OXYCONTIN PATENT DEEMED INVALID IN FEDERAL COURT

A federal appeals court found that Purdue Pharma had deliberately misled the government to win patent protection for the painkiller OxyContin and ruled patents on the drug as unenforceable. The unanimous ruling by a three-judge panel of the US Court of Appeals opens the door for increased generic competition and potentially huge legal awards against Purdue. This is also a victory for Endo Pharmaceuticals (based in Chadds Ford, PA), which is seeking to market a generic form of OxyContin.

OxyContin is a timed-release formulation of oxycodone. Over the last five years, its annual sales have averaged approximately $1.5 billion. The drug has also gained notoriety because of widespread abuse.

Purdue Pharma, based in Stamford, CT, stated that it believed that it had properly obtained patent protection for OxyContin and that it planned to seek to have the court's full panel of 12 judges hear an appeal.

"Purdue believes that the court's decision is contrary to principles of patent law," the company said.

The appellate decision surprised some analysts and lawyers because it upheld the most critical and damaging portion of a trial court ruling against Purdue Pharma last year. In that ruling, Judge Sidney H. Stein of the US District Court in Manhattan found that Purdue Pharma had intentionally deceived patent officials by implying that the company had clinical evidence showing that OxyContin was easier for doctors to use to control pain, when in fact such data did not exist. That finding of "inequitable conduct" invalidated Purdue's patent. The three-judge Court of Appeals panel also found, in reviewing the facts of the case, that Purdue had "failed to disclose material information that was inconsistent with its arguments for patentability."

The financial consequence of the decision could be significant for Purdue. To date, 65 lawsuits have been filed by insurers and others seeking to force the drug maker to disgorge "monopoly," or excessive profits as a result of the improper patent and the higher prices of OxyContin. Any damages awarded against Purdue in those cases could be substantial because OxyContin is an expensive drug and because the law allows for a potential tripling of any awards in such cases as a way of penalizing a manufacturer. (Source: *New York Times*, June 8, 2005.)

GENERIC OXYCONTIN TO BE DISTRIBUTED BY MIAMI–BASED COMPANY

The Ivax Corporation, based in Miami, FL, has begun to distribute four strengths (10, 20, 40, and 80 mg) of a generic version of OxyContin. Ivax's subsidiary, Ivax Pharmaceuticals Inc., will sell an "authorized generic" for OxyContin's manufacturer, Purdue Pharma, LP. The move is intended to counter a generic version manufactured by Endo Pharmaceuticals Inc. Purdue Pharma will make the product for Ivax and receive a share of the profits.

The sudden entry of two generic versions of the controversial painkiller, which has been linked to drug abuse in many parts of the country, comes after a three-judge panel on a federal appeals court in Washington ruled that Purdue Pharma's patents for OxyContin were unenforceable.

Under federal law, Endo gets six months of exclusivity to sell its generic version. But the US Food and Drug Administration also allows the so-called "authorized generics," such as the one to be sold by Ivax, to compete for consumer acceptance. Authorized generics are identical to the brand-name drug and manufactured by the brand-name company, but marketed by another firm. Ivax spokesman David Malina said his company has previously marketed authorized generics for GlaxoSmith-Kline and Johnson & Johnson. (Source: Press release, *http://www.ivax.com*, June 8, 2005; and Ft. Lauderdale Sun-Sentinel, June 9, 2005.)

PHASE III STUDY OF REMOXY FOR OSTEOARTHRITIS

Pain Therapeutics, Inc., a biopharmaceutical company, has completed the enrollment and initiation of dosing in its Phase III study with Remoxy, an abuse-resistant form of long-acting oxycodone.

This double-blind, randomized, multicenter Phase III clinical study will evaluate the safety and efficacy of twice-a-day Remoxy against placebo over a one-month treatment period. More than 200 US patients with moderate to severe pain due to advanced osteoarthritis were enrolled. Pain Therapeutics expects to announce study results in the third quarter of 2005, and also expects to initiate a second Phase III study with Remoxy in the fourth quarter of 2005.

"Pain is a complex and chronic condition in these patients," said Remi Barbier, Pain Therapeutics' President and Chief Executive Officer. "Oxycodone can help, but its potential for abuse and illicit diversion remains of great concern to health officials and law enforcement groups. Remoxy's unique formulation makes it exceedingly difficult and frustrating for drug abusers to extract the oxycodone in Remoxy for purposes of getting high. We believe this feature strongly differentiates Remoxy

from currently marketed forms of long-acting oxycodone."

Remoxy is a novel, abuse-resistant form of long-acting oxycodone. Oxycodone is the active ingredient in Oxycontin, a brand-name drug with sales of nearly $2 billion. Remoxy's unique formulation incorporates several abuse-deterrent properties. (Source: PRNewswire, June 8, 2005.)

OPIATE COCKTAIL MAY REDUCE MORPHINE TOLERANCE

Although morphine is well known as a highly effective analgesic, its clinical use is limited by the development of tolerance and physical dependence, and the requirement for increasing doses to maintain analgesic effect. In the June 7, 2005, issue of *Current Biology*, Li He and Jennifer Whistler of the Ernest Gallo Clinic and Research Center and the University of California, San Francisco (UCSF) report a new study showing that the administration of a drug cocktail containing morphine along with small doses of two versions of methadone, a related opioid, significantly reduced tolerance and dependence in test animals.

The analgesic effects of morphine arise through the interaction of the drug with a specialized protein on the surface of cells, the μ opioid peptide receptor, or MOP receptor. MOP receptors are also activated by other opioid drugs and by endogenous opioids, such as endorphins. Morphine is unique, however, in that unlike other opioids, it does not cause the MOP receptor to be internalized into the cell's interior after activation. It is thought that the activated receptor's persistence at the cell surface leads to a compensatory overactivation of a particular signaling pathway in the cell, a signaling imbalance that is a hallmark of opiate tolerance and dependence. This suggests that the promotion of MOP receptor internalization might prevent such signaling imbalances, and indeed past work from author Whistler indicates that mutant versions of the receptor that are more readily internalized were associated with reduced levels of morphine tolerance in mice.

In the new work, He and Whistler sought a more clinically practical approach to facilitating MOP-receptor internalization in the presence of morphine. Reasoning that because other opioid drugs promote internalization of MOP receptors, and that their presence in combination with morphine may prevent the persistence of activated MOP receptors at the cell surface, the authors developed their drug cocktail containing morphine and two chemical versions of methadone.

He and Whistler found that the combination of morphine with the methadone mixture prevented the activation of cellular signaling pathways associated with morphine tolerance and dependence. They also showed, perhaps most importantly, that whereas rats receiving only morphine develop tolerance to the drug, those rats receiving the morphine/methadone cocktail did not show tolerance. Moreover, past work has not indicated whether the promotion of MOP-receptor internalization could altogether prevent the development of morphine dependence; however, in the new study, the authors discovered that rats receiving the morphine/methadone cocktail experienced reduced morphine dependence.

In light of their findings, the authors propose that an opiate cocktail that combines morphine with small doses of methadone would increase the effectiveness of morphine for the treatment of chronic pain.

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