LOEB & LOEB LLP

FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

Pacira sues FDA, alleging it illegally attempted to restrict truthful and non-misleading speech about its post-surgery pain drug Exparel

The drugmaker filed a First Amendment suit seeking an injunction to prevent the regulator from taking enforcement action against it over what Pacira says is truthful and non-misleading promotion of Exparel, and alleging the FDA retroactively attempted to revise the drug's label to limit its approved indication.

Pacira v. FDA joins *Solis v. Millennium* and *Amarin v. FDA* among First Amendment cases for the pharmaceutical industry to watch in 2015. According to a complaint filed in New York federal court, the FDA issued a Warning Letter to Pacira ordering it to stop sharing certain information with surgeons, anesthesiologists and other "sophisticated audiences" about using Exparel for purposes other than bunionectomy or hemorrdoidectomy surgeries. The letter stated some of the drugmaker's speech established "new intended uses" for the painkiller.

However, Pacira says the drug's FDA-approved label reflects that it's approved for use in surgical sites generally, not exclusively in bunionectomy or hemorrdoidectomy surgical sites. Thus, the company contends the FDA is trying to retroactively narrow Exparel's indication to restrict its use to bunionectomy or hemorrdoidectomy surgeries.

Pacira's complaint goes beyond defending what it believes is its on-label marketing, pointing to 2012's *United States v. Caronia* decision in the 2nd Circuit and U.S. District Judge Paul Engelmayer's ruling last month in the Amarin case to argue that off-label marketing is allowed as long as it's done truthfully. Thus, Pacira claims even if Exparel's approved uses were limited to bunionectomy or hemorrdoidectomy surgeries, the FDA isn't authorized to prohibit the company from communicating truthful and non-misleading information to surgeons

and anesthesiologists about the use of the drug to control post-operative pain in other surgical sites.

FDA draft guidance describes procedures, policies for resolving scientific and medical disputes

The agency issued guidance on the resolution of disputes that arise from disagreements between sponsors and the CDER or CBER, going over the procedures in the CDER and CBER for resolving scientific and/or medical disputes that can't be settled at the decision level.

In its guidance document, the FDA describes the formal dispute resolution (FDR) procedures for appealing issues to the office or center level.

The document notes there are occasions over the course of review of an IND, NDA, BLA or ANDA, during which a range of scientific and medical issues are discussed, where there is a disagreement between a sponsor and the FDA on a matter. The disputes that arise from the disagreements often concern complex scientific and medical matters, so procedures must be in place to ensure "open, prompt discussion of such disputes," the FDA says.

In going over considerations regarding the submission of a formal dispute resolution request, the FDA enumerates five points sponsors should weigh prior to submitting a formal dispute resolution request (FDRR). First, the document addresses what an appropriate FDRR matter is, listing complete response letters and denials of a request for a proprietary name as examples of regulatory actions appropriate for FDRRs. Second, the FDA discusses when a matter isn't appropriate for an FDRR, noting that advice communicated in meeting minutes and general advice letters isn't considered a CDER or CBER regulatory action and therefore isn't suitable for a request. FDRRs also won't be accepted if a sponsor hasn't sought reconsideration of an issue, is engaged with other FDA entities and/or is pursuing other pathways on the same matter simultaneously. The document also talks about new information, noting the review of a decision that was appealed needs to be based on the same information relied on to make the original decision. Thus, new information can't be submitted as part of an FDRR, but rather can be submitted to an application for review by the original deciding official, should the sponsor wish to have the CDER or CBER consider it in case it may affect the original decision. The FDA also addresses meetings related to FDRRs, noting sponsors can request a meeting with an appeal's deciding official after submitting an FDRR to discuss the issues at hand. Sponsors can also request that an advisory committee review a scientific dispute.

The FDA also describes submission procedures, explaining how sponsors can request an FDRR. In addition, the document covers content and format, listing elements that should be contained in each request, including the application number, a brief but "comprehensive" statement about each issue to be resolved and a statement of whether an advisory committee review is requested, among others.

Also included in the document is information concerning FDA action, including responses to an appeal and additional considerations about responses to appeals. The FDA notes the Formal Dispute Resolution Project Manager or CBER Ombudsman serve as the contact for all FDRR-related issues and will communicate and explain to the sponsor all regulatory processes relating to an FDR. If the FDRR is accepted, the appeal will be forwarded to the appropriate CDER or CBER management level, and an acknowledgment letter will be sent to the sponsor identifying the deciding official, due date for response and the date of a meeting, if applicable. In the event that an FDRR is declined, the sponsor will be notified in a letter and informed of the reason for the denial.

The document ends with information about repeat appeals, with the FDA noting that if a sponsor's FDRR isn't accepted at one management level, the sponsor

can appeal the same matter to the next higher management level.

ICH addendum to GCP guideline addresses patient safety, clinical trial design and monitoring, data integrity

The amendment relates to improving clinical trials and the use of electronic records, addressing the changing clinical trial terrain in which clinical trials are growing in scale, complexity and cost. It discusses various aspects of clinical trials, from design and protocol to oversight and data recording, in addition to standards related to electronic records and essential data documents, with a focus on patient safety and data integrity.

On July 30, 2015, the ICH released an addendum to the ICH E6 Good Clinical Practice guideline for public consultation, after completing Step 2b of the ICH process in June. The addendum is meant to supplement and modernize the harmonized ICH E6 guidelines finalized in 1996, with the addition of recommendations designed to ease implementation of new trial methodologies in the EU, Japan and the U.S.

The guideline, which was developed with consultation of current GCP in the EU, Japan, the U.S., Australia, Canada, Nordic countries and WHO, is meant to be followed when conducting clinical trials to be submitted to regulatory authorities. The addendum emphasizes the importance of data integrity, particularly when modifying computerized systems, and the need to monitor risks and ensure patient safety.

Slight adjustments were made to the role of the investigator. If an investigator delegates a study task, the addendum stipulates that he/she is responsible for overseeing the party or individual undertaking the task. The investigator is also responsible for ensuring any outside parties or individuals are qualified to perform study tasks. To do so, the addendum suggests they establish procedures to ensure the integrity of study tasks performed and any data generated. Additionally, the addendum states that investigators are responsible for maintaining sufficient and accurate source documents and trial records.

Significant additions were added to the role of the sponsor, particularly regarding quality management and trial monitoring. The addendum calls for the implementation of risk-based management systems to ensure quality throughout the design, conduct, recording, evaluation, reporting and archiving of trials, with a focus on trial participant protection and the reliability of trial results. The system should identify, evaluate and control risks, while ensuring stakeholders are alerted to risk management activities. The addendum suggests sponsors create a monitoring plan designed to protect participants and data, in addition to a risk-based approach to monitor clinical trials that is either centralized, on-site or a combination of both. Monitoring results should be provided to sponsors for review in a timely fashion and should be documented in enough detail to allow for compliance verification.

Stakeholders in the U.S., EU, Japan, Canada and Switzerland are discussing the addendum. In the U.S., the deadline for comments to the FDA is Jan. 31, 2016.

Obama administration nominates Robert Califf as FDA commissioner

On Sept. 15, the Obama administration listed the nominees for several key administration posts, nominating Califf, a former Duke University researcher and deputy FDA commissioner for medical products and tobacco, as the next FDA commissioner.

After being named deputy commissioner earlier this year, reports have cited speculation that Califf would likely be named as Commissioner Margaret Hamburg's replacement. Hamburg stepped down in March, and Stephen Ostroff, who then served as the FDA's chief scientist, has been serving as acting commissioner since.

Califf was the founding director of Duke's Clinical Research Institute and he led the university's efforts on translational research. He has more than 1,200 publications in peer-reviewed literature and has worked closely with the pharmaceutical industry, leading the clinical trial that assessed Johnson & Johnson's blood thinner Xarelto — a drug that generated $1.52 billion in sales last year.

Califf's nomination is subject to Senate confirmation. If confirmed, Califf will take over an agency that is restructuring how it handles food safety, trying to figure out how to regulate biosimilars and expanding its oversight of conventional tobacco and new e-cigarette products.

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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