FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

OPDP issues untitled letter to Nascent for commercializing investigational cancer drug before approval

The letter reprimands Nascent for making claims suggesting the investigational brain cancer treatment pritumumab has been established as safe and effective and for failing to clearly disclose that the product is an investigational new drug that has not been approved for commercial use in the U.S.

The FDA's Office of Prescription Drug Promotion (OPDP) issued an untitled letter to Nascent Biotech after discovering that a website for the investigational brain cancer treatment pritumumab made conclusory representations in a promotional context about the drug's safety and efficacy. The letter, which is the OPDP's sixth untitled letter and eight enforcement action of 2019, directs the company to immediately stop using the violative materials.

The Federal Food, Drug, and Cosmetic Act includes exemptions from adequate directions for use requirements for drugs that adhere to conditions under Section 505(i). However, the FDA determined that pritumumab fails to meet those conditions because Nascent presented claims in a promotional manner suggesting it is safe or effective for treating brain cancer, though no marketing authorizations have been granted. As such, the drug is rendered misbranded. The FDA explains that the provision prohibiting claims of efficacy and safety in a promotional manner is not meant to restrict the exchange of scientific information, but "to preclude commercialization of the drug before it is approved for commercial distribution."

The untitled letter takes specific issue with claims suggesting the investigational treatment has "cured a rare form of brain cancer," and claims that data on the overall survival rate show "antibodies are safe and effective." Such claims are particularly troublesome given the seriousness of the disease being treated and the lack of adequate safety and efficacy data for the drug. Given that the benefit-risk profile of the drug has not been established, the conclusions reflected in the claims create a misleading impression about pritumumab. The letter also cites Nascent for failing to clearly disclose that the drug is an investigational new drug that has not been approved for commercial distribution in the U.S. Together with the conclusionary claims about its safety and effectiveness, the website wrongly suggests the drug has an established role in treating brain cancer.

FDA issues draft guidance detailing risk-based approach to postmarket safety surveillance

As part of its effort to improve the efficiency of its postmarket drug safety surveillance practices and implement Cures Act requirements, the FDA published draft guidance outlining a risk-based approach to postmarket safety surveillance and explaining its principles for postmarket safety surveillance. The guidance describes the risk-based principles the agency uses to support ongoing postmarketing safety surveillance.

The Cures Act amended the Federal Food, Drug, and Cosmetic Act (FDCA) to eliminate the requirement that the FDA develop a summary analysis of adverse drug reaction reports received for a drug by 18 months following approval of the drug or after 10,000 individuals have used the drug, whichever occurs later. The legislation also included a provision requiring the agency to make public its best practices for drug safety surveillance. To fulfill its mandate, the FDA issued draft guidance describing its approach for timely postmarket analyses of drugs and biologics and outlining how the agency takes into consideration a product's characteristics and use to support a risk-based approach.

Products the agency typically considers to require more extensive monitoring include new drug applications that are new molecular entities; original biologics license applications; biosimilars; first-in-class approvals; newly approved formulations or indications; products being used in new patient populations; and products with complex pharmacokinetic or pharmacodynamic characteristics or complex compositions or manufacturing processes. The agency also monitors the safety of compounded products, though they aren't subject to premarket review and approval, and homeopathic products.

The draft guidance describes drug safety surveillance principles and best practices based on lessons learned in preparing and publicly releasing the summary analyses of adverse drug reaction reports previously required under Section 505(r) of the FDCA. An FDA study assessing the impact of these summary analyses on regulatory actions determined that such summaries were largely redundant to the surveillance practices already in place and were not an efficient use of FDA resources. In addition, many drugs and biological products for rare diseases never achieved the 10,000-individual use threshold.

The document addresses topics such as a multidisciplinary life cycle approach to the management of drug and biologic safety and general considerations to inform the frequency and extent of systematic drug and biologic safety monitoring, as well as additional considerations based on specific product types and patient populations. It also discusses safety signal identification based on the

screening and data mining of the FDA Adverse Event Reporting System (FAERS) and other data sources, a multidisciplinary evaluation of the identified safety signal that integrates data gathered from all available sources, an assessment of the causal link between the identified adverse event and the product, and an overview of actions—regulatory or otherwise—that can be taken in response to an identified safety signal.

The guidance also discusses other products, such as over-the-counter monograph, compounded and homeopathic products, and provides an overview of other data sources, tools and methods, as well as drug safety surveillance activities that extend beyond those of the FAERS in order to contextualize and provide a general overview of the FDA's safety surveillance process.

FDA finalizes guidance on denials of export certificates for medical devices

The FDA issued final guidance explaining how it handles denials of requests for a certificate to foreign government (CFG), which is used to assure foreign governments that a device being exported adheres to U.S. regulations for medical devices.

The FDA finalized guidance, initially published in August 2018, outlining how it handles denials of requests for a CFG for medical devices and how to request a review when a CFG is denied. CFGs are used to assure foreign governments that a device being exported adheres to U.S. regulations, including the Quality System Regulation. The guidance delineates reasons the FDA may deny a CFG request, such as if there is an injunction, proceeding or seizure action; if a device has been subject to a recall; or if an establishment is out of compliance with Current Good Manufacturing Practice regulations.

Per the guidance, the FDA will provide a substantive summary explaining the major noncompliance issues that support a denial. In instances in which a requestor of a denied CFG is not the owner or operator of the establishment making the device, the agency will instead inform the requestor that the denial is due to issues related to the manufacturer. In such cases, the FDA will provide only a summary of issues to the out-of-compliance manufacturer, due to disclosure requirements. The guidance indicates that the FDA "does not intend to deny a CFG for an establishment with a No Action Indicated (NAI) or Voluntary Action Indicated (VAI) classification for the most recent quality system inspection."

The final version includes several clarifications to the draft in response to comments received during the public consultation on the guidance. Updates include:

- Clarification that the Center for Devices and Radiological Health and Center for Biologics Evaluation and Research will provide information to requestors in collaboration with the Office of Regulatory Affairs.
- Additional details on how the FDA will handle plans of correction submitted following a denial of a CFG. The guidance explains that the owner, operator or agent in charge of the establishment should submit a plan that includes steps to be undertaken to address and prevent the recurrence of the inspectional observation, along with documentation showing the planned or completed corrective and preventive actions. The FDA will review the plan and notify the requestor whether the plan is sufficient to address the violations. If it believes clarification is needed, the FDA may further discuss with the requestor prior to making a decision. The FDA intends to provide a response to a plan of correction within 90 days.

- Clarification that the FDA will base its decision on a CFG request for recalled products on the current status of the products, including documentation and final testing submitted to the agency as part of the recall review process. In instances of lot-specific recalls, devices in other lots "may be included on a CFG provided the firm signs a statement indicating that it will not ship the lots of the product that are subject to recall."

FDA updates draft guidance on postmarketing studies following implementation of ARIA system, SUPPORT Act

The FDA updated draft guidance to clarify the factors it considers when determining whether a postmarket study or clinical trial will be needed or if postmarketing reports and the FDA's postmarket Active Risk Identification and Analysis (ARIA) system are enough to assess a drug's or biologic's risk in the postmarket setting.

Under Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA), the FDA is authorized to require certain postmarketing studies and clinical trials for prescription drugs and biological products. The guidance, initially published in 2011, provides an overview of the types and purposes of postmarket studies and clinical trials, including those agreed upon between the agency and an applicant (i.e., postmarketing commitments). The updated guidance was prepared by the Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research to reflect the operationalization of the ARIA system, which was still in early development when the guidance was initially published. Since the system has become fully operational, it needs to be considered when making determinations around whether a postmarket study or clinical trial is needed.

The updated guidance also reflects a provision of the 2018 Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT Act) that gives the FDA the ability to require postmarketing studies to explore the potential reduction in the efficacy of a drug. While the SUPPORT Act centers on opioids and other controlled substances, the agency said it doesn't expect to treat controlled substances differently than other prescription drugs.

The guidance explains that postmarketing studies and clinical trials may be required for any or all of the following purposes:

(1) To assess a known serious risk related to the use of the drug

(2) To assess signals of serious risk related to the use of the drug

(3) To identify an unexpected serious risk when available data indicate the potential for a serious risk

Prior to requiring a postmarketing study, the FDA needs to find that adverse event reporting under Section 505(k)(1) of the FDCA and the ARIA system will not be sufficient to meet such purposes. Applicants are required to report on the status of their studies and clinical trials of certain postmarketing requirements (PMRs) and postmarketing commitments (PMCs).

The guidance explains the FDA's approach to determining whether reports under Section 505(k)(1), relating to data on clinical experience and other data or information associated with drugs, are sufficient for addressing serious risk. The approach includes consideration of adverse event information reported through the FDA Adverse Event Reporting System and Vaccine Adverse Event Reporting System databases that contain individual case safety reports

(ICSRs) applicants submit based on information provided by consumers, patients and health care providers, as well as ICSRs submitted directly to the FDA and ICSRs of adverse events reported in scientific literature and postmarketing studies.

As it relates to benefit-risk assessments, the guidance indicates that the FDA will review the data obtained under a PMR and assess its effect on the benefit-risk profile of the drug in the context of the serious risk being evaluated. This review may lead to labeling changes under Section 505(o)(4) of the FDCA. The guidance describes the procedures that apply to PMRs issued under Section 505(o)(3) of the FDCA as well as the process applicants need to take to appeal a PMR. The guidance also outlines the process for the FDA to enforce PMRs and PMCs, including its process for dealing with applicants that fail to comply with the timetable, periodic report submissions and other requirements. Enforcement action could include charges under Section 505 of the FDCA, misbranding charges and/or civil monetary penalties.

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