FDA Regulatory and Compliance Monthly Recap

MAY 2019

KEY FINDINGS

FDA issues warning letter to Abaxis over unapproved changes to diagnostic

According to the letter, the diagnostics company made changes impacting the performance of its potassium assay without notifying the FDA. Since the changes raise new safety and effectiveness issues, the FDA determined that a new premarket 510(k) application is required.

The FDA issued a warning letter to Abaxis after inspectors determined that it was manufacturing and distributing an adulterated Class III device. Abaxis manufactures Class I and II in-vitro diagnostic reagents, such as the Piccolo Xpress chemistry analyzer, and the Class III Piccolo Potassium assay, used in conjunction with the analyzer. Inspectors determined that the potassium assay is adulterated and misbranded because Abaxis failed to notify the FDA about changes it made to the device.

Inspectors found that Abaxis made changes to the calibration specifications for the assay, which according to customer complaints altered the performance of the device. Inspectors determined that the change to the calibration of the assay raised new issues of safety and effectiveness, as a falsely low potassium result may lead to serious adverse consequences. As such, the modification to the assay necessitates a new premarket notification. The inspectors further noted that an intentional adjustment to calibration is, by nature, a change to device performance specifications, which requires a new 510(k), but Abaxis failed to test whether the changes may have impacted the safety and effectiveness of the device.

The warning letter also takes issue with Abaxis' lack of procedures for design change, noting that Abaxis' failure to establish preapproved acceptance criteria or evidence of performance of risk evaluation prior to changing the potassium assay is a violation of Quality System

regulations. Although Abaxis responded to the FDA on multiple occasions following an initial Form 483, the FDA determined its responses were insufficient as the company never investigated whether the modifications to the assay could have significantly altered the safety or effectiveness of the device.

The letter directs Abaxis to provide the FDA with its plans for corrective actions, which the letter indicates need to address "systematic problems," along with a timeline for implementation. It cautions that the issues cited "may be symptomatic of serious problems" in Abaxis' manufacturing and quality management systems, and recommends the company undertake an investigation to ascertain the causes of the issues and bring the product into compliance.

HHS finalizes rule to require disclosure of drug prices in DTC television advertisements

The rule requires drugmakers to disclose the wholesale acquisition cost in DTC television advertisements for certain drugs covered under Medicare or Medicaid. It is meant to provide an incentive to drugmakers to lower their prices and is part of President Trump's American Patients *First blueprint to lower drug costs.*

The Department of Health & Human Services (HHS) finalized a rule from the Centers for Medicare & Medicaid Services (CMS) amending regulations for the Medicare and Medicaid programs to require that direct-to-consumer (DTC) advertisements for prescription drugs and biologics covered under the programs disclose the Wholesale Acquisition Cost (WAC or list price). The rule is meant to improve the administration of the federal health care programs by incentivizing drugmakers to reduce their prices, improving drug price transparency and informing consumer decision-making.

The final rule, which was left relatively unchanged from its draft form, requires that DTC television advertisements for prescription drugs and biologics for which reimbursement is directly or indirectly available through Medicare or Medicaid include the list price. Advertisements must include a statement outlining the list price of a typical 30-day regimen or course of treatment, as of the first day of the quarter during which the ad is being broadcast, if the WAC is equal to or greater than $35 for that supply. Per the rule, the statement should be as follows:

> "The list price for a [30-day supply of] [typical course of treatment with] [name of prescription drug or biological product] is [insert list price]. If you have health insurance that covers drugs, your cost may be different."

The statement must be provided in a "legible textual statement" at the end of the ad, placed appropriately and with enough time to read it. If the course of treatment varies based on the indication being treated, the list price disclosed should reflect the typical course for the primary indication addressed in the ad. The rule allows drugmakers to include an accurate list price of a competitor's product so long as it's done in a truthful, nonmisleading way and within the confines of existing laws.

Per the rule, the expectation is that the threat of action under the Lanham Act for false and misleading advertising will serve as the primary enforcement vehicle for the rule. As such, the intent is that the rule will preempt any state-law-based claim that depends on any pricing statement required in the rule. "No state or political subdivision of any state may establish or continue in effect any requirement that depends in whole or in part on any pricing statement required by these regulations," the rule states. To incentivize compliance, the rule also directs the HHS secretary to maintain a public list of prescription drugs and biologics advertised in violation of the rule.

Although standing to file suit under the Lanham act is limited to competitors and those that can allege an injury to a commercial interest, the CMS said competitors are best positioned to identify and act upon advertisements that violate the regulation. The CMS also said that, despite comments suggesting it's impossible to show competitive harm from the omission of required pricing information, it's well established that a statement can be actionable if it's "untrue as a result of failure to disclose a material fact." The rule notes that omission of the price may suggest to consumers that the drug is an excepted pharmaceutical, with a list price of less than $35, making the advertisement inherently false and misleading.

The FDA received a total of 147 comments on the proposed rule, with industry groups such as PhRMA arguing that price disclosures would be misleading and that First Amendment principles preclude the CMS from mandating list prices in DTC ads. However, the CMS ultimately changed little in the final rule, with the exception of a minor technical change. The CMS disagreed with assertions that the rule is beyond its authority, arguing that it is permissible within CMS' authority to ensure the efficient administration of Medicare and Medicaid, citing a broad rulemaking authority that permits regulations reasonably related to Medicare or Medicaid.

The CMS shot down arguments that WAC isn't a meaningful measure of what a patient will pay, saying it's "a highly relevant data point with significance in both federal and commercial health care," and that "the absence of a drug's WAC would make a DTC television advertisement potentially misleading because consumers appear to dramatically underestimate their OOP costs for expensive drugs." The CMS also said the speech at issue doesn't implicate First Amendment interests and it's been established in the courts that "government may, consistent with the First Amendment, require the disclosure of factual information in marketing commercial products where the disclosure is justified by a government interest and does not unduly burden protected speech."

FDA issues draft guidance outlining process for submitting real-world evidence in regulatory submissions

The guidance is meant to encourage the use of a simple, uniform format for sponsors to provide information on their use of real-world evidence as part of regulatory submissions for drugs and biologics. The FDA is planning to track submissions containing RWE in support of regulatory decisions of safety and effectiveness for drugs or biologics to inform its RWE program.

The FDA published draft guidance describing a uniform format for sponsors and applicants using real-world data (RWD) to generate real-world evidence (RWE) as part of a regulatory submission to provide information to the agency on their use of RWE. The FDA wants sponsors using RWE in investigational new drug applications (INDs), new drug applications (NDAs) and biologics license applications (BLAs) in support of a regulatory decision on safety or effectiveness to provide information on how they used the RWE. Relevant submissions may include an IND for clinical trials using RWD to capture clinical outcomes of safety data, protocols for single-arm trials using RWE as an external control, observational trials generating RWE in support of an efficacy supplement, and clinical or observational studies using RWE to meet a postmarketing requirement.

The guidance delineates a format for submitting information, noting that the cover letter should indicate the submission contains RWE. Sponsors should provide the following information, either in the cover letter or in table form:

- **The purpose for using the RWE** in the submission, be it evidence in support of the safety or effectiveness of a new product, in support of labeling changes to an existing product, or as part of a postmarketing requirement
- **The study design(s) using RWE**
- **The RWD sources used to generate the RWE**, which may include data from EHRs, medical claims or billing data, product orW disease registry data, or other sources that may inform health status, such as data from mobile technologies or patient-generated data

FDA finalizes guidance updating Q-Submission program for device makers

The guidance describes mechanisms through which medical device makers can request feedback from the FDA on device submissions through the Q-Submission program. The guidance reflects the FDA's commitment under MDUFA IV to establish a performance goal for the timing of FDA feedback on Pre-Submission. It outlines the Q-Submission process from content submission to submission tracking and meetings.

The FDA finalized guidance delineating the mechanisms through which industry may ask for feedback from or a meeting with the FDA over a planned medical device application as part of the Q-Submission (Q-Sub) program. The finalized version was left relatively unchanged from the draft issued in 2018, though the FDA eliminated one of the uses for the program related to informal meetings to discuss requesting a waiver for requirements under 21 CFR 812.28, which describes requirements for the agency to accept data from clinical trials conducted outside the U.S. The finalized version also added cybersecurity as a topic for Pre-Submission questions.

The Q-Sub program includes Pre-Submissions (Pre-Subs), which include a formal written request for FDA feedback prior to an intended submission of a premarket submission, as well as additional opportunities to engage with the agency. It provides an avenue for device makers to ask for feedback during the Pre-Submission phase of an array of device-related submissions, including investigational device exemption (IDE), premarket approval (PMA) and 510(k)s. It also applies to investigational new drug applications (INDs) and biologics license applications (BLAs) for devices regulated as biologics under the Public Health Services Act. The FDA cautions, however, that while interactions tracked in the Q-Sub program may be used throughout the product life cycle for a device, the program isn't meant to be an iterative process and the number of Q-Subs should be judiciously considered.

The guidance explains that requests for Pre-Subs should include specific questions about review issues pertinent to the planned application, such as nonclinical testing protocols or the design of clinical trials. The Q-Sub program is voluntary, but the FDA encourages sponsors to make use of the opportunity for early engagement with the FDA to help improve the quality of the submission, which may reduce review times and facilitate the development process. The FDA believes that feedback may be most effective when requested before a submitter conducts planned testing. Though issues raised in a Pre-Sub don't need to be resolved in a subsequent submission, the FDA cautions that any future submission related to the topic should address why a different approach was taken or why the issue was left unsettled. While the Pre-Sub program allows the FDA to provide feedback on regulatory strategy and approach, the guidance cautions that requests for a prereview of data are generally not appropriate.

Separately from Pre-Subs, submitters may also submit Submission Issue Requests (SIRs) to ask for feedback on a proposed approach to address issues

with hold letters related to marketing submissions, Clinical Laboratory Improvement Amendments (CLIA) Waivers by Application (CW), IDEs or INDs. These may include requests for further information for marketing submissions, letters citing major deficiencies, complete response letters for BLAs, or nonapproval or approval with conditions letters. The SIR feedback pathway is designed to facilitate interaction with the FDA to resolve or elucidate issues identified to help development progress. Submitters may also request a Study Risk Determination to request feedback on whether a planned clinical study is significant risk, nonsignificant risk or exempt from IDE regulations. Alternately, submitters may ask for informational meetings to share information with the FDA without the expectation of feedback.

The guidance indicates that Q-Subs should include:

- An indication of what type of submission is being sought
- The purpose of the submission
- An overview of the device function and general scientific concepts supporting the device
- The proposed indications for use or intended use
- A list of relevant previous communications with the FDA about the device

The guidance provides a breakdown of the review process for each type of Q-Sub, with time frames and recommended contents for submissions. For Pre-Subs, the FDA asks submitters to provide a list of clear questions about review issues related to a planned application, which it recommends be limited to no more than three or four substantial questions. Background information and supporting documentation should also be provided to allow the FDA to give feedback on the questions. Within 15 days of receiving a Pre-Sub, the FDA will conduct an acceptance review, using an acceptance checklist. Written feedback will be given within 70 days. If a meeting is requested for a Pre-Sub, written feedback will be provided at least five days before the scheduled meeting. There is no acceptance review for a SIR or informational meeting. The FDA said it will prioritize SIRs submitted within 30 days of the marketing submission hold, IND clinical hold or IDE letter.
