FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

FDA finalizes guidance on product name displays in drug promotions, labeling

The guidance, initially published as a draft in 2013, offers examples to draw attention to prominence issues and addresses the direct conjunction of proprietary and established names, as well as the frequency of use of the established name. It offers recommendations for drugs with one active ingredient and those with two or more.

The FDA finalized guidance outlining its expectations for the inclusion of prescription drug names in promotional labeling and advertisements. The guidance addresses the placement, size, prominence and frequency of product names in traditional print media, including journals and brochures, audiovisual and broadcast advertisements, and electronic and computer-based promotions, including social media and e-mail advertisements. It also addresses the instances in which the FDA will refrain from enforcement of the requirements.

Per the guidance, an established name should be placed directly to the right or directly below a proprietary name. Names should not be separated by any intervening matter that would detract from or obscure the established name or the relationship between the proprietary and established name. For example, the proprietary and established names shouldn't be separated by material such as a logo or other graphic. The guidance states, however, that trademark symbols or controlled substance symbols will not be considered intervening matter. When displaying both the established name and proprietary name in the running text of labeling or advertisements, the guidance recommends they be presented in the same type size. When the proprietary name is displayed in type larger than that of the surrounding text, the established name should be displayed in font at least half as large.

The established name should have a prominence proportional to the prominence of the proprietary name. The guidance indicates that the FDA will take into account all methods used to achieve adequate prominence, including factors such as contrast, type size and spacing. In traditional print media, the guidance suggests the FDA will not object to fewer appearances of the established name, so long as the established name is included alongside the proprietary name once per page or spread where the proprietary name is most prominently displayed. For audiovisual and broadcast advertisements, the FDA will not object to fewer appearances of the established name in superimposed text if it is placed in direct conjunction with the most prominent display of the proprietary name. The guidance recommends that the established name be displayed on the screen for the same amount of time as the proprietary name. In text displaying at the bottom of the screen, the established name doesn't need to accompany the proprietary name. For electronic and computer-based media, the agency will not object to fewer appearances of the established name as long as it is provided alongside the proprietary name at least once per webpage. In instances in which the proprietary name is not featured but part of the running text, the established name should be provided.

For products with two or more active ingredients without a single corresponding established name, or for a proprietary name that refers to a combination of active ingredients in a single preparation, the guidance offers similar recommendations. The guidance recommends the active ingredients be placed directly to the right or below the proprietary names. It suggests the proprietary name and information about active ingredients not be separated by intervening matter, such as a logo or other graphic. The presentation of active ingredients should be given a prominence proportional to the prominence of the proprietary name, with similar emphasis and contrast.

OPDP targets Amherst Pharmaceuticals in third warning letter of 2017 for missing risk information

The letter raises issues with claims made on the company's website and at a medical conference that omits risk information and misleadingly suggests the drug is superior to other products. The promotional material wasn't the subject of a Form FDA-2253 and made claims without references to support them.

The Office of Prescription Drug Promotion (OPDP) issued a warning letter to Amherst Pharmaceuticals citing issues with online promotional material for Zolpimist Oral Spray and Magna Pharmaceutical's exhibit booth at a medical conference. Inspectors found the promotional material made false to misleading claims or representations about the drug's risks and efficacy, rendering it misbranded under the FDCA.

Inspectors found both the product information on Amherst's webpage and Magna's exhibit at the SLEEP 2017 Annual Meeting of the Associated Sleep Societies (APSS) included claims or representations about the efficacy of the drug but failed to disclose any risk information, consequently providing a misleading impression of the drug's safety. The webpage makes claims suggesting the drug can "outperform the oral tablets" and offers a mode of delivery with "very clear advantages" over others. It also suggests the drug "induces three times faster than oral tablets." The conference material suggests the drug can help mitigate tablet-formulation dependency. The FDA determined that the claims misleadingly suggest the drug is clinically better than other zolpidem products, but no references are cited to support the claims.

The agency also determined that a claim that the drug can induce sleep in 10 minutes misleadingly suggests the therapeutic onset of action of the drug is 10 minutes, though no references cited support the

claim. Similarly, a claim that the drug's efficacy and safety aren't mitigated by food is misleading because the product information for the drug indicates that its effect may be slowed by ingestion with or immediately following a meal. A food-effect crossover study cited in the product information also indicated that the drug shouldn't be administered with or following a meal.

The warning letter also takes issue with Amherst not submitting a Form FDA-2253 for the promotional material at the time of initial dissemination or publication, with a copy of the existing labeling. Based on the violations, the warning letter calls on Amherst and Magna to provide a list of all promotional material for the drug that contains such misleading statements, as well as a plan to disseminate truthful, non-misleading and complete corrective messages addressing the violations. The letter recommends that the corrective message include a description of the violative claims as well as information to correct the messages. The corrective messages should not include promotional claims or representations and should be distributed through the same media channels, where possible.

FDA issues draft guidances to update recommendations on CLIA waiver applications, 510(k) dual submissions

The two draft guidance documents offer insights for IVD makers requesting a CLIA waiver or wanting to leverage the dual 510(k) and CLIA waiver pathway. The first guidance document describes options for demonstrating accuracy and a low risk of erroneous result, while the second discusses studies IVD makers should carry out to support a dual submission.

The FDA issued draft guidance documents to update its recommendations for markets of in vitro diagnostics (IVDs) requesting a waiver from requirements under the Clinical Laboratories Improvement Amendments (CLIA) based on provisions in the Cures Act and MDUFA IV. CLIA requires clinical laboratories to secure a certificate to perform complex diagnostic tests, or a waiver from requirements to perform tests with "an insignificant risk of erroneous result," including those approved for home use or those for which the likelihood of an incorrect result is so low as to be negligible.

Generally, those making devices for CLIA-waived settings take a sequential approach, securing FDA clearance or approval first and then providing data for CLIA waiver determination. The first draft guidance outlines two options for such a sequential route for a CLIA waiver.

1. As part of the marketing submission, the sponsor demonstrates the accuracy of the test when performed by trained operators (defined as a laboratory professional who meets qualifications to carry out moderate complexity testing and has previous training in performing the test) as compared to a traceable calibration method. This data can then be used in combination with a new study to validate agreement between results of the test by untrained operators and trained operators in the submission for a waiver.

2. The sponsor demonstrates substantial equivalence or safety and efficacy of the test when conducted by trained operators in the marketing application, without demonstrating accuracy in comparison to a traceable calibration method. For the waiver application, the sponsor will then need to demonstrate accuracy of the test when performed by untrained operators by directly comparing to a traceable calibration method or other comparative method in a laboratory setting by trained operators.

The guidance cautions that since the first option includes two comparisons in a step-wise manner, it may introduce more potential sources of bias and a higher degree of uncertainty in the estimation of the test's performance by untrained operators compared to the second option. If using the first option, the FDA recommends sponsors provide a summary of information about the study demonstrating the accuracy

of the test when conducted by trained operators, including the duration of the comparison study and sources of variability and type of comparator method used.

The draft guidance provides recommendations for qualitative, quantitative and semi-quantitative tests and notes that, regardless of study design, test performance should be tested in settings that replicate, as closely as feasible, the actual CLIA-waived setting by including:

- Testing sites that are representatives of the intended use population;
- Intended operators with the least amount of training that may be encountered at the types of sites the device is meant to be used in;
- Intended sample type and matrix; and
- Testing over time.

The second draft guidance provides recommendations for manufacturers looking to leverage the dual 510(k) and CLIA waiver by application pathway. Although use of the pathway is optional, the FDA believes it provides the least burdensome and quickest approach for obtaining a CLIA-waived categorization and 510(k) clearance for new IVD devices. Under MDUFA IV, industry committed to informing the FDA of plans to submit a dual submission during the pre-submission process. The draft recommends the interaction be used to address study designs for comparison and reproducibility studies to support by 510(k) and CLIA waiver by application requirements.

The guidance recommends that dual submissions include:

- A device description that demonstrates it is simple to use;
- A risk analysis, including the identification of possible sources of error;
- The result of risk evaluation and description of measures implemented to circumvent the risk of errors and validation or verification studies showing that failure alert or fail-safe mechanisms mitigate the risk of errors;
- The findings from flex studies showing insensitivity of the test system to environmental and usage variations under conditions of stress;
- A description of the design and results of reproducibility studies of the device as used by untrained professionals; and
- Proposed labeling, including instructions for use that align with a "simple" device.

FDA moves to update regulation of digital health with draft, final guidance documents

The agency issued two draft guidance documents and one finalized guidance document as part of its efforts to modernize its regulation of digital health products. The guidance documents reflect the agency's desire to encourage innovation, while maintaining the "gold standard for oversight" and increasing access to information for patients.

The FDA released a group of guidance documents outlining its approach to the oversight of digital health tools, in recognition of their increased use among consumers and the impact regulation can have on development. Commissioner Scott Gottlieb said the agency recognizes that its traditional approach to regulation may not align with new innovations, so policies need to adapt and evolve.

The guidance documents, which are part of the agency's Digital Health Innovation Action Plan, address provisions in the Cures Act related to the FDA's role in digital health. The first draft guidance outlines which types of clinical decision support (CDS) software that either don't meet the definition of a device or that do meet the definition but for which the FDA doesn't intend

to enforce compliance. The Cures Act established the four criteria for software functions that may be excluded from the definition of a device:

1. Not intended to acquire, process or analyze a medical image;

2. Intended to display, analyze or print medical information from a patient or other medical information, such as clinical studies;

3. Intended to support or provide recommendations to healthcare practitioners about the prevention, diagnosis or treatment of a disease or condition;

4. Allows practitioners to independently review the basis of the recommendations provided so that it's not the intent that the practitioners rely primarily on the recommendations to make a clinical diagnosis or treatment decision.

Per the guidance, the FDA takes the term CDS to mean software functions that meet the first three criteria, but only when the fourth is met will a CDS function be excluded from the definition of a device. For patient decision support software, the FDA applies the first two criteria and a third requiring that the software be intended to provide a recommendation to a patient in understandable terms about prevention, diagnosis or treatment. The guidance provides a list of examples of CDS that would not be considered devices, as well as a list of those that remain devices.

The second draft guidance addresses the amended definition of a device under the Cures Act, which states that the definition doesn't include certain software functions, including (1) those for administrative support; (2) those designed to help maintain or promote a healthy lifestyle; (3) those that serve as electronic patient records; or (4) those for the transfer, storage, conversion or displaying of clinical laboratory test or other device data and results. The guidance outlines modifications to existing guidance documents related to the regulation of such software.

The finalized guidance established principles for regulators when assessing the safety, efficacy and performance of software as a medical device (SaMD), adopting principles agreed upon by the International Medical Device Regulators Forum. The guidance outlines a converged approach for clinical assessment of SaMD to establish a valid clinical association between an output and the targeted clinical condition and to verify that the software provides the expected data. The guidance addresses the need for clinical assessment to be an iterative and continuous process and explains that certain SaMD may necessitate independent review of the results of clinical testing, similar to peer or design review. It also addresses the uniqueness of software in its connectivity, which may provide for the continuous monitoring of safety, efficacy and performance.

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.