New world, new dangers

The atypical antipsychotic **Zyprexa** is Eli **Lilly** and Co.'s best-selling product and one of the 10 top-selling prescription medicines worldwide, but with success has come controversy. Lilly agreed in January to pay $500 million to 18,000 claimants who allege a failure to warn that the drug could cause diabetes, bringing the total paid out by Lilly for such claims to $1.2 billion. The company's image suffered a more serious trauma in December 2006 when a series of articles in the *New York Times* accused Lilly of marketing Zyprexa off-label and downplaying the drug's potential side effects to doctors. The *Times* articles were based on internal Lilly documents that had been leaked from the civil litigation around Zyprexa and quickly found their way onto the Internet. Legal and marketing experts agree that the story behind the leaked Zyprexa documents is reflective of a new environment for pharmaceutical companies, in which executives must face the realities of potentially damaging internal communications being rapidly distributed on a large scale.

Lilly's difficulties began when the company released more than 11 million pages of documents to the plaintiffs during the discovery process of the Zyprexa failure-to-warn litigation. As is common in such cases, the documents were placed under a protective order by the court that strictly limited their use and to whom they could be released. According to the order, all materials produced and designated as confidential by Lilly could only be used for the prosecution or defense of the litigation, and not for any other purpose. Individuals to whom the documents could be released for purposes of the litigation were required to sign an endorsement of the order, in effect a non-disclosure agreement.

In August 2006, the Lanier Law Firm, one of the firms representing plaintiffs in the Zyprexa litigation, began consulting with David Egilman, M.D., a professor at Brown University Medical School with experience in medical-liability cases. Dr. Egilman signed an endorsement of the document protective order in November 2006 and was given access to the Lilly internal documents.

According to later court findings, Dr. Egilman then conferred with Alex Berenson, a *New York Times* reporter, about finding a way to get the documents into Mr. Berenson's hands. Since the protective order contained an exception allowing for access to the documents through subpoena of other courts or agencies if certain procedures were followed, Dr. Egilman and Mr. Berenson decided to contact James Gottstein, an Alaska-based attorney for the Law Project for Psychiatric Rights.

Mr. Gottstein and the Law Project for Psychiatric Rights are involved in a strategic litigation campaign against forced psychiatric drugging. Hospitals or mental-health authorities have the ability to go to court and try to get the courts to order people to take certain drugs. Mr. Gottstein contends that in the case of Zyprexa, judges are making a decision about who should be taking the drug when critical information about the safety of the drug has been hidden. As a result, any documents that might cast Zyprexa or similar drugs in a bad light would be of significant value to Mr. Gottstein and his case.

At Mr. Gottstein's request, the superior court in Alaska issued a subpoena to Dr. Egilman for the Zyprexa documents Dec. 6. As required by the protective order, Dr. Egilman sent a copy of this subpoena to Lilly, offering the company an opportunity to object.

In the section on subpoena by other courts, the Zyprexa protective order states, "In no event shall confidential documents be produced prior to the receipt of written notice by the designating party and a reasonable opportunity to object." No specific amount of time is given. This was a crucial oversight by Lilly, according to William Childs, assistant professor of law, Western New England College. Mr. Childs is a tort law expert whose research focuses on the problems of document leaks in the Internet age.

"One lesson that a pharmaceutical executive should take away from this is to make sure that protective orders are written clearly," Mr. Childs says. "That way you do not have a fight about what a reasonable time is."

Dec. 13, Lilly contacted the Lanier Law Firm to inform them that the company intended to file a motion to quash Mr. Gottstein's subpoena. The following day, Lilly sent a letter to Dr. Egilman asking him to refrain from producing the documents and another to Mr. Gottstein asking him to refrain from seeking production of the documents until the superior court in Alaska could rule on the company's motion. By then Dr. Egilman, having judged that Lilly had been given more than sufficient time to respond and had not done so, and having received a second, amended subpoena from Mr. Gottstein requesting production of the documents by Dec. 12, had already begun transferring the documents to Mr. Gottstein. According to later court findings, Lilly was never informed of or given an opportunity to respond to this second subpoena.

Dec. 15, having learned that Dr. Egilman had transferred the documents, Lilly's attorneys wrote another letter to Mr. Gottstein, asking him to return any protected materials to the company, request return of the materials from any individuals to whom he had sent them, and refrain from any further publishing or publicizing of the materials. When the Lanier Law Firm learned that Dr. Egilman had disclosed the documents, the firm demanded that he return all of the documents and ended his consultancy on the litigation.

By this time, however, Mr. Gottstein had already distributed the documents to a number of individuals, including Mr. Berenson, Steve Cha of the House of Representatives Committee on Government Reform staff, and Snighda Prakash, a reporter for National Public Radio.

Mr. Gottstein insists that he did nothing wrong, since the original protective order did not apply to him. "Lilly didn't object in time," he says. "They had a reasonable opportunity to object, and then didn't. Once I received the documents, they had lost all protection. I don't feel like I had any obligation under the protective order. But I was very clear with Dr. Egilman that he did, and that he was supposed to follow the protective order. The whole point of my subpoenaing the documents was to follow the protective order, not violate it, because if Dr. Egilman had wanted to violate it, he could have just surreptitiously given those documents to the *New York Times*."

Lilly's attorneys, and eventually the courts, saw the case differently. Lilly's motion for a temporary injunction against further distribution of the documents was granted Dec. 19, with the judge finding that, "Mr. Gottstein has deliberately and knowingly aided and abetted Dr. David Egilman's breach" of the protective order. A permanent injunction was granted Feb. 13 by Senior U.S. District Judge Jack B. Weinstein against further distribution of the documents by Mr. Gottstein and most of the other individuals to whom he had distributed the documents. Mr. Gottstein filed a notice of appeal in mid-March, and litigation is continuing as of early April.

Media attack

The court's intervention was too late to save Lilly from taking a beating in one of the world's most widely read newspapers. Between Dec. 17 and Dec. 21, a series of three articles appeared in the *New York Times* under Mr. Berenson's byline, all based on the Zyprexa documents, and all attacking Lilly for behavior allegedly described in them. The first, on Dec. 17, accused the company of playing down Zyprexa's risks in communications with doctors, in particular the drug's links to obesity and tendency to raise blood sugar, both known risk factors for diabetes. The second, published the following day, charged the company with marketing Zyprexa off-label for dementia — a particularly damaging accusation, since Zyprexa's labeling includes a specific warning against use for dementia-related psychosis. The third, appearing Dec. 21, claimed that for at least a year Lilly had provided information to doctors about the blood-sugar risks of Zyprexa that did not match data that the company circulated internally when the company first reviewed its clinical-trial results.

Lilly's responses to the *Times* articles were immediate and emphatic. The company cited numerous studies that failed to find causal links between Zyprexa and diabetes, noted that the drug's label had always included information about potentially clinically significant weight gain, and categorically denied any off-label marketing.

In all responses, the company emphasizes that the documents leaked to Mr. Berenson were only a small number of the total and did not represent actual company strategies or actions.

"The *Times* failed to mention that these leaked documents are a tiny fraction of the more than 11 million pages of

documents provided by Lilly as part of the litigation process," says Steven Paul, M.D., executive VP of science and technology at Lilly (lilly.com). "They do not accurately portray Lilly's conduct. As part of Lilly's commitment to patients and health-care professionals, many high-level Lilly physicians and researchers, along with researchers from outside Lilly, were engaged for a number of years to study the issue of Zyprexa and diabetes. Leaked documents involving these discussions do not represent an accurate view of company strategy."

Company management acknowledges, though, that the contents of the leaked documents look bad. In response to questions from *Med Ad News*, Marni Lemons, a Lilly spokesperson, agreed that the documents taken by themselves give the appearance of inappropriate behavior. Ms. Lemons insists that this appearance is inaccurate. "Judge Weinstein's order acknowledges the undeserved reputational harm Lilly has suffered as a result of the selective, out-of-context delivery of these documents," Ms. Lemmons says.

Mr. Gottstein disagrees. "The fact that these documents are only a small number of the total is no excuse for hiding them," he says. "Lilly released millions of pages of documents to the plaintiffs, and so of course you want to go through and find the relevant ones. If they've got other information that rebuts these documents, then they can bring that up, and the public will benefit by a public discussion of all the facts. They have every right to release any of the documents they want to."

Lilly may have such a right, but releasing more documents would only hurt the company in a different way, according to Ms. Lemons. "The protective order affords protection for our trade secrets and other confidential information," she says. "Lilly has no intention of waiving these protections by disclosing additional confidential information."

The company is faced with this impossible choice — either letting the leaked documents stand on their own in the public eye even though the company admits that they look bad, or revealing even more confidential information and trade secrets in order to rebut them — because the documents have found their way onto the Internet. When filing for the permanent injunction against further distribution of the documents, Lilly's attorneys included five Websites in their list of parties to be enjoined. But Judge Weinstein refused to enjoin any of the sites. His reasons for doing so are reflective of the new environment of communications in which pharmaceutical companies must learn to operate.

"A perplexing issue is presented by Lilly's request for an injunction against Websites to which the conspirators sent the documents or which might have been used for further dissemination by those to whom the documents were originally sent," Judge Weinstein says in his ruling. "The Internet, with its almost infinitely complex worldwide web of strands and nodes, is a major modern tool of free speech and freedom both here and abroad. Its reach extends as far as, and perhaps exceeds, that of newspapers and other traditional media. The law is rightly hesitant about allowing government — including the courts — to inhibit and restrict the use of such modern instruments of communication."

Later in his ruling, Judge Weinstein notes that enjoining Websites would be a useless exercise. "Prohibiting five of the Internet's millions of Websites from posting the documents will not substantially lower the risk of harm posed to Lilly," he says. "Websites are primarily fora for speech. Limiting the fora available to would-be disseminators by such an infinitesimal percentage would be a fruitless exercise of the court's equitable power."

The ruling also notes that the court would be unable to effectively enforce an injunction against the Internet at large and that attempting to do so would constitute a dubious manifestation of public policy.

Mr. Childs believes that the exemption of the Websites from Judge Weinstein's injunction may be the most critical lesson for pharmaceutical companies to learn from Lilly's experience. "Historically, at least in most of these cases, the documents get out and that has not made that big of a difference, because there has not been the quick and widespread distribution," he says. "We are in a different practical world now. But it's still the same legal world, which is one of the things that makes this case interesting — the obvious frustration of the court in trying to use the old legal system in a new practical world."

Lilly is still dealing with the repercussions of the distribution of the Zyprexa documents and may be doing so for some time. March 1, the company received a letter from the House Committee on Government Reform

requesting access to all of the documents leaked to Mr. Gottstein, as well as an enormous range of additional materials related to Zyprexa. In the letter, committee chairman Henry Waxman, D-Calif., cites the *New York Times* articles as a major reason for the committee's request.

A similar letter has been sent to Lilly by Senator Charles Grassley, R-Iowa. According to published reports, federal prosecutors and at least five states are investigating Lilly's marketing of Zyprexa.

In addition, having finally settled the majority of the failure to warn claims against Zyprexa, Lilly is now faced with additional lawsuits for allegedly misleading its shareholders about the drug. April 2, a class-action lawsuit was filed in the U.S. District Court for the Eastern District of New York on behalf of all purchasers of Lilly stock between March 28, 2002, and Dec. 22, 2006. The complaint charges the company with violations of the Securities Exchange Act of 1934 for misrepresenting to investors known adverse side effects associated with the use of Zyprexa, and failure to disclose a systematic and illegal campaign to increase Zyprexa sales by marketing the drug for unapproved off-label uses. The suit cites a loss of more than $30 billion in equity value during the period in question due to this alleged fraud as its cause for damages. The stock market certainly responded poorly to the *Times* articles, with Lilly shares falling 5.8% during the week of Dec. 18 to Dec. 22.

The new practical world

Lilly could have avoided many of these traumas to the company's image if Lilly's marketers had not pushed the envelope quite so hard, according to some marketing experts. "This sounds like what Eli Lilly was doing was de-emphasizing a piece of the puzzle because it might change doctors' perspective on the use of Zyprexa," says Bretton Holmes, president, **Holmes World Media**, a media-relations and image-development company (holmesworldmedia.com). "But discretion might have been the better part of valor in this instance, and it doesn't look like they realized that."

Mr. Holmes criticizes Lilly's argument that the leaked documents are not representative of company policies and actions. "If it looks like a duck and walks like a duck, it's probably a duck," he says. "The leaked documents may not provide a complete picture from Lilly's perspective, and obviously they're going to say that. That's damage control. But if this small portion of the whole speaks to actual negative end results with actual people, it's going to carry more weight than it would as a part of the whole."

At this point, according to Mr. Holmes, Lilly's options are limited. "Now that they're in this mess, the only choice they've got is to apologize," he says. "Their concern is that they'd be admitting that they were wrong. But once your foot is stuck in the mud pit, it's time to start thinking in different ways."

An apology is in order even if the leaked documents are in fact unrepresentative of the whole, Mr. Holmes says, because the appearance is bad, and much of a company's image is about appearances.

A perception of corrective steps being taken is also critical. "Lilly is going to have to be proactive about coming out and saying that new standards will be put in place to prevent future problems," Mr. Holmes says.

According to Mr. Childs, Lilly's most costly error from a legal perspective, and the most important lesson learned for other pharmaceutical executives, may have been the seven-day wait to respond to Mr. Gottstein's initial subpoena. "If there is something that could have been handled better, it was probably what I consider a fairly slight delay in responding to the notice of the subpoena that went to the general counsel's office," Mr. Childs says. "If Lilly had done a quicker job of getting that passed through the system, there wouldn't have been any argument about whether it was done within a reasonable time."

Mr. Childs believes that pharmaceutical executives need to be aware of another key element of the new practical world that helped exacerbate Lilly's problem. "The new practical world does not stem only from the speed of communication on the Internet," he says. "This has a lot to do with a fairly lively anti-pharmaceutical, and in particular anti-psychiatric pharmaceutical community. The speed with which these documents were distributed was largely attributable to that. It's not something pharmaceutical executives have any ability to control. But I suspect that they wish it wasn't there."

According to Mr. Childs, Lilly's effort through the courts to get the documents back under wraps once they had

already appeared on the Internet was a futile gesture. "Pretty early on in the process, it seemed that the effort to get the documents back was almost certainly going to be a failure," he says. "And sure enough, the effort was, largely speaking, a failure."

In fact, Mr. Childs will be using the Zyprexa documents case as a primary example in "When the Bell Can't Be Unrung: Document Leaks and Protective Orders in Mass Tort Litigation," a research article examining the appropriate approach by courts to violation of protective orders in the Internet age.

Mr. Holmes agrees. "If you've gotten to that point, you don't try to put the genie back into the bottle," he says.

Zyprexa still shows vitality

Fortunately for Lilly, the Zyprexa brand remains strong in spite of all the negative attention. According to a report released in February 2007 by **Decision Resources** Inc., Zyprexa will remain the gold standard for the treatment of schizophrenia through 2015. The Decision Resources report credits this to Zyprexa's superiority in efficacy to all other current therapies, particularly on measures that are most important to prescribers such as impact on global symptoms and responder rate.

The report, "Schizophrenia: Turning Physician Insight into Projected Patient Share," is based on responses from more than 3,000 physicians and compares a number of antipsychotics, including Invega, asenapine, and bifeprunox.

Invega, comprising paliperidone, is marketed by **Janssen** LP (janssen.com) and indicated for the treatment of schizophrenia and bipolar mania. **Asenapine** is being developed by **Organon** USA Inc. (organon-usa.com) and is in Phase III clinical trials for the treatment of schizophrenia and acute mania in bipolar disorder. **Bifeprunox** is being developed jointly by **Solvay** Pharmaceuticals Inc. (solvaypharmaceuticals-us.com) and **Wyeth** Pharmaceuticals (wyeth.com) and is in Phase III clinical trials for the treatment of schizophrenia and bipolar disorder.

"Invega is a metabolite of risperidone and is likely to have efficacy similar to that of risperidone, which scored slightly lower than Zyprexa overall," says Nitasha Manchanda, Ph.D., analyst, Decision Resources (decisionresources.com). "Asenapine also lacks the differentiation to replace Zyprexa as the gold standard because it does not make as significant an impact on global symptoms, and bifeprunox is significantly inferior to Zyprexa in all primary efficacy measures and is not capable of surpassing Zyprexa."

Lilly as a whole remains in a strong position to bounce back from its troubles. Even after the *Times* articles, the fall in the company's stock value, the latest costly settlement of Zyprexa failure to warn litigation, and news of state and federal investigations into the company's marketing methods, Lilly's financial reputation remains solid.

Standard & Poor's analysts announced in January 2007 that its ratings and outlook for Lilly (AA/Stable/A-1+) have been unaffected, citing the shrinking number of remaining lawsuits, the declining average dollar amount per lawsuit, the likelihood that there will be a decreasing number of additional claims given Zyprexa's label change in 2003 specifically warning of risks, and the company's continued strong free cash flows. Standard & Poor's (standardandpoors.com) analysts also note that Zyprexa's sales remain solid and Lilly has launched several new drugs in recent years that are beginning to generate meaningful earnings.

Lilly management is well aware that the controversy surrounding the Zyprexa documents is far from over. Company executives hope to be able to reframe the issue around the drug's considerable benefits, rather than the side effects highlighted by the popular press.

"We know that this situation has not ended for Lilly or Zyprexa," Ms. Lemons says. "Our biggest concern about the series of articles on Zyprexa in the *New York Times* — and much of the follow-on coverage in other media — is that it is completely focused on the side effects of Zyprexa and virtually ignores any potential benefits of the medication."

Ms. Lemons points out that the drug has been used by more than 20 million people worldwide and that doctors continue to prescribe Zyprexa to treat two of the most terrible mental illnesses — schizophrenia and bipolar

disorder.

"FDA has looked at the entire body of evidence that Lilly has continued to provide over the years and has affirmed the benefit that this medicine can give to patients when accompanied by appropriate labeling regarding benefits and risks," Ms. Lemons says. "Over the past 11 years, Zyprexa has helped millions of people with serious mental illnesses like schizophrenia and bipolar disorder regain control of their lives."