LOEB & LOEB LLP

FDA Regulatory and Compliance Monthly Recap

JULY 2019

KEY FINDINGS

FDA issues two draft guidance documents to improve consistency, clarity of drug labeling

The first guidance document addresses the content and format of drug abuse and dependence labeling for certain drugs, while the second provides recommendations for the instructions for use section of patient labeling for drugs, biologics and combination products. The FDA said the guidance documents are part of ongoing efforts to ensure health care practitioners and patients have access to accurate information to inform treatment decisions.

The Food and Drug Administration (FDA) issued two draft guidance documents to ensure FDA-approved labeling provides clear and complete information about the potential for abuse and how drugs or biologics should be used. In a joint statement, Acting Commissioner Ned Sharpless of the FDA and Director Janet Woodcock of the FDA's Center for Devices and Radiological Health (CDRH) said the guidance documents reflect the FDA's efforts to ensure both health care professionals and patients have up-to-date, accurate and actionable information about prescription drugs to inform treatment decisions.

The first draft guidance provides recommendations on the content and format of the Drug Abuse and Dependence section of labeling for prescription drugs controlled under the Controlled Substances Act (CSA), as well as for those that are not controlled under the CSA but that require providers to know important information related to abuse and dependence. Per the guidance, the Drug Abuse and Dependence section should be concise and clearly written to accurately summarize a product's potential for abuse, misuse, addiction, dependence and tolerance, as well as any abuse-deterrent properties. To reduce redundancies whenever possible, other sections of the labeling

should discuss drug abuse and dependence aspects only if they are relevant to the scope and purpose of those sections; otherwise, cross-referencing among sections should be used instead. The guidance also recommends drugmakers include definitions of terms such as “abuse,” “misuse” and “addiction,” as they are commonly confused or misinterpreted. However, the guidance recommends that lengthy definitions other than those recommended for inclusion not be included. The guidance also recommends sponsors avoid including detailed information on the proper disposal of controlled substances, as that is generally included in other sections. The section may not include speculative or promotional language.

For drugs scheduled under the CSA, the labeling must identify, in a single sentence, the schedule under which the drug is controlled and must clearly identify the proprietary name and the active ingredients or drug substances that are controlled. For instance, the labeling may state: “DRUG-X contains active ingredient-Y, a Schedule II controlled substance.” If a drug has no proprietary name, the active ingredient or drug substance controlled should be identified—for instance: “Active ingredient-Y is a Schedule II controlled substance.” For drugs for which CSA scheduling is pending, the labeling should include a statement such as the following: “DRUG-X contains active ingredient-Y. (Controlled substance schedule to be determined after review by the Drug Enforcement Administration.)” Upon DEA scheduling, the labeling must be updated. For drugs that are not controlled under the CSA but for which providers need to be given abuse and dependent information, labeling should make clear that the active ingredient or drug isn’t controlled.

The second draft guidance offers recommendations to ensure the Instructions for Use (IFU) document for prescription drugs, biologics, and combinations of devices and drugs or biologics submitted under a new drug application or biologics license application provide clear and concise information that is easily understood for safe and effective product use. The IFU, which is developed for products that have complicated or detailed patient-use instructions, is developed by a sponsor and then reviewed and approved by the FDA. The guidance directs sponsors to ensure they submit true representations of both the content and format of the IFU, including graphic design and color, for the FDA’s review.

Per the guidance, the IFU should provide “detailed, action-oriented, step-by-step written and visual instructions in a patient-friendly manner,” but should be scientifically accurate and consistent with prescribing information (PI). It must not be false or misleading. The guidance recommends that the IFU include relevant information from the PI that describes how to use the product, such as information from the dosage and information section, along with additional details not traditionally included in the PI that are important for safe and effective use. The IFU should be written in nontechnical language that clearly delineates the actions a patient should take to use the product. The guidance recommends that sponsors use active voice and command language, and that sentences begin with an action verb. For instance, an instruction may read, “Wash your hands” instead of “You should wash your hands.”

FDA Pre-Cert pilot confirms potential for streamlined review, excellence appraisal of SaMD

The Pre-Cert team tested previously reviewed submissions and found an accelerated review yielded the same level of reasonable assurance of safety and effectiveness as did traditional review pathways. Going forward, the CDRH will test the mechanism that defines whether a premarket review or a streamlined review is needed.

In a midyear update, the FDA said retrospective testing supported the streamlined review of software

as a medical device (SaMD) under the CDRH Software Precertification (Pre-Cert) pilot. As part of its test plan, the FDA is applying a proposed Pre-Cert pathway involving an excellence appraisal, a review pathway determination, a streamlined review and real-world performance alongside the traditional review pathway, to compare outcomes and the basis for regulatory decision-making. The retrospective testing has been completed, and the results will be used to refine the excellence appraisal and streamlined review components.

For the testing, the FDA developed a mock excellence appraisal summary and created streamlined review packages based on elements from the initial submission. During the test, the excellence appraisals ranged from three to four days and were conducted either on-site at the company or at the FDA's headquarters. FDA staff who completed appraisals included a software expert, a clinical expert, a premarket review expert, a compliance expert and a business operation expert. Agency reviewers carried out mock reviews to determine whether a regulatory decision could be made using the excellence appraisal summary and the streamlined review.

The reviewers determined that a decision could typically be made, though there are opportunities to simplify both the appraisal and the review processes for sponsors and reviewers. Based on their experience, they recommended aspects of the submission identified in the working model be in a structured format for submissions included in the prospective testing. Results from the retrospective testing were used to develop review processes and work instructions for reviewers and staff, to support the streamlined review during prospective testing. Overall, the retrospective testing confirmed the feasibility of the streamlined review package and the excellence appraisal for premarket review of SaMD. The test team also confirmed that the elements identified in the Pre-Cert working model can provide a comprehensive view of an organization's capabilities. The FDA believes that using a collaborative, capability-based approach for appraisals "creates an open and transparent evaluation that identifies organizational strengths and appropriate strategies for driving opportunities for improvement."

The test team also created SaMD product-level elements using cleared or approved SaMDs, testing whether they could support streamlined review and be used to determine the SaMD risk category. The FDA is seeking additional input from patient groups and the digital health community to ascertain whether the SaMD product-level elements are understandable to SaMD users. The FDA is also assessing the practicality of identifying real-world performance analytics elements using specific test cases.

The prospective testing is ongoing, with the FDA testing program components by using a mock streamlined review package for selected premarket submissions. The agency is working with pilot participants and other stakeholders who have volunteered to conduct an excellence appraisal and to test Pre-Cert program components through the review of a De Novo request or 510(k) submission. The agency is also planning to use the Pre-Submission (Pre-Sub) process to test voluntary Review Pathway Determination Pre-Subs. Going forward, the FDA will continue to test the Pre-Cert program, including on new SaMD submissions. Information gathered from testing will be used to determine whether the pathway meets requirements for safety and effectiveness.

FDA issues final rule outlining process for appealing CDRH decisions

The rule meets requirements set under the FDASIA and the Cures Act to clarify procedures and time frames for appealing "significant decisions" to CDRH supervisors. It outlines which decisions are considered "significant" and subject to appeal.

The FDA issued a final rule implementing regulations for supervisory review of significant decisions by the CDRH. Under the Cures Act, Section 603 of the FDA Safety and Innovation Act (FDASIA) was amended to include provisions establishing procedures and time frames for supervisory review of significant decisions by the CDRH related to devices. The final rule codifies those procedures and time frames and sets procedural requirements for supervisory review of other CDRH decisions not covered in FDASIA and the Cures Act.

Under Section 517A of the Federal Food, Drug, and Cosmetic Act (FDCA), any person may request a supervisory review of any significant decision by the CDRH about a submission or review of a report under a 510(k), an application under Section 515 such as a premarket approval or humanitarian device exemption, a request for breakthrough designation, or an application for investigational device exemption. Under the rule, the FDA defines a "517A decision" as a significant decision. The agency uses the term "517A decision" instead of "significant decision" so as not to imply other decisions by the CDRH beyond 517A are not significant. The final rule makes clear that the procedures established for 517A decisions also apply to requests for supervisory review of CDRH decisions beyond the scope of Section 517A.

Per Section 517A, a request for review must be made no later than 30 days after the significant decision in question. The FDA must schedule the requested interaction—either an in-person meeting or a teleconference review—within 30 days of receiving a request. A decision must then be issued no later than 30 days after the interaction. If the requester doesn't ask for an in-person meeting or a teleconference review, the FDA must issue a decision within 45 days of the request for review. As part of its efforts to improve transparency and predictability, the CDRH applies the same procedures and time frames to sequential requests for supervisory review. Requests for review of non-517A decisions must be made no later than 60 days after the date of the decision. Any requests received after 60 days will be denied as untimely.

One comment on the proposed rule suggested the FDA expand the definition of significant decision to include decisions on Clinical Laboratory Improvement Amendments (CLIA) waivers and De Novo classification requests. The FDA decided not to do so, however, as the CLIA waived categorization doesn't fall under the Public Health Service Act as a regulatory decision that triggers the requirements of Section 517A. The FDA said De Novo requests fall within the regulatory category of non-517A decisions.

Federal judge rules against HHS on rule to require drug pricing disclosure in TV advertisements

A district court judge sided with a coalition of drug companies and an advertising trade body, barring the HHS from implementing a policy, scheduled to go into effect July 9, that would have required drugmakers to disclose list prices in TV ads. The judge held the agency lacked the authority to implement the rule.

A judge in the U.S. District Court for the District of Columbia ruled that the U.S. Department of Health & Human Services (HHS) lacks the statutory authority to adopt a rule requiring drugmakers to disclose the wholesale acquisition cost (WAC) of certain drugs. The lawsuit, filed by Merck, Amgen, Eli Lilly and the Association of National Advertisers (ANA), argued the

rule exceeded the authority of the HHS and violated the First Amendment.

In adopting the rule, the HHS had cited its authority under the Social Security Act to ensure the efficient administration of Medicare and Medicaid programs. The judge held, however, that the HHS lacks the statutory authority to adopt the rule, as the Social Security Act doesn't imply an intent by Congress to grant the agency the authority to issue a rule compelling the disclosure of drug list prices. The judge noted, "For a regulation to have the force of law, Congress must communicate through legislation, either expressly or impliedly, its intent for the agency to make rules in that specific area. When Congress has not communicated such intent, the agency has no power to act." While the judge made clear that the court "does not question the HHS's motives" in adopting the rule, "no matter how vexing the problem of spiraling drug costs may be, HHS cannot do more than what Congress has authorized."

The drugmakers and ANA had argued in their complaint that the question of deciding whether the rule exceeded the HHS' authority should be resolved under the *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.* precedent, under which "applying the ordinary tools of statutory construction, the court must [first] determine 'whether Congress has directly spoken to the precise question at issue.'" The HHS had maintained, however, that the court should follow the standard in the pre-*Chevron* ruling in *Mourning v. Family Publications Services*. In *Mourning*, the court held that if the empowering provision of a statute merely states that an agency can set "rules and regulations as may be necessary to carry out the provisions" of the statute, the validity of the regulation will be upheld as long as it reasonably relates to purposes of the regulation. The judge ruled, however, that *Chevron* controls, as the U.S. Supreme Court has held that in every challenge to agency actions, the key issue is "simply, whether the agency has stayed within the bounds of its statutory authority," which is answered using the Chevron *framework*.

Since the Social Security Act doesn't expressly grant the HHS the authority to compel disclosure of the WAC, the court must look under the *Chevron* test at the statute's text, legislative structure and purpose, as well as at other legislative acts, to determine whether Congress provided authority to the agency to enact the rule at issue. In this case, the judge held HHS exceeded the authority enacted to it by Congress under the Social Security Act. As part of the reasoning, the judge noted that Congress expressly legislated drug marketing under the FDCA. The judge noted that HHS has never before tried to leverage the Social Security Act to regulate the pharmaceutical market.

The court did not address the First Amendment challenge.

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5958 REV1 07.30.2019