LOEB & LOEB LLP

FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

OPDP issues untitled letter to Collegium over promotional material creating misleading impression of opioid painkiller

The letter follows previous advice from the OPDP about promotional material that failed to sufficiently display risk information. An OPDP representative found that the company's exhibit panel for the opioid painkiller prominently displayed information about its abuse-deterrent properties but failed to sufficiently display risk information.

The OPDP issued its first untitled letter of 2018 to Collegium Pharmaceuticals over exhibit material for opioid painkiller Xtampza ER – an oral oxycodone extended-release drug. The letter takes issue with the company's exhibit display for the drug at the American Society of Health-System Pharmacists (ASHP) Summer Meetings and Exhibition held in Minneapolis, Minnesota, in June 2017, which the OPDP determined made misleading representations about the drug, misbranding the drug under the FDCA. The letter raises concerns about Collegium promoting the drug in a way that fails to sufficiently present its risks, despite direction from the OPDP to do so.

Xtampza ER is indicated for "the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." Due to the risks of addiction, abuse and misuse, the drug is not indicated as an as-needed treatment. The prescribing information (PI) for the drug includes a boxed warning about addiction, abuse and misuse, as well as other risks such as life-threatening respiratory depression and neonatal opioid withdrawal syndrome.

According to the letter, the OPDP previously advised Collegium of potential issues with promotional materials for the drug. In September 2016, the office provided advisory comments on similar presentations of the drug and recommended that Collegium adjust them so as not to misrepresent the approved indication or leave out important context,

risk information and other material information. In its comments, the OPDP cautioned that the material needs to display risk information with a "prominence and readability reasonably comparable to the presentation of benefits."

The OPDP noted similar issues with the exhibit material at ASHP, finding the exhibit booth failed to sufficiently provide material information about Xtampza ER's limitations of use and serious adverse events that may arise from the drug's use, creating a misleading impression about its safety. The booth prominently displayed benefit claims about the abuse-deterrent properties of the drug but failed to include any [FDA's emphasis] information about its limitations of use or any information about serious or life-threatening risks.

Although the booth included a side panel with certain information from the PI, this panel was located several feet away from the principal display. The principal display used a blue background and large font, whereas the side panel used a noticeably smaller font and plain background, without any visual elements linking it to the principal display. In addition, the OPDP noted that benefit claims were clearly displayed at eye level in an easy-to-read format, whereas the PI was displayed near the floor and obscured by a table and chair. The letter noted that displaying the information in such a way doesn't adequately ensure the claims about abuse-deterrent properties are truthful and non-misleading.

Given the current opioid crisis, the FDA says promotional material describing abuse-deterrent properties should indicate which routes of abuse deterrence have been established and sufficiently display information explaining that, even with such properties, abuse is only made more difficult, rather than impossible. The drug's labeling should make clear that opioid drugs with abuse-deterrent properties still impose risks of addiction, abuse and misuse. In order for promotional material for Xtampza ER not to be false or misleading, risks of serious and potentially life-threatening results need to be sufficiently and prominently disclosed. The OPDP requested that Collegium provide a list of promotional materials for the drug that contain similar statements and explain its plans for discontinuing violative promotion.

FDA issues draft guidance on product title, date of initial approval in "highlights" section of labeling

The guidance offers content and formatting recommendations for the "Product Title" and "Initial U.S. Approval" portions of the "Highlights" section of drug labeling. It offers recommendations for products with special nomenclature considerations, discusses what not to include in the product title section and addresses implications for container and carton labeling.

The FDA published draft guidance outlining its expectations for the content and format of the product title and initial U.S. approval date under the "Highlights of Prescribing Information" section of drug and biological product labeling. The guidance applies to biological products licenses under the Public Health Service Act, though the FDA notes that certain biological products, such as vaccines, may require a different approach because of their special characteristics. It states that the product title needs to be in bold print and must include the proprietary and nonproprietary name, dosage form, route of administration and, when applicable, the controlled substance symbol. The product title should be in the same typeface as the rest of the text in the highlights section and shouldn't include slash marks, descriptors such as "single-dose vial," and inactive ingredients or lack thereof.

Proprietary names should be in uppercase letters, with the nonproprietary name appearing in parentheses in lowercase letters. The guidance provides two options for the placement of parentheses, corresponding to the proprietary name preceding the nonproprietary name. If the proprietary name corresponds to a drug product available in a

single dosage form, the entire nonproprietary name should be in parentheses. However, if the intention is to make other dosage forms from the same active ingredient under the same proprietary name, only the referenced chemical portion of the nonproprietary name should be in parentheses. For example, "MYDRUG (drugozide nasal spray)" indicates the proprietary name is assigned only to the nasal spray dosage form, whereas "MYDRUG (drugozide) nasal spray" indicates the proprietary name may be assigned to multiple dosage forms.

The guidance recommends dosage forms appear in lowercase letters, with the plural noun used unless the drug product is supplied as a single unit. If labeling addresses multiple dosage forms for a drug under the same proprietary name, each dosage should be presented on a separate line. When a drug product is a solid that needs to be reconstituted before administration, the word "for" should be used before the dosage [e.g., MYDRUG (drugozide) for oral suspension]. If a product includes a delivery system, such as an inhaler or pen injector, the delivery system should not be included in the nonproprietary name but should be presented elsewhere in the labeling. However, the proprietary name of a delivery system may be included in the product title if it is part of the official proprietary name [e.g., MYDRUG NEWHALER (drugozide) inhalation solution, for oral inhalation use].

Generally, for the dosage forms other than tablets, capsules and injections, the route of administration precedes the dosage forms. However, in cases in which the dosage form isn't preceded by the route of administration, it should be presented as "for [route] use" [e.g., MYDRUG (drugozide) ointment, for topical use]. If a drug is assigned a controlled substance schedule by the DEA, the controlled substance symbol must appear at the end of the product title, written as a "C" followed by the Roman numeral designating the schedule. If scheduling of the substance is pending when the application is approved under the FDCA or PHSA, the product title should reflect this by being presented as "MYDRUG (drugozide) oral solution, [controlled substance schedule pending]."

The guidance notes that product information in the product title should be as consistent as possible with the container and carton labeling, though it acknowledges that differences may exist. For instance, dosage and route of administration may be presented underneath the drug or biological product name on the container and carton labeling, whereas it needs to be on the same line in the highlights section. There may also be differences in the route of administration information in the highlights section and on containers or labels. For instance, when important for safety information, the word "only" may be included with route of administration on the container or carton, though this should not be included in the product title in the highlights section.

On the line immediately underneath the product title, the statement "Initial U.S. Approval" should appear with a colon and the four-digit year in which the NME was approved. For a drug that is not a biological and contains only a single moiety, the initial approval is the year in which the first drug containing the active moiety was approved. For drugs with multiple dosage forms, the initial approval is the year of the first approval of the NME, new biological product or new combination of active ingredients, irrespective of dosage form and even if the labeling doesn't refer to the older formulations. For fixed-combination and co-packaged drug products, the initial approval is dependent on the novelty of the combination. If the combination contains components that have each been approved individually or if the combination contains at least one component not previously approved, the U.S. approval is the year of the approval of the combination.

CDRH publishes updated guidance on 510(k), PMA refuse-to-file or -accept policies

The updated guidance documents outline instances in which the FDA may refuse to accept or refuse to file 510(k)s and PMA applications. They provide checklists of required elements and contents for a complete application, and address Cures Act provisions for device-led combination products and MDUFA IV goals.

The CDRH updated two guidance documents on refuse-to-accept policies for 510(k)s and premarket approval (PMA) application reviews to address provisions under the Cures Act and new performance goals under MDUFA IV. The documents provide checklists for sponsors to identify required elements and contents for a complete application. Both documents recommend sponsors engage in pre-submission interaction with FDA review staff.

Under the updated PMA guidance, the FDA separated the criteria for PMA filing into two groups: acceptance and filing. The guidance remains relatively unchanged from previous PMA filing guidance, however, as filing criteria have not changed and the preliminary questions remain the same. Per the guidance, acceptance decision questions ascertain whether the file is administratively complete, whereas filing decision questions assess whether data are consistent with protocol, final device design and the proposed indications. Within 15 calendar days of the document control center (DCC) receiving an application, the FDA will let an applicant know whether any elements are missing. Per the guidance, the review clock under MDUFA doesn't begin if an application is designated not accepted or not filed. Once an application has been accepted and filed, the clock begins as of the date of receipt of the most recent submission or amendment that rendered the application complete.

The guidance provides a checklist for use by FDA review staff of the requirements elements and contents of a complete PMA application. The guidance states that the FDA may refuse to file a PMA if:

- The application isn't complete and is missing information required under the FDCA.
- Information is missing, and justification for the omission is inadequate.
- The applicant has a pending 510(k) application for the same device, and the agency hasn't determined whether the device falls within the scope of section 814.1(c).
- The application includes a false statement of material fact.
- No statement of either certification or disclosure is provided with the application.

Under the Cures Act, section 503(g) of the FDCA was amended to require that sponsors of combination products identify the products as such. Per the amended section, submissions of device-led, device-drug combination products must include the patent certification or statement and provide notice if the combination contains a constituent part of an approved drug. Submitters of combination products that contain a constituent part of an approved drug are asked to provide pertinent patent information, including certification of one of the following:

- Patent information has not been filed.
- The patent has expired.
- The date on which the patent will expire.
- The patent is invalid or will not be infringed by the manufacture, use or sale of the drug constituent part.

The 510(k) guidance applies to traditional, special and abbreviated 510(k)s and outlines the administrative elements needed for a submission to be accepted,

which are identified as "refuse to accept" (RTA) in the checklist. The guidance recommends sponsors complete and submit the acceptance checklists alongside their submissions, identifying the location of supporting information for each RTA element. If one or more RTA items is not presented and no explanation for the omission is provided, the submission will be deemed unacceptable. Similar to the PMA guidance, the 510(k) guidance sets a 15-calendar day timeline for conducting acceptance reviews, which will be conducted on original 510(k) submissions and RTA communications, but not supplements or amendments. The checklist includes organizational elements, which will not generally lead to an RTA decision but which the FDA encourages submitters to consider. The checklist also includes categories and subcategories of information needed to support a statement indicating a device is similar to or different from products of a comparable type. The guidance recommends that submissions include a statement indicating whether the categories apply. For each RTA item, the guidance directs agency staff to take into account only the presence or omission of the element or rationale for the omissions.

FDA enforcement statistics signal decline in CDRH letters, increase in CDER and CBER letters

The agency's annual enforcement statistics show a slight increase in the number of warning letters, though only a marginal number related to drugs, devices or biologics. The CDRH experienced a small decline, while the CDER and CBER experienced a slight uptick. The OPDP saw the number of warning letters issued hold steady, despite an overall decline in letters issued.

The FDA published its enforcement statistics for FY2017, which signaled a slight uptick in the overall number of warning letters, with a marginal increase in letters published by the CDER and CBER but a decline among those from the CDRH. Overall, the agency issued 15,318 warning letters in FY2017, up from 14,590 in FY2016, though the CTP accounted for the majority.

The number of warning letters increased gradually from 2012 to 2014 and peaked at 17,232 in FY2015. The CDRH accounted for only 42 letters in FY2017, down from 85 in FY2016. The CDER accounted for 161 letters, up slightly from 151 in FY2016. The CBER experienced a marginal increase, issuing six letters in FY2017, versus four in FY2016.

Notably, the OPDP issued only three warning letters in FY2017 – the same number of warning letters issued in FY2016, though the office's total number of letters issued declined from 11 to five.

The agency's enforcement statistics also indicate the agency conducted three seizures and issued 12 injunctions in FY2017, with 2,945 recall events throughout the year and five drug product debarments. The CDER accounted for the most (six) injunctions while the CDRH and CBER accounted for none. The overall number of injunctions continued what has been a downward trend since 2015. The CDRH was second in terms of most recalled products, after the CFSAN. In all, 3,226 products were recalled by the CDRH, 1,176 by the CDER and 900 by the CBER. The CDRH accounted for the most Class II recalls, while the CBER accounted for the most Class III recalls.

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.