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Client Alert Commentary

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Lessons from Latham & Watkins' Representation of Pacira Pharmaceuticals In Ground-Breaking Settlement with FDA

FDA rescinds warning letter and admits to incorrect interpretation of drug's labelling. What can the life sciences industry learn?

On December 15, 2015, Pacira Pharmaceuticals, Inc. (Pacira) announced that the US Food & Drug Administration (FDA) had withdrawn its accusations, made in the form of a Warning Letter to Pacira (Warning Letter), that the company had engaged in unlawful off-label promotion of its non-opioid pain drug (EXPAREL®) by promoting the drug for uses other than the two that were specifically studied in the company's pivotal clinical trials. As part of the groundbreaking resolution, which followed a novel legal challenge developed by the regulatory team at Latham & Watkins working closely with Pacira, FDA rescinded the Warning Letter and publicly renounced the regulatory position on which it was based.

In this *Client Alert*, Latham & Watkins reflects on Pacira's legal case and lessons for the life sciences industry.

FDA's Allegations of Off-Label Promotion

FDA approved EXPAREL on October 28, 2011, for "administration into the surgical site to produce postsurgical analgesia." The approval was based on two pivotal Phase 3 studies that evaluated the safety and effectiveness of EXPAREL for producing postsurgical analgesia — one following hemorrhoidectomy surgeries and the other following bunionectomy surgeries. The "Clinical Studies" section of the approved Prescribing Information described these two trials, along with the statement that "EXPAREL has not been demonstrated to be safe and effective in other procedures." However, the "Indications and Usage" section stated generally that EXPAREL was "indicated for administration into the surgical site to produce postsurgical analgesia" without any limitation to bunionectomy and hemorrhoidectomy procedures. Moreover, while the "Dosage and Administration" section of the labelling contained specific dosage information for bunionectomy and hemorrhoidectomy surgeries, it also stated that "[t]he recommended dose of EXPAREL is based on the surgical site and the volume required to cover the area." Consistent with the broad indication, Pacira marketed EXPAREL following approval for postsurgical analgesia via administration into the site of various surgical procedures.

Nearly three years after EXPAREL's approval, and without any prior notice, Pacira received a Warning Letter from FDA on September 22, 2014 which alleged that the company's promotion of EXPAREL for use in procedures other than bunionectomy and hemorrhoidectomy constituted unlawful off-label promotion. Specifically, the Warning Letter objected to Pacira's distribution of administration guides that described individual physicians' experiences administering EXPAREL into the sites of laparoscopic cholecystectomy and open colectomy procedures, as well as other similar materials that described the

use of EXPAREL in knee arthoplasty, gastric sleeve, open hysterectomy, lumbar interbody fusion, abdominoplasty and other surgical procedures. The Warning Letter also characterized Pacira's advertising claims that EXPAREL provides pain control that lasts for up to 72 hours as misleading and overstating the drug's efficacy.

Pacira objected to FDA's construction of the scope of EXPAREL's approval in its initial response to the Warning Letter. However, in the interest of resolving the issue quickly, Pacira agreed to cease distributing the promotional materials at issue and to distribute corrective messages to address the issues discussed in the Warning Letter. As a result, Pacira ran a number of corrective advertisements and issued a Dear Healthcare Provider Letter to customers stating that EXPAREL's approval "was based on studies of bunionectomy and hemorrhoidectomy, and the drug has not been demonstrated to be safe and effective for any other specific type of surgery."

Latham & Watkins Advises Pacira on Its Challenge to the Warning Letter

In early 2015, Pacira engaged Latham & Watkins after submitting its initial Warning Letter response and corrective actions to FDA. Mere months later, Pacira received a subpoena from the US Attorney's Office for the District of New Jersey requesting a broad range of documents pertaining to marketing and promotional practices related to EXPAREL.

In its role as outside counsel, Latham & Watkins worked with Pacira to develop a comprehensive legal strategy to challenge FDA's pre-enforcement actions and to defend Pacira's promotion of EXPAREL for postsurgical analgesia when administered into any surgical site. As part of that strategy, The team constructed the novel legal theory that FDA had violated the Administrative Procedure Act (APA) by attempting to revise the broad scope of EXPAREL's original approval through threats of enforcement. Specifically, the team argued that FDA's actions exceeded the authority that Congress granted the agency under the Federal Food, Drug, and Cosmetics Act (FDCA) and FDA's own implementing regulations. This argument focused on the fact that FDA's allegations of off-label promotion ignored the broadly stated indication in the "Indications and Usage" section of the EXPAREL Prescribing Information and, instead, relied solely on a selective reading of portions of the "Dosage and Administration" and "Clinical Studies" sections. The team asserted that FDA's attempt to narrow the approved indication through these other sections of the labelling violated the FDCA and FDA's regulations, and represented an unlawful, retroactive revision of the drug's original broad approval.

To support this argument, the team reconstructed the written record from EXPAREL's clinical development, FDA review and approval — including meeting minutes, emails and written notes — and interviewed key participants to show FDA intended to approve EXPAREL with the broad indication for use. The team also reviewed Pacira's post-approval correspondence with FDA, including communications related to Pacira's promotional materials, pediatric investigations and other development programs, to show FDA had retroactively narrowed the broad indication the agency had originally granted. The team then systematically analyzed the FDCA text and legislative history, as well as FDA's regulations, preambles to proposed and final rules, guidance documents, and approval and enforcement precedent, to demonstrate that the new construction of the EXPAREL approval FDA advanced in the Warning Letter unlawfully narrowed the approved indication by ignoring the broad language in the "Indications and Usage" section of the approved Prescribing Information, and relying instead on language in other sections of the Prescribing Information.

Latham & Watkins asserted these legal arguments against FDA on Pacira's behalf in a 33-page legal white paper, and threatened FDA with a lawsuit under the APA and the First and Fifth Amendments to the United States Constitution if the agency refused to agree to an amicable resolution. Receiving no

constructive response from FDA, Pacira escalated its legal arguments to Federal Court by filing a Complaint and Motion for Preliminary Injunction through litigation counsel from Ropes & Gray, working with Latham & Watkins and Lowenstein Sandler. The three-count Complaint against the United States, FDA, and the US Department of Health and Human Services asserted the novel APA claim, as well as the Due Process and First Amendment claims, threatened in the white paper.

Pacira Settles Federal Litigation Upon FDA Concession on EXPAREL Label

Shortly after Pacira filed its lawsuit, the parties initiated settlement discussions. The resulting settlement, announced on December 15, 2015,[1] was a resounding victory for the company. As part of the agreement, FDA publicly announced it had rescinded the Warning Letter issued as a result of FDA's erroneous construction of the EXPAREL labelling.[2] The announcement also conceded Pacira's APA claim, by confirming that FDA had determined that the indication for EXPAREL approved on October 28, 2011 was *never* limited to bunionectomy and hemorrhoidectomy procedures, but had always broadly encompassed all surgical sites. FDA also approved a labelling supplement for EXPAREL,[3] which the agency announced was intended to clarify that EXPAREL's indication was never limited to bunionectomy and hemorrhoidectomy procedures, and which revised the description of the duration of EXPAREL's effect to provide needed clarity.

Notably, the revised labelling does not contain the sentence, previously found in the "Clinical Studies" section, that "EXPAREL has not been demonstrated to be safe and effective in other procedures [other than bunionectomy and hemorrhoidectomy]." The revised labelling also clarifies that the specific dosing information for bunionectomy and hemorrhoidectomy surgeries in the "Dosage and Administration" section are "examples" for use "[a]s general guidance in selecting the proper dosing for the planned surgical site" and specifies that the recommended dose of EXPAREL is based on a number of factors, including the size of the surgical site, the volume required to cover the area, and the individual patient factors that may impact safety.

Lessons From the Pacira Settlement

This settlement not only represents a precedent-setting victory for Pacira and its mission to provide non-opioid options for pain control, but also provides a few key lessons for industry:

1. FDA Is Accountable for Its Construction of Authorizing Statutes

FDA can only act within the bounds that Congress authorizes through statute. While courts will defer to the agency's construction of an ambiguous statutory authorization, they can — and will — strike down agency action that exceeds statutory authority. This concept underlies every action FDA takes, and (as here) targeting FDA's statutory authority can serve as an effective way to challenge unlawful FDA actions.

2. Warning Letters Are Not Unassailable

The immediate impact of receiving an FDA Warning Letter (including potential impacts on share value, shareholder litigation and publicity), combined with the ambiguity surrounding the avenues available to Warning Letter recipients to bring legal challenges, tend to incentivize quick concession to FDA's Warning Letter assertions. While concession may be in a company's best interest in some instances, the Pacira settlement is a reminder that Warning Letters can be successfully challenged with a sound regulatory strategy and perseverance.

Warning Letter recipients should carefully consider responses, and clearly and unequivocally state objections to FDA's positions, even if the recipient ultimately decides in the interest of resolution to implement FDA's requested changes. Though FDA's complete rescission of the Pacira Warning Letter is

historic — we are aware of only two other cases of FDA rescinding warning letters in the agency's history — the strength of the administrative record can be a critical factor in determining the ultimate outcome. Accordingly, Warning Letter recipients should carefully consider what arguments to assert in their Warning Letter correspondence, with an eye toward creating the best possible record. Moreover, if the recipient legitimately disagrees with FDA's allegations of violation, it may be beneficial as part of the overall strategy to push aggressively to meet directly with the agency before the agency moves forward with additional enforcement activities using a faulty violation theory.

3. Watch for Changes to FDA's Enforcement of Off-Label Promotion

The life sciences trade press has been predicting a sea change in the way FDA enforces off-label promotion for some time, because of intensifying scrutiny of the agency's current compliance with the First Amendment. FDA's concessions regarding the lawfulness of Pacira's promotion of specific uses within a broad indication may offer some insight into how FDA will balance First Amendment requirements with the agency's enforcement mandate under the FDCA going forward. We expect more changes in FDA's enforcement of off-label promotion in the coming year. Indeed, the 2016 priorities for the Center for Drug Evaluation and Research include as a "front burner priority" to "re-evaluate FDA's regulation of drug advertising and promotion in light of current jurisprudence around the 1st Amendment."[4]

Latham & Watkins Team

The Latham & Watkins FDA regulatory team was led by Partner and Global Co-Chair of the Healthcare & Life Sciences Practice John Manthei, counsel Rebecca Brandt and associate Morgan Rettig. The white collar litigation team is led by Managing Partner of Latham & Watkins' Washington, D.C. office Alice Fisher, and Partner Benjamin Naftalis. Partner and Global Co-Chair of the Healthcare & Life Sciences Practice Daniel Meron, and associates Benjamin Snyder and Scott Gallisdorfer, contributed to the First Amendment theories in the FDA white paper.

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Endnotes

1 News Release, "Pacira Pharmaceuticals Announces Favorable Resolution With U.S. Food and Drug Administration, Which Reaffirms the Broad Indication for EXPAREL®" (Dec. 15, 2015), http://investor.pacira.com/phoenix.zhtml?c=220759&p=irol-newsArticle&ID=2122491.

2 Letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, to David Stack, Chief Executive Officer and Chairman, Pacira Pharmaceuticals, Inc. (Dec. 14, 2015), *available at* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/enforcementactivitiesbyfda/warninglettersandnoticeofviolationletterstopharmaceuticalcompanies/ucm477250.pdf.

3 Prescribing Information, EXPAREL (Bupivacaine Liposome Injectable Suspension), http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022496s019lbl.pdf.

4 J. Woodcock, "CDER 2016 Priorities," *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM477299.pdf.