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Axinn Insights:
Pharmaceutical Experience Matters in Defending Pharmaceutical Securities Cases

It is no secret that the number of securities class actions filed against pharmaceutical companies has soared in recent years. From a historical average of 12 per year from 1997-2016, the number of securities cases against pharmaceutical companies rose to 30 in 2017 and 24 in 2018.[1] In recent years, the pharmaceutical industry has been the single largest recipient of securities suits across all listed companies.

What is the best response to this tsunami of securities filings? A firm grasp of securities law fundamentals is obviously critical. But does expertise and experience in the pharmaceutical industry matter as well?

Recent case law shows that pharmaceutical industry knowledge can lead to better results in securities suits in the pharmaceutical industry. Stand-out early resolutions of securities claims against pharmaceutical companies reflect the defendant's ability to talk knowledgeably about such industry-specific issues as:

- Clinical studies and special protocol reviews
- Interaction of patent applications with clinical studies
- Comparisons of a drug candidate with other drugs
- Significance of statements at various stages of clinical trials
- Pronouncements by the FDA and independent committees

These "technical" points go to the central securities-law elements of whether a misrepresentation was made, its materiality, the defendant's scienter, and damages. In many industries, securities defense amounts to a formulaic consideration of these elements, with little regard to the industry at issue. As the cases discussed below attest, in the pharmaceutical world, industry experience can be crucial in constructing a winning securities defense.

The balance of this memorandum summarizes recent securities decisions illustrating the relevance of pharmaceutical industry knowledge and experience to the successful defense of securities claims against a pharmaceutical defendant.

1 Cornerstone Research, *Securities Class Action Filings: 2017 Year in Review* 31, available at https://www.cornerstone.com/Publications/Reports/Securities-Class-Action-Filings-2017-YIR; Cornerstone Research, *Securities Class Action Filings: 2018 Year in Review* 34, available at https://www.cornerstone.com/Publications/Reports/Securities-Class-Action-Filings-2018-Year-in-Review.

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Hirtenstein v. Cempra, Inc., 348 F.Supp.3d 530 (M.D.N.C. 2018)

Cempra demonstrates the value of counsel's experience and facility with clinical trial data. In *Cempra*, the defendants' ability to effectively explain the significance of clinical trial data helped persuade a court that a statement was not misleading in view of the clinical data and information available to investors. Defense counsel was also able to demonstrate to the court that in view of trial data and technical findings, the defendants' statements were made in good faith and therefore not actionable.

Cempra's stock dropped from $18.65 to $7.30 after the FDA Antimicrobial Drugs Advisory Committee published a briefing document stating (i) that Cempra's clinical trials of the antibiotic solithromycin ("SM") revealed a "genuine liver injury signal" and (ii) that Cempra's attempt to distinguish SM from a similar drug, Ketek, which had received a black box warning label, was "hypothetical" and "unproven." A securities suit followed.

The plaintiffs based their securities fraud claim largely on Cempra's public statements regarding (i) the safety results of Phase 3 clinical trials of SM for the treatment of pneumonia and (ii) molecular and clinical differentiation between SM and Ketek. Purportedly fraudulent statements included remarks during earnings calls and industry conferences, including:

- "But let me again say: there is no liver toxicity. There is no hepatic toxicity."
- "And our clinical trial data really shows that this has had a great deal of efficacy and all of those ALT [a liver enzyme] [elevations] were reversible and asymptomatic, as you remember."
- "[W]e have very clearly differentiated solithromycin from Ketek based on its mechanism of action and the reason for its adverse event."

The plaintiffs alleged that the statements regarding liver toxicity in the Phase 3 trials were false because the FDA briefing document found a potential for liver injury, specifically noting eight instances of potential "solithromycin-induced liver injury." The plaintiffs also alleged that the statements differentiating SM from Ketek were false because the FDA's briefing document found that a lower potential for liver injury was "so far unproven" and that "hepatic adverse effects seen with solithromycin during its clinical trials exceed the pre-marketing hepatic signal seen with [Ketek]."

The court dismissed the complaint in its entirety. It found that while the defendants had "den[ied] any actual cases of liver toxicity," they had not denied "the potential for some form of liver injury." The court went on to hold that even if the defendants' statements were misleading, they were not material "[w]hen considered within the 'total mix' of information available to investors," which included information about elevated liver enzymes associated with SM and other data available to the public in articles and SEC filings. Finally, the court relied on the fact that the clinical data was open to multiple differing, but reasonable, interpretations, negating any inference of scienter, or bad intent.

As for Cempra's statements about Ketek, the court observed that Cempra had conducted a detailed comparison of its clinical results with adverse events observed with Ketek, and "relied on a complex computation model of [drug-induced liver injury], performed by an independent service." The court took judicial notice of the fact that the computational model was discussed in the FDA Advisory Committee's briefing document. The court thus concluded that "Defendants had a good faith belief in their interpretation of the clinical data" when they distinguished SM from Ketek, which as a matter of law could not support the allegation of scienter.

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In re CytRx Corporation Securities Litigation, 2017 WL 5643161 (C.D. Cal. Aug. 14, 2017)

CytRx demonstrates how a sophisticated understanding of pharmaceutical development processes can be determinative at the early stages of a securities case. The motion to dismiss in this case turned on a very close analysis of how open-label studies work in practice, how deviations from planned protocols can affect outcomes, and how FDA guidance affects drug developers. The defendants' success in eliminating some, but not all, claims depended on their ability to effectively explain the relevant drug trial process.

CytRx's share price declined 59.7% after it announced that a Phase 3 clinical trial "did not show a significant difference between [CytRx's chemotherapeutic drug candidate] aldoxorubicin ("AR") and investigator's choice therapy for [progression-free survival]" and that CytRx would have to conduct a second trial involving longer patient follow-up. Securities suits followed.

CytRx had conducted the Phase 3 clinical trial of AR under a Special Protocol Assessment agreement ("SPA") with the FDA. The SPA provided that "191 [progression-free survival] events [i.e., death or a tumor] [were] required for 90% power to detect th[e] difference" between AR's expected 5.6 months of progression-free survival versus 3.5 months for the investigator's choice. CytRx explained that under the SPA, "[a]ssuming an 18 month accrual period and a 15 month follow-up period after enrollment of the last subject, approximately 400 patients were needed to achieve the total of 191 PFS events."

CytRx, however, shortened the follow-up period. A partial clinical hold placed on the trial by the FDA also interrupted enrollment and resulted in exclusion of many enrollees in the trial. CytRx had access to enrollment and event rates because the trial was conducted as an open-label, rather than double-blind, study.

The securities plaintiffs alleged that CytRx committed securities fraud by stating:

- That the Phase 3 trial was "being conducted under a Special Protocol Assessment, or SPA ... [this] means that the FDA agrees that the design and analyses proposed in the Phase 3 trial protocol are acceptable to support regulatory approval"; and
- That the trial was "on track" or "ahead of schedule."

The plaintiffs alleged that these statements were false or misleading because:

- CytRx's trial was not conducted under the SPA, because CytRx's trial relied on a timeline that did not provide for a full 15-month follow-up period.
- CytRx "necessarily knew[ ] that the event rate was at least 2.5 times faster than assumed, indicating that there were too many patients hitting a PFS event earlier than the SPA assumed," increasing the risk that the trial would not show a statistically positive result.

The court upheld the claim based on statements that the study was being conducted under an SPA, on the basis that the deviation from the follow-up period could be inconsistent with complying with the SPA. That key holding turned on whether the SPA's follow-up period was merely one assumption, among others, that could provide statistical viability for the result, or was an essential part of CytRx's compliance with the SPA. The court held that CytRx's statement was material because the failure to follow the SPA risked lack of approval even if the trial was successful.

The court dismissed the claim based on statements that the study was "on track." The court found that while CytRx could have calculated the event rate and inferred from late patient enrollment that the trial was at risk because the trial was open-label, the complaint contained no factual allegation that CytRx actually had made the necessary calculations or had this understanding.

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Khoja v. Orexigen Therapeutics, Inc., 899 F.3d 988 (9th Cir.)

The *Orexigen* appeal again demonstrates how sophisticated knowledge of FDA procedures and resulting investor expectations can make the difference between success and failure in defense of securities claims against pharmaceutical companies. While the claims in this case were dismissed by the trial court, the Ninth Circuit re-instated them based on technical and industry-specific arguments about the significance of preliminary clinical trial results, the structuring of clinical trials, and the basis for seeking and publicizing the attempt to obtain patent protection for a product still in trials. Arguments about FDA procedures and related patent practices were at the heart of this case. Whether a different approach would have been more successful on appeal is a matter of opinion; but there can be no doubt that pharmaceutical-specific expertise was crucial to this securities case, and that pharmaceutical-specific issues determined the result.

The FDA required Orexigen to conduct a study to assess whether its anti-obesity drug candidate Contrave increased the risk of major adverse cardiovascular events ("MACE"). An independent Executive Steering Committee ("ESC") oversaw the study. After the 25% interim results of the MACE study "indicated that Contrave reduced cardiovascular events by 41% compared with a placebo," Orexigen filed a provisional patent application covering cardiovascular benefits and containing the 25% interim results. It also issued a press release and SEC Form 8-K highlighting the patent application and the results on which it was based.

Shortly thereafter, *Forbes* reported that an FDA official stated that the SEC filing was "unreliable," "misleading," and "likely false." Orexigen's stock dropped shortly afterwards. Later, Orexigen disclosed that the 50% results showed no positive cardiovascular effect, and the chair of the ESC disclosed that the study "ha[d] been halted by the [ESC]." Shareholder suits followed soon after.

The plaintiffs based their securities fraud claims on Orexigen's statement in a form 8-K that "[t]he 371 Patent and the Provisional Patent Applications contain claims related to a positive effect of Contrave on CV outcomes," as well as its publication of a graph showing lower occurrence of MACE in patients on Contrave. They alleged that Orexigen fraudulently failed to disclose that the 25% interim results were allegedly unreliable in view of FDA communications. The plaintiffs further claimed that Orexigen's statement, "The clinical trial program also includes a ... trial known as the [MACE] Study," failed to disclose that the ESC had voted to discontinue the MACE study. Finally, the plaintiffs claimed that Orexigen fraudulently failed to disclose that it needlessly included the 25% interim results in its patent application.

The district court dismissed all counts. It found that Orexigen did disclose that the 25% results were unreliable because it disclosed that the results were interim and did not claim they were statistically significant. It held that Orexigen had no duty to disclose its involvement in the patent application's mentioning the 25% results because disclosure may have been required to establish "enablement" under patent law.

The Ninth Circuit reversed. It held that labeling the 25% results "interim" was not the same as saying that they were "unreliable": "[T]elling investors that the data might change is different from saying the data already has 'a high degree of uncertainty' and is likely to change."

The Ninth Circuit also rejected additional arguments advanced by the defendants that relied on practices for pharmaceutical approval and patent applications. The court held that "enablement" under patent law was a factual question that should go to the jury. It further held that Orexigen did have a duty to disclose adverse results that materially disagreed with disclosures about earlier positive results. And it held that the plaintiffs had sufficiently alleged that the EMC had authority to actually terminate the MACE study, again raising a jury question about the EMC's authority and resulting status of the MACE study at the time of the statement in question.

Of course, it cannot be known whether a different approach would have led to a different result in the Ninth Circuit. But it is clear that the nuts and bolts of FDA and patent procedure were front and center in this case, and that arguments about procedures around the development of pharmaceutical products were the determinative issue in deciding whether securities claims against a pharmaceutical company should go to a jury.

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