WIGGIN AND DANA

Counsellors at Law

BioInsights

BIOTECHNOLOGY & LIFE SCIENCES PRACTICE GROUP

From January 1, 2008 to date, Wiggin and Dana has represented its pharmaceutical, biotechnology and life sciences clients in corporate partnering and M&A transactions totaling in aggregate more than $3.1 Billion.

Wiggin and Dana and its Clients in the News

Biovitrum/Amgen - Biovitrum AB (publ) acquired the marketed biologics Kepivance(R) (palifermin) and Stemgen(R) (ancestim) and the licensing of worldwide, exclusive rights to Kineret(R) (anakinra) for its current approved indication from Amgen.

NeuroNova/Genentech - NeuroNova AB entered into a collaboration with Genentech, Inc. to develop the use of VEGF (Vascular Endothelial Growth Factor) as a potential treatment of Amyotrophic Lateral Sclerosis (ALS). NeuroNova has an exclusive royalty-bearing worldwide license under Genentech's intellectual property for the development and commercialization of certain types of products containing VEGF in the treatment of ALS, subject to Genentech's option for an exclusive royalty-bearing license under NeuroNova's intellectual property for the development and commercialization of certain types of products containing VEGF in ALS for the USA, Canada and Mexico with predetermined opt-in and milestone fees.

EffRx/Nycomed - EffRx, Inc. entered into a license with Nycomed (Zurich, Switzerland) of exclusive rights to develop and commercialize effervescent alendronate to treat musculoskeletal diseases, except hypercalcemia of malignancy, in Canada, Europe, Latin America, the Middle East, North Africa and Russia. EffRx will receive up to $59 million in

Drug Company Settlements for Off-Label Promotions Surpass US $1 Billion

Article reprinted with permission from the TerraLex newsletter.

Off-label promotions of drugs by pharmaceutical companies continue to be a concern of the United States Food and Drug Administration (FDA) and United States Department of Justice (DOJ). In January 2009, Pfizer's US $2.3 billion settlement and Eli Lilly's US $1.42 billion settlement in connection with off-label promotions have been two of the largest payouts to date.

While doctors are free to prescribe drugs for any treatment, pharmaceutical companies are prohibited from promoting drugs for any purposes not approved by the FDA. Each drug's label must contain "adequate directions for use," meaning that the label must describe the uses for which the drug manufacturer received the FDA's approval. Any promotion of a drug for a use that is not indicated on its labeling is an "off-label promotion."

One concern the FDA has is that potentially dangerous uses of a drug that have not been vetted through the clinical trials required for the FDA's approval will be encouraged through off-label promotions. Another FDA concern is that off-label promotions can cost federal and state government programs millions of dollars. Patients get reimbursed for drugs they are taking for off-label uses that are not reimbursable pursuant to those programs' guidelines.

The FDA does not have the resources to investigate or act upon all instances of off-label promotions. However, the FDA has had help in recent years. Current and former employees and competitors of pharmaceutical companies, as well as consumers, have brought civil "whistleblower" (or qui tam) actions against pharmaceutical companies under the False Claims Act (FCA) in connection with prohibited activities, including off-label promotions. These lawsuits are often the basis for federal civil investigations by the DOJ and, in some cases, are accompanied by federal criminal investigations.

The FCA originated as a Civil War-era law used to prosecute profiteers engaged in fraud against the Union Army. Today, it has become the federal government's primary method for pursuing fraud, achieving over $20 billion in recoveries since 1986. FCA actions are especially prevalent in the health care and pharmaceutical industries. The FCA prohibits knowingly submitting an inaccurate, deceptive, or misleading claim of entitlement to money or property, or making a false statement to get such a claim approved. The statute defines "knowing" to include actual knowledge, deliberate disregard, or reckless disregard of false claims. The government does not have to show a specific intent to defraud.

continued

Wiggin and Dana and Its Clients in the News

upfront payments and milestones, plus double-digit royalties.

Santaris/Wyeth - Santaris Pharma A/S entered into a collaboration with Wyeth Pharmaceuticals to discover, develop and commercialize new medicines based on Santaris Pharma's proprietary Locked Nucleic Acid (LNA) drug platform, which allows specific targeting of microRNAs and messenger RNAs. Under the agreement, Wyeth will make a $10 million equity investment in Santaris Pharma and pay an additional upfront of $7 million in cash. Santaris Pharma may also receive additional milestone payments of up to $83 million for each of 10 potential targets and royalties on worldwide product sales.

Via/Roche - VIA Pharmaceuticals, Inc. entered into an exclusive, worldwide license from Roche to further develop and commercialize a thyroid hormone receptor (THR) beta agonist and multiple compounds from Roche's preclinical diacylglycerol acyl transferase 1 (DGAT1) metabolic disorders programs.

Nerviano/Genentech - Nerviano Medical Sciences S.r.l. entered into collaboration with Genentech, Inc. to discover antibody drug conjugates (ADCs) for the development of potential anticancer agents. NMS has primary responsibility for synthesizing and manufacturing drug reagents, and Genentech has an exclusive license to fully develop and commercialize licensed products containing ADCs. Financial terms include payment to NMS of

The FCA's power lies in its steep damages provisions, as well as its qui tam relator rights of action. Otherwise known as whistleblowers, qui tam relators include current and former employees, competitors, contractors, consumers, and others who have information about potential fraud against the government. Qui tam relators are provided with strong incentives under the FCA with the right to share between 15-30% of the ultimate recovery as well as costs and attorneys fees. With penalties ranging between $5,500 and $11,000 per claim, and the potential for up to triple damages, this can be quite a sizeable amount for the potential relator.

Compounding the risk to companies, a qui tam relator files his or her complaint under seal. The DOJ is then compelled to conduct an investigation in order to determine whether it will intervene in the suit. This investigation can take months or even years, and may even be unknown to the company. Indeed, qui tam suits typically result in protracted investigations and often receive more attention because government agents perceive whistleblowers to possess inside information. The DOJ intervenes in less than 25% of qui tam actions, but relators can pursue the suit on their own and are rewarded with higher shares of any recovery.

Eli Lilly's $1.42 billion settlement on January 15, 2009 was the result of a qui tam action. Another recent whistleblower action resulting in a settlement was announced on September 29, 2008, involving drug manufacturer, Cephalon Inc. and totaling approximately US $443.9 million dollars. Both civil settlements involved multiple qui tam relators, the federal government and several states and included recoveries of millions of dollars for each of the qui tam relators. Each company pleaded guilty to one misdemeanor criminal charge of misbranding and paid fines. Eli Lilly agreed to pay the largest criminal fine ever in a health case: US $515 million, plus forfeited assets valued at US $100 million. In addition, Eli Lilly and Cephalon each entered into a corporate integrity agreement with the Department of Health and Human Services under which each company will be monitored for five years.

Pfizer announced its $2.3 billion settlement with DOJ on January 26, 2009. Neither Pfizer nor DOJ released any further details about this record settlement.

In each of these three cases, the drug company promoted certain of its drugs for uses not approved by the FDA presenting severe risks to patients.

Eli Lilly was accused of off-label promotions of Zyprexa from September 1999 through at least November 2003. Zyprexa is approved for treatment of schizophrenia, bipolar disorder and psychotic disorders. Eli Lilly was accused of promoting it for treatment of aggression, agitation, hostility, dementia,

continued

Wiggin and Dana and Its Clients in the News

an initial one-time-license-fee, milestones and royalties for licensed products as well as milestones on a target-by target basis.

Athera/Dyax - Athera Biotechnologies AB entered into collaboration with Dyax Corporation to discover and develop therapeutic products for the prevention and treatment of cardiovascular inflammatory diseases. Upon successful completion of the discovery phase, Athera and Dyax will have the option to advance lead candidates into clinical development under the terms of a global co-development and commercialization agreement.

Wiggin and Dana and Jim Farrington, Chair of the Biotechnology and Life Sciences Practices, ranked in Global Counsel.

The rankings of this publication are entirely based on feedback the researchers receive from private practitioners active in market and clients.

Alzheimer's dementia, depression and sleep disorder, none of which were approved by the FDA. Aside from studies yielding mixed results regarding effectiveness, the health risks included a higher mortality rate in the elderly, as well as a tendency for weight gain and metabolic disorders -- such as diabetes -- that were particularly pronounced in children. Eli Lilly allegedly targeted its off-label marketing for both populations.

To read the entire article, please see the reprint following this page.

BIOTECHNOLOGY & LIFE SCIENCES LEAD PRACTICE GROUP PARTNERS

JIM FARRINGTON, *Chair*
203.363.7614
jfarrington@wiggin.com

TODD GARABEDIAN, PH.D
860.297.3716
tgarabedian@wiggin.com

MERT GOLLAHER
203.498.4362
mgollaher@wiggin.com

PATTI MELICK
203.363.7615
pmelick@wiggin.com

TERRALEX connections

Monday, March 16, 2009 Volume 1/Issue 6

Drug Company Settlements for Off-Label Promotions Surpass US $1 Billion

By Colette Goodkin Wolff* & Iris Gafni-Kane**

Off-label promotions of drugs by pharmaceutical companies continue to be a concern of the United States Food and Drug Administration (FDA) and United States Department of Justice (DOJ). In January 2009, Pfizer's US $2.3 billion settlement and Eli Lilly's US $1.42 billion settlement in connection with off-label promotions have been two of the largest payouts to date.

While doctors are free to prescribe drugs for any treatment, pharmaceutical companies are prohibited from promoting drugs for any purposes not approved by the FDA. Each drug's label must contain "adequate directions for use," meaning that the label must describe the uses for which the drug manufacturer received the FDA's approval. Any promotion of a drug for a use that is not indicated on its labeling is an "off-label promotion."

One concern the FDA has is that potentially dangerous uses of a drug that have not been vetted through the clinical trials required for the FDA's approval will be encouraged through off-label promotions. Another FDA concern is that off-label promotions can cost federal and state government programs millions of dollars. Patients get reimbursed for drugs they are taking for off-label uses that are not reimbursable pursuant to those programs' guidelines.

The FDA does not have the resources to investigate or act upon all instances of off-label promotions. However, the FDA has had help in recent years. Current and former employees and competitors of pharmaceutical companies, as well as consumers, have brought civil "whistleblower" (or *qui tam*) actions against pharmaceutical companies under the False Claims Act (FCA) in connection with prohibited activities, including off-label promotions. These lawsuits are often the basis for federal civil investigations by the DOJ and, in some cases, are accompanied by federal criminal investigations.

The FCA originated as a Civil War-era law used to prosecute profiteers engaged in fraud against the Union Army. Today, it has become the federal government's primary method for pursuing fraud, achieving over $20 billion in recoveries since 1986. FCA actions are especially prevalent in the health care and pharmaceutical industries. The FCA prohibits knowingly submitting an inaccurate, deceptive, or misleading claim of entitlement to money or property, or making a false statement to get such a claim approved. The statute defines "knowing" to include actual knowledge, deliberate disregard, or reckless disregard of false claims. The government does not have to show a specific intent to defraud.

The FCA's power lies in its steep damages provisions, as well as its *qui tam* relator rights of action. Otherwise known as whistleblowers, *qui tam* relators include current and former employees, competitors, contractors, consumers, and others who have information about potential fraud against the government. *Qui tam* relators are provided with strong incentives under the FCA with the right to share between 15-30% of the ultimate recovery as well as costs and attorneys fees. With penalties ranging between $5,500 and $11,000 per claim, and the potential for up to triple damages, this can be quite a sizeable amount for the potential relator.

Compounding the risk to companies, a *qui tam* relator files his or her complaint under seal. The DOJ is then compelled to conduct an investigation in order to determine whether it will intervene in the suit. This investigation can take months or even years, and may even be unknown to the company. Indeed, *qui tam* suits typically result in protracted investigations and often receive more attention because government agents perceive whistleblowers to possess inside information. The DOJ intervenes in less than 25% of *qui tam* actions, but relators can pursue the suit on their own and are rewarded with higher shares of any recovery.

Eli Lilly's $1.42 billion settlement on January 15, 2009 was the result of a *qui tam* action. Another recent whistleblower action resulting in a settlement was announced on September 29, 2008, involving drug manufacturer, Cephalon Inc. and totaling approximately US $443.9 million dollars. Both civil settlements involved multiple *qui tam* relators, the federal government and several states and included recoveries of millions of dollars for each of the *qui tam* relators. Each company pleaded guilty to one misdemeanor criminal charge of misbranding and paid fines. Eli Lilly agreed to pay the largest criminal fine ever in a health case: US $515 million, plus forfeited assets valued at US $100 million. In addition, Eli Lilly and Cephalon each entered into a corporate integrity agreement with the Department of Health and Human Services under which each company will be monitored for five years.

Pfizer announced its $2.3 billion settlement with DOJ on January 26, 2009. Neither Pfizer nor DOJ released any further details about this record settlement.

In each of these three cases, the drug company promoted certain of its drugs for uses not approved by the FDA presenting severe risks to patients.

Eli Lilly was accused of off-label promotions of Zyprexa from September 1999 through at least November 2003. Zyprexa is approved for treatment of schizophrenia, bipolar disorder and psychotic disorders. Eli Lilly was accused of promoting it for treatment of aggression, agitation, hostility, dementia, Alzheimer's dementia, depression and sleep disorder, none of which were approved by the FDA. Aside from studies yielding mixed results regarding effectiveness, the health risks included a higher mortality rate in the elderly, as well as a tendency for weight gain and metabolic disorders — such as diabetes — that were particularly pronounced in children. Eli Lilly allegedly targeted its off-label marketing for both populations.

From the period of 2001 to as late as 2006 in certain cases, Cephalon was accused of promoting three drugs for uses not approved by the FDA. Actiq is a pain killer in the form of a lollipop containing fentanyl, approved for use by opioid-tolerant patients with breakthrough pain caused by cancer. Provogil is a pill approved for treatment of narcolepsy. Gabitril is a treatment approved for epilepsy. Cephalon's promotion of Actiq for off-label treatment by doctors other than oncologists for pain, including migraine headaches, injuries, sickle cell anemia pain crises, wound dressing changes, and pre-procedural treatment prior to doses of radiation in opioid-tolerant patients, was considered especially egregious. Actiq is up to 100 times more powerful than morphine, and its use can result in addiction, hypoventilation and death, particularly in patients other than non-opioid tolerant patients.

Other recent whistleblower cases against drug companies involving off-label promotions and resulting in large settlements include

- an agreement by Bristol-Myers Squibb in 2007 to pay more than US $515 million to settle an array of civil allegations including off-label promotions of the sale and use of Abilify, an atypical antipsychotic drug, for pediatric use and dementia-related psychosis;
- a settlement by Pfizer of civil and criminal charges for a total of US $430 million in 2004, for off-label promotions of Neurontin by its predecessor, Warner Lambert, as well as interstate sales for unapproved uses;
- a settlement by Jazz Pharmaceuticals for US $20 million in 2007, including a guilty plea by its subsidiary, Orphan Medical, Inc., for off-label promotions of Xyrem, a drug that is approved to treat narcolepsy but is highly controlled because it is sold illegally on the streets. Misuse can suppress breathing, cause comas and even death; and
- a settlement by Medicis Pharmaceutical Corp. in 2007 for US $9.8 million for sales personnel pushing the use of Loprox, a skin topical preparation, for use on children under 10 years old, including for diaper rashes, even though this was not an approved indication.

In practice, confusion remains as to which activities drug companies are permitted to undertake in connection with promoting their drugs and which are prohibited. The FDA has yet to issue definitive guidance to dispel the existing confusion. However, the cases discussed here shed some light on what drug companies should not do in connection with off-label promotions.

Activities that got these companies in trouble included training sales force to promote off-label uses, management involvement, expenditure of resources to promote to doctors and facilities whose only purpose for a drug could be an off-label use, providing only one-sided or self-interested information without disclosing this fact, and rewarding doctors for promoting or prescribing the drug. More specifically:

- Management training of the sales force to promote off-label uses, including
  - o the use of questioning techniques to prompt off-label discussions,
  - o focusing conversations with doctors on symptoms rather than indications;
  - o creating fictional examples of patient profiles for the sales force to use in discussions;
- Management direction to the sales force to visit doctors and facilities, who, by the nature of their practice, would be more likely to prescribe for off-label uses, in order to convince them to prescribe for such uses;
- Distributing drug samples to specialty practices whose only possible use for the drug would be off-label;
- Management instruction to sales representatives on coaching physicians to document off-label treatments in ways to get paid by insurers who would not pay for off-label uses;
- Downplaying the differences between approved and off-label uses to its sales force to encourage visits to a broader spectrum of medical care providers than those who would prescribe for approved indications;
- Promoting adverse events, such as weight gain or somnolence, as a therapeutic benefit
- Misrepresenting safety of the drug;
- Management's creation of sales quotas and bonus structures so that the only way sales representatives could reach sales goals was by promoting and selling off-label;
- Providing prizes and other encouragement to sales representatives for engaging in off-label promotions;
- Employing sales representatives and retaining doctors specifically to speak with doctors about off-label uses;
- Using grants to fund continuing medical education programs to promote off-label uses and to otherwise encourage use of the company's products;
- Promoting off-label uses at continuing medical education presentations that are ostensibly non-promotional;
- Inviting doctors to lavish resorts for consultant meetings to expose them to the off-label use message;

- Making deceptive use of scientific data when promoting the drug to doctors:
  - o Disseminating written materials representing that the drug covers a broader range of conditions than were approved by the FDA;
  - o distributing positive studies on the off-label use without disclosing the FDA's rejection of the particular use;
- Ghost-writing articles and studies with an appearance of impartiality; and
- Creating written records and marketing strategies that describe a drug's use for off-label indications and noting expectations or plans for company growth based even partially on these uses.

It has been suggested that pharmaceutical companies can successfully work around the FDA's prohibitions by hosting continuing education sessions, even for multiple days in lavish settings. However, in a number of the suits above, including those against Cephalon, Pfizer, and Bristol-Myers Squibb, one component of the companies' wrongdoing was payment made to doctors to speak on off-label uses and payment made for doctors' travel to hear the off-label use message.

There are certain communications from which pharmaceutical companies are clearly not restricted. A company's research scientists may discuss off-label uses with other research scientists, and drug companies can report new results of studies to their investors. In January 2009, the FDA finalized guidance to allow drug and device makers to disseminate articles regarding off-label uses. The articles must come from peer-reviewed journals that are independent of the drug company, be accompanied by prominent warnings of the lack of FDA approval and meet a number of other requirements intended to ensure their truth and reliability. Go to http://www.fda.gov/oc/op/goodreprint.html to see the specific limitations of the guidance.

The final guidance helps to fill a gap created by the 2006 expiration of a FDA safe harbor under Section 401 of the 1997 Food and Drug Administration Modernization Act. The expired statute allowed pharmaceutical companies to distribute to physicians peer-reviewed scientific articles describing research results of off-label uses. However, it required companies to comply with an onerous process of applying to the FDA for permission and seeking FDA approval for the off-label uses discussed in the article. In practice, the FDA tended not to enforce the statute's burdensome requirements, provided that the dissemination of the reported study was neither against public health nor part of a larger off-label usage campaign. While, on paper, the final guidance would be a relaxation of the expired statute, in reality it may be more limiting because of the FDA's lenient enforcement of the expired statute.

Still, the expired statute and final guidance only address one aspect of off-label promotions: the reprinting and dissemination of medical journal articles and scientific reference publications. There is a long way to go before drug companies will be able to gain certainty regarding all aspects of off-label promotions, and the spate of whistle-blower actions makes it even more precarious to take the risk.

---

*Colette Goodkin Wolff practices in the Business Practice Group in the Stamford, Connecticut office of Wiggin and Dana and her practice focuses on life sciences.

**Iris Gafni-Kane practices in the Health Care, White-Collar Defense, Investigations, and Corporate Compliance, and Research Regulation and Compliance Groups in the New Haven, Connecticut office of Wiggin and Dana and her practice focuses primarily on health care regulatory compliance, government investigations, and self-disclosures.

Reprinted with permission from TerraLex, TerraLex Connections, March 16, 2009, Volume 1/Issue 6. For more information visit us on the web at www.terralex.org.