FDA Regulatory and Compliance Monthly Recap

DECEMBER 2016

KEY FINDINGS

FDA takes issue with misleading TV ads in untitled letters to Celgene, Sanofi-aventis

The OPDP issued untitled letters to two drugmakers requesting they stop airing direct-to-consumer television ads that downplay treatment risks by using compelling visuals that detract from the information.

The FDA's Office of Prescription Drug Promotion (OPDP) issued untitled letters to Celgene and Sanofi-aventis calling on the drugmakers to cease broadcasting video advertisements deemed to be misleading. The letters raise similar concerns about how the advertisements use stimulating visuals unrelated to the risk information, making it challenging for consumers to grasp the information being presented properly.

The letter to Celgene takes issue with an advertisement for Otezla, a treatment for active psoriatic arthritis, that used "attention-grabbing" visuals and audio while discussing risks, undermining the information being provided and misleadingly downplaying the risks of the drug. For example, one part of the ad jumps back and forth between a woman at a party turning the music up and dancing and a man stringing lights across a rooftop, during which information about possible weight loss is presented.

Similarly, the letter to Sanofi-aventis cites issues with a promotional video for Toujeo, a drug for glycemic control in adults with diabetes mellitus, for using "fast paced" visuals that don't align with the statement of risks being presented in the audio. The advertisement features a man dancing to music throughout various scene changes, all of which are unrelated to the risk information in the audio and on-screen text.

The letter indicates that the advertisements misbrand the drugs per the meaning of the Federal Food, Drug, and Cosmetic Act and that their distribution is violative. The letter also states that the nature of the misbranding is concerning from a public health perspective, as it provides

misleading impressions about the drugs. The letters, therefore, ask the drugmakers to reply with a list of all promotional materials that contain such violations, as well as plans for discontinuing the violative materials.

Finalized guidance provides roadmap for clinical pharmacology labeling for drugs, generics, biologics

The guidance provides a general framework for completing the clinical pharmacology section of labeling for drug, generic and biologic submissions and amendments to labeling. Initially published as a draft in 2009, the guidance is designed to meet the objectives of the Physician Labeling Rule.

The FDA finalized guidance to help applicants submitting new drug applications (NDAs), abbreviated NDAs and biologic license applications, as well as supplements to approved applications, put together the clinical pharmacology section of prescription drug labeling with the proper format and content.

The guidance was initially published as a draft in 2009 and subsequently updated in 2014. The finalized version is similar to the revised version, but includes several new paragraphs, including a clarification that companies are not required to submit a labeling supplement to address minor formatting changes. Instead, such changes should be documented in the product's annual report.

The guidance provides a general framework that may be adapted to specific drugs and their conditions of use. It states the clinical pharmacology section should be understandable to healthcare providers who may not have expertise in clinical pharmacology and should include relevant positive or negative findings useful for the safe and effective use of the drug. Information should not be promotional in tone, nor should it include subjective wording such as "fast" or "rapidly." It must include accurate information on:

- **The mechanism of action:** A summary or the drug's established MOAs and a description of target selectivity when it may be related to toxicity or effectiveness. This section should not include the MOA for unapproved uses or indications, nor speculative claims of untested MOAs or suggestions of therapeutic advantages.
- **Pharmacodynamics:** A description of the biochemical or physiologic pharmacologic effects of the drug or active metabolites related to efficacy, adverse events or toxicity, including information related to effects on pertinent PD biomarkers. This section should include details about key study designs and results of drug interaction or population studies pertinent to PD.
- **Pharmacokinetics:** A description of general, clinically significant PK properties of the drug and its metabolites, as well as clinically useful information regarding the expected exposure of the drug, drug concentration and changes in PK over time.

Information may also be provided on the drug's microbiology and pharmacogenomics when appropriate. The microbiology section may include information pertinent to microbiology characteristics, including the antimicrobial MOA, while the pharmacogenomics section should include data on the effect of genetic variations.

FDA to see $500M in funding to support development of new guidance documents as Cures Act signed into law

After winning in landslide votes in both the House of Representative and the Senate, the long-awaited Cures Act was signed into law. The legislation, which went through months of negotiations, includes several provisions to enhance the development of prescription drugs and medical devices and amends the Federal Food, Drug, and Cosmetic Act.

With the signature of President Barack Obama, the 21st Century Cures Act became law after a long journey through the legislature. The act was initially

introduced in early 2015 and passed by the House. Concerns about loosened FDA regulation, however, led the Senate to draft its own package of 19 bills as companion legislation. Ahead of the votes, a new version of the act was unveiled by House and Senate leaders. The act includes $500 million in funding for the FDA, as well as several provisions designed to modernize and accelerate the development process for drugs and medical devices.

The act includes provisions to move toward more patient-focused drug development and directs the Secretary of Health and Human Services, through the Commissioner of Food and Drugs, to establish a plan to create guidance documents on the collection and use of patient experience data. The act established a timeline of 18 months for the publication of first draft guidance. Guidance documents will address methodological approaches to collecting patient experience data, methods to collect and analyze clinical outcome assessments for regulatory decision-making, the form required for submissions and how patient experience data will be used for risk-benefit assessments. The act also calls on the HHS to publish a report exploring the use of patient experience data in regulatory decision-making, including the use of patient-focused drug development tools.

The act also amends Chapter V of the Federal Food, Drug, and Cosmetic Act by adding a section on the qualification of drug development tools (S. 507). The act establishes a process for qualification of drug development tools, noting that a comprehensive review will be undertaken to determine whether the tool is qualified for its proposed context of use based on scientific merit. Per the act, a qualified drug development tool may be used to support approval, licensure or investigational use of a drug or biological product. The act requires the FDA to publish biannually information regarding each qualification submission, as well a comprehensive list of all qualified development tools. It also requires that guidance be published within three years to implement S. 507 and provide a framework for standards and approaches to support the development of biomarkers, as well as explain the requirements to seek approval of a drug development tool.

The act calls on guidance to be published on the use of complex adaptive and other novel trial designs to support drug and biologic approval, including on the recommended analysis methodologies and the types of information that should be supported for review. The FDA is required to publish a draft within 18 months, and finalize the guidance within one year after public comment ends. The act also amends the FD&C Act by adding a section on the use of real-world evidence to support the approval of a new indication for an approved drug, as well as to support postapproval study requirements. This will require the publication of guidance, within five years, detailing when sponsors may rely on real world evidence, as well as standards and methods for collecting such evidence.

In addition to these provisions, the act also establishes:

- A new framework for approving supplemental applications based on qualified data summaries;
- An expanded access policy for investigational drugs;
- An accelerated approval pathway for regenerative therapies;
- A limited population pathway for antibacterial and antifungal drugs; and
- A program to expedite the development of breakthrough devices.

It also establishes new regulations for combination products and requires the HSS to assign a primary agency to regulate these products.

FDA finalizes guidance on public notification of emerging signals for medical devices

The finalized guidance provides an overview of what the CDRH will consider when making decisions about whether to publicly disclose emerging signal information. It describes the instances in which emerging signal information will be disclosed, as well as factors considered in the process of making such decisions.

The FDA finalized guidance outlining the Center for Devices and Radiological Health's (CDRH) policy for notifying the public about emerging safety signals for medical devices. It describes what factors will be considered when determining whether to notify the public about an emerging signal, as well as the processes and timelines CDRH will follow in issuing notifications.

An emerging signal is defined as:

- New information about a medical device that supports a novel causal association or aspect of a known association between a device and an adverse event; or
- Information for which the FDA has conducted a preliminary assessment and determined it has the potential to impact patient management decisions or the device's benefit/risk profile.

The FDA does not consider unconfirmed or unreliable data lacking adequate evidence as an emerging signal. The guidance applies to any product that meets the definition of a device regulated by CDRH, irrespective of classification, but not to investigational devices under the FDA's Investigational Device Exemptions (IDE) regulations.

When the FDA receives information about device-related signals, a CDRH signal management team is brought together to assess the signal and any additional information from other data sources, including from the device manufacturers and other stakeholders. The goal is to better understand the nature of the adverse event, including the likelihood of a causal relationship between the device and event, and to investigate whether the issue is limited or may have a wide-ranging impact. As a more comprehensive understanding of the signal emerges, the management team may identify regulatory actions, such as labeling changes or postmarket studies, to circumvent any identified risks.

In assessing emerging signals, the CDRH will assess factors such as:

- The likelihood of the adverse event;
- The magnitude of the harmful event and the magnitude of the benefit from the device;
- The extent of patient exposure;
- The potential to prevent, identify, monitor and circumvent the risk; and
- The availability of alternative therapies.

The guidance makes clear that the decision to make information public does not mean the FDA has definitively concluded there is a causal relationship between the device and emerging signal. The guidance further makes clear that public notifications will not be used unless:

- Reliable evidence supports a new causal relationship but the FDA needs more time to make a definitive conclusion; or
- The agency determines a causal relationship exists but more time is needed to develop recommendations.

The guidance indicates that the contents of public notifications may differ based on the type of information available and the specific benefits/risks of the device. However, they will generally include a description of the device, a summary of the emerging

signal and evidence on which the public notification is based, as well as information on the established benefits and risks of the device. The guidance notes that impacted companies will be informed prior to a public notification being issued, unless it's not feasible or time doesn't allow it because of the risk to patients.

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.