants.
- **Use of more detailed racial and ethnic categories:** In situations where appropriate, the FDA recommends using more detailed categories by geographic region to provide sponsors the flexibility to adequately characterize race and ethnicity. For INDs, NDAs and BLAs, the agency recommends the submission of tabulated demographic data based on the Demographic Rule for all clinical trials using the characterizations of race and ethnicity described in this guidance.

Per the updated guidance document, the FDA expects sponsors to enroll participants who reflect the demographics for clinically relevant populations with regard to age, gender, race and ethnicity. A plan to address inclusion of clinically relevant subpopulations should be submitted to the agency for discussion at the earliest phase of development and, for drugs and biologics, no later than the end of the Phase 2 meeting.

For more information on any of these FDA regulatory and compliance updates, please contact Scott S. Liebman at sliebman@loeb.com.

Loeb & Loeb LLP's FDA Regulatory and Compliance Practice

Loeb & Loeb's FDA Regulatory and Compliance Practice comprises an interdisciplinary team of regulatory, corporate, capital markets, patent and litigation attorneys who advise clients on the full spectrum of legal and business issues related to the distribution and commercialization, including marketing and promotion, of FDA-regulated products. Focusing on the health and life sciences industries, including pharmaceuticals, biologics, medical devices, wellness products, dietary supplements and organics, the practice counsels clients on regulatory issues, compliance-related matters and risk management strategies; advises on laws and regulations related to product advertising and labeling; counsels on FDA exclusivity policies and related Hatch-Waxman issues; and provides representation in licensing transactions and regulatory enforcement actions.