FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

OPDP warns Duchesnay over Kim Kardashian's social media endorsement of morning sickness drug

The regulator issued a warning letter stating Kardashian's endorsement of the company's Diclegis pill on social media was misleading because she failed to include risk information and limitations of use.

As reported by *RAPS*, in July, Kardashian posted a photo of herself to Instagram with the following accompanying text:

"OMG. Have you heard about this? As you guys know my #morningsickness has been pretty bad. I tried changing things about my lifestyle, like my diet, but nothing helped, so I talked to my doctor. He prescribed me #Diclegis, and I felt a lot better and most importantly, it's been studied and there was no increased risk to the baby. I'm so excited and happy with my results that I'm partnering with Duchesnay USA to raise awareness about treating morning sickness. If you have morning sickness, be safe and sure to ask your doctor about the pill with the pregnant woman on it and find out more www.diclegis.com; www.DiclegisImportantSafetyInfo.com."

Diclegis is indicated to treat nausea and vomiting in pregnant women, and is contraindicated in women with "known hypersensitivity to doxylamine succinate, other ethanolamine derivative antihistamines, pyridoxine hydrochloride or any active ingredient in the formula, as well as women who are taking MAOIs." The PI also notes the drug wasn't studied in women with hyperemesis gravidarum. The PI for the drug also contains warnings about activities that require mental alertness and concomitant medical conditions, and notes somnolence as the most common adverse reaction reported.

The FDA issued a warning letter to Duchesnay, citing a number of claims included in Kim Kardashian's Instagram post for Diclegis, writing that the post is misleading because while it contains efficacy

claims about the drug, it omits all risk information. The letter notes that the statement "find out more www.diclegis.com; www.DiclegisImportantSafetyInfo.com," which appeared at the end of the post, failed to mitigate the deceptive omission of risk information. The post excludes material information about the possible consequences of using the drug, and thus misleadingly implies it is safer than has been shown, the FDA wrote.

The letter also targets the post's failure to provide material information about Diclegis' full approved indication, specifically failing to convey that the drug hasn't be studied in women with hyperemesis gravidarum.

Court prohibits FDA from bringing charges against drugmaker Amarin for promoting fish oil drug for off-label uses

A New York federal judge granted Amarin's bid for "preliminary relief," allowing the drugmaker to promote its Vascepa pill for off-label use without the threat of an FDA misbranded action, as long as its communications are truthful and nonmisleading.

Vascepa is approved by the FDA to treat patients with very high levels of triglycerides that have been linked to diabetes, kidney failure and pancreatic cancer. Amarin also wishes to market the pill to physicians for patients who have more moderately elevated levels of triglycerides in spite of already taking statins. While the FDA didn't dispute that an approved ANCHOR study demonstrates that Vascepa significantly reduces triglyceride levels in patients with persistently high triglyceride levels, the agency refused to grant approval to Vascepa for such use.

After receiving a Complete Response letter from the FDA threatening Amarin with a misbranded action for promoting its fish oil drug to healthcare professionals for off-label use, the company filed a complaint claiming the regulator's ban on off-label promotion, as it relates to truthful speech, is unconstitutional under the First Amendment.

In its complaint, Amarin said the FDA's threat of a misbranded action was stopping it from telling doctors about the study, and sought relief so that it could promote its product for off-label use without the threat of criminal prosecution.

U.S. District Judge Paul Engelmayer in Manhattan granted Amarin's bid for preliminary relief, in a decision that could open the door for pharma companies to more openly encourage doctors to try medications for uses the FDA hasn't approved, *Bloomberg* suggests. While the decision is a preliminary injunction and not a final order, Engelmayer noted Amarin was likely to prevail.

Courts have considered First Amendment protection for off-label marketing before, Reuters reported, noting that in 2012, the Second Circuit overturned the conviction of a drug sales representative for off-label marketing — though it was still unclear whether that ruling shielded truthful off-label marketing in all cases. Engelmayer determined it did.

The 2012 appeals court decision, in United States v. Caronia, played a key role in Engelmayer's decision, according to a *New York Times* article. The Second Circuit ruled "the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug." What tipped the scale in Judge Engelmayer's decision is that the statements Amarin wants to make are truthful, which the FDA largely acknowledged. Engelmayer thus determined the decision in the Caronia case prevents the regulator from taking any enforcement action based on statements about a drug that are true.

As predicted by the *Times*, the FDA will most likely appeal Engelmayer's decision because it would eliminate an area in which the regulator has aggressively policed. The Times noted the FDA reached major criminal and civil settlements with GlaxoSmithKline ($3 billion), Abbott Laboratories ($1.5

billion), Merck ($950 million) and Amgen ($762 million) related to off-label promotions of their products over the past few years.

FDA guidance explains how it will determine whether a 510(k) submission should be accepted for substantive review

The regulator issued guidance to go over the necessary elements and contents of a complete 510(k) submission in a bid to enhance the consistency of acceptance decisions.

The guidance document, Refuse to Accept Policy for 510(k)s, describes the procedures and criteria the FDA will use to evaluate whether a 510(k) submission should be accepted for substantive review. It's meant to provide FDA staff with a "clear, consistent approach for acceptance review for traditional, special and abbreviated 510(k) notifications."

The guidance document covers pre-submission interaction, policies and procedures, and principles, and includes checklists and tables.

The 510(k) acceptance review is aimed at evaluating whether a submission is "administratively complete," meaning it contains all the information required for the FDA to review and determine substantial equivalence. In order for a device to be substantially equivalent, the regulator must determine it has the same intended use as the predicate device, and either has the same technological characteristics or has different technical characteristics, but the submission includes information showing the device as being as safe and effective as the predicate. The device can't raise different safety and effectiveness questions.

According to the guidance, the FDA will base its acceptance review of all traditional, special or abbreviated 510(k)s on objective criteria using the applicable Acceptance Checklist included in the document. The submission can only be accepted if all the administrative elements identified as RTA items are included — or the submitter has provided an explanation for elements that were omitted. The FDA has, however, the discretion to decide whether a missing checklist element is required in order for the submission to be complete and accepted, and can request a missing item interactively during the review. If a submission isn't accepted, the submitter can respond to the RTA notification by providing the omitted information.

The FDA also goes over the basic principles of its review policies and procedures, stating that acceptance will be based on whether submissions contain all the necessary elements to start a substantive review. The information's adequacy to support a finding won't be considered — this is only considered during the substantive review. The FDA also says it must determine whether a justification was provided for any alternative approaches or element omissions, and if so, must determine its adequacy. The agency will also consider any device-specific and cross-cutting guidances, as well as applicable recognized standards and regulations when making RTA determinations.

The document contains a preliminary questions checklist, going over questions that should be answered by reviewers as an initial screening of the submission. The FDA lists six preliminary questions, including whether the submission is with the appropriate center, whether the device type is eligible for a 510(k) submission and whether there is a pending PMA for the same device with the same indication for use, among others.

A checklist of eight items covers acceptance review. The FDA goes over organizational elements and elements of a complete submission, which are explicitly necessary to a substantive submission review and substantial equivalence determination. The document also explains how to apply the checklist, and how to deal with elements marked "not applicable" and "no." The list also covers conversions

of special 510(k)s to traditional ones, with the FDA noting it developed separate checklists to address the nuances in content for special and traditional 510(k) submissions.

The guidance ends with three tables — "Acceptance Checklist for Traditional 510(k)s," "Acceptance Checklist for Abbreviated 510(k)s" and "Acceptance Checklist for Special 510(k)s" — which should be completed and included as part of submissions.

FDA revises draft guidance on brief summary and adequate directions for use in DTC print ads and promotional labeling for prescription drugs

In a bid to give consumers better and more actionable information, the regulator revised recommendations for disclosing risk information in DTC prescription drug ads and promotional labeling in print media as it relates to the brief summary requirement and the requirement that adequate directions for use be included with promotional labeling.

Consumer-directed print ads often include the complete risk-related sections of the PI — also known as the "traditional approach" —to satisfy the brief summary requirement, and generally use the full PI to meet the adequate directions for use requirement.

Because many consumers lack the technical background to comprehend some of the information contained in the PI, the FDA doesn't believe these approaches are ideal. Further, some of the information included may be of limited use to consumers. The FDA says the brief summary should be focused on the most important risk information without including an "exhaustive" list, and the information should be presented in a way that consumers will likely comprehend. The FDA also notes the sheer volume of material included in the PI, along with the format and technical language, could make it more difficult for consumers to understand the information.

The agency is thus issuing guidance explaining an alternative disclosure approach referred to as the "consumer brief summary." This alternative approach to developing content can satisfy both the brief summary requirement for DTC print ads as well as the promotional labeling requirements, according to the guidance document.

In going over options for disclosing risk information, the FDA recommends that companies use consumer-friendly language in consumer-directed material. The consumer brief summary should contain language designed for comprehension by a broad target audience with various levels of literacy skills, and technical language, scientific terms and medical jargon shouldn't be included. The guidance notes that a conversational tone or language meant to engage the reader may be useful, citing examples like using "drowsiness" rather than "somnolence," or "fainting" rather than "syncope."

The FDA also specifies that the consumer brief summary needs to be presented in a "readable format," pointing to deadlines and subheadings as examples for communicating important information. Logos and brand colors can also help readers understand, and font size and style should be chosen with readability in mind. The FDA also recommends the use of double spacing and indentations rather than plain block paragraphs, among other things.

With regard to content, the document calls for the inclusion of clinically significant information on the most serious and common risks associated with the product, and the omission of less pertinent information. In going over the content, the FDA points to several reference points for selecting risk information, and notes the types of information the consumer brief summary should include and which information it should omit. In addition, if the risk information in the consumer briefing summary isn't comprehensive, the FDA calls for the inclusion of a statement reminding consumers that the information

included isn't comprehensive, or advising them to talk to their healthcare provider, call a provided number or visit a website for product labeling.

The document also covers format, recommending a prescription drug facts box or a Q&A format. The FDA says with the former, information can be presented within a box similar to the OTC Drug Facts box, with standardized headings like "uses," "do not use if you" or "warnings," for example. With a Q&A format, the information can appear in columns or a similar layout, with headings framed in the form of questions, such as "What is this drug for?" and "What are the side effects?"

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

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