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**THE EVER-WIDENING  
LEGAL MORASS AROUND  
OFF-LABEL COMMUNICATION**  
by  
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# **THE EVER-WIDENING LEGAL MORASS AROUND OFF-LABEL COMMUNICATION**

by

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The continued onslaught of criminal and civil cases based on the alleged promotion of off-label uses of drugs and devices has caused a massive diversion of resources and attention in these industries. The legal ramifications of alleged off-label activity have spread from merely defending against government investigations to anticipating and defending against civil whistleblower cases and parallel class actions. Nonetheless, the Food and Drug Administration (FDA) seems to acknowledge there is a proper role for the dissemination of off-label information to healthcare providers. Similarly, several of the most active U.S. Attorneys in these industry investigations recently acknowledged that, to a degree, interactions between device makers and physicians for the purpose of developing and testing products and providing feedback to manufacturers on what does and doesn't work in a clinical setting may be more appropriate than interaction between physicians

and drug makers.<sup>1</sup> Of course the regulated companies are left to figure out the best way to balance these competing perspectives, while still complying with the law. This CONTEMPORARY LEGAL NOTE summarizes the recent settlements in civil and criminal off-label investigations and class actions, the recent FDA guidance on dissemination of off-label reprints, and a discussion of the best practices to mitigate the risk of communications about the off-label uses of drugs and devices.

## **I. GOVERNMENT-INITIATED INVESTIGATIONS**

The federal government claims multiple statutory bases empower its pursuit of off-label promotion cases. These include the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. §§ 331(a), (b), and (k) which make it illegal to introduce into interstate commerce adulterated or misbranded drugs. Under this statute, a party can be charged with a criminal misdemeanor (up to one year in prison and \$100,000 individual penalty or \$200,000 for corporations), or a felony (up to three years in prison and \$250,000 individually or \$500,000 corporate fine).<sup>2</sup> Under 18 U.S.C. § 3571(d), the fine may be increased depending on the pecuniary gain from the activity to the company or loss to the government.

In addition to the FFDCA, the government also uses the False Claims Act

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<sup>1</sup>See “Federal Prosecutors Say Device Makers Face Different Issues than Pharma Industry,” Health Care Daily Report June 16, 2009.

<sup>2</sup>See 18 U.S.C. § 3571(e) (fines set forth in § 3571 override penalties set forth in FFDCA at 21 U.S.C. §§ 333(a)(1) & (a)(2)).

(FCA), 31 U.S.C. § 3729, which prohibits knowingly presenting or causing to be presented a false or fraudulent claim for payment to the government. Proof of specific intent to defraud is not required, and liability arises for both facially false claims and claims procured through a fraudulent course of conduct. These cases are often started by a *qui tam* complaint filed by a relator (see below discussion), who can be inside or outside the company.

If the government successfully prosecutes under either the FFDCFA or FCA, it also has the authority to exclude the company from participating in government healthcare programs through mandatory or permissive exclusion.<sup>3</sup> Because of the potentially devastating consequences exclusion creates for pharmaceutical and device companies, most of these off-label prosecutions of companies have been settled. A negotiated settlement can take the form of a plea agreement, deferred prosecution agreement (DPA), or a non-prosecution agreement, depending on the facts and circumstances of the case. The settlement will also generally require the company to sign a corporate integrity agreement (CIA), administered by the Office of Inspector General of HHS.

## **II. WHISTLE BLOWER-INITIATED INVESTIGATIONS**

The filing of whistle-blower complaints by employees or persons familiar with pharma and device company marketing or sales programs have initiated many off-label promotion investigations. In 2008, of the 375 *qui tam*

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<sup>3</sup>See 42 U.S.C. § 1320a-7(a) (mandatory exclusion); 42 U.S.C. § 1320a-7(b) (permissive exclusion); 42 C.F.R. § 1001.101 (mandatory exclusion regulations); 42 C.F.R. § 1001.201 (permissive exclusion regulations).

complaints filed, over 60% (228) were HHS-related. These complaints are initiated under the civil provisions of the False Claims Act, which (unlike the FFDCFA) allow private citizens to file a lawsuit in the name of the U.S. government for fraud by entities that receive or use government funds. The FCA allows the filing person (the relator) to share in the funds recovered (15% to 30%), to participate in the litigation, and to be insulated under federal and state laws from employer retaliation.<sup>4</sup> The government must be notified of the claim and has an opportunity to intervene in the case. *Qui tam* claims must be plead with particularity and the plaintiffs must demonstrate causation between the alleged off-label promotion and the filing of a false claim by a healthcare provider. For example, earlier this year, a *qui tam* claim against a pharma company survived a motion to dismiss by including 200 Medicaid claims with codes revealing the drug, the dose, the medical diagnosis, and the dispensing date.<sup>5</sup> However, many claims are dismissed because of a lack of specificity.<sup>6</sup> Similarly, merely alleging off-label promotion is not adequate; the relator must be able to allege that the pharma or device company caused the healthcare provider to submit the false claim.<sup>7</sup>

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<sup>4</sup>Whistle blower employees have protection under both the Sarbanes-Oxley Act of 2002, 18 U.S.C. §1514A, and various state laws such as the New Jersey Conscientious Employee Protection Act (“CEPA”) N.J. § 34: 19-3 (2008).

<sup>5</sup>See *United States ex rel. Rost v. Pfizer, Inc.*, 253 F.R.D. 11, 15 (D. Mass. 2008).

<sup>6</sup>See, e.g., *United States ex rel. Polansky v. Pfizer, Inc.*, Civ. No. 04-0704, 2009 U.S. Dist. LEXIS 43438, at \*14 (E.D.N.Y. May 22, 2009) (dismissing claims for failure to satisfy particularity requirements under Federal Rule of Civil Procedure 9(b)); *United States ex rel. Poteet v. Lenke*, 604 F. Supp. 2d 313, 323 (D. Mass. 2009).

<sup>7</sup>*United States ex rel. Rost*, 253 F.R.D. at 17.

The current economic and political climate will likely inspire an increase in the number of whistle-blower claims filed under the FCA. The Obama administration and Congress recently signaled their support of this approach to uncovering healthcare fraud through the inclusion in the Stimulus bill of protections for whistleblowers<sup>8</sup> and by enhancing the provisions of the FCA to make it easier and more lucrative for both the government and private individuals to bring complaints in connection with alleged off-label activities.<sup>9</sup>

### **III. SUMMARY OF RECENT OFF-LABEL SETTLEMENTS**

Over the years, there have been a large number of high profile government off-label investigations in the pharma industry, and some in the device industry. Whistle-blowers initiated several of these cases. These cases have involved a wide array of traditional promotional activities, which either individually or in the aggregate, were alleged to provide evidence of promoting the drug or device product for uses not approved by FDA. Because of the substantial risk of exclusion based on a criminal conviction, no cases of this type have been litigated. Rather all have resulted in negotiated settlements.<sup>10</sup> These have included:

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<sup>8</sup>See American Recovery & Reinvestment Act, PL 111-5, Title XV, Sub. C, Sec. 1553.

<sup>9</sup>See The Fraud Enhancement and Recovery Act of 2009; A New Day has Dawned for the False Claims Act, Morgan Lewis webcast, June 26, 2009 available at: <http://www.morganlewis.com/index.cfm/publicationID/9ed08996-24d2-4e45-822d-f3eae5bccfb7/fuseaction/publication.detail>.

<sup>10</sup>Not all off-label investigations are conclusively pursued by the government; based on a lack of evidence produced during the investigation, the government can decline to prosecute the case. If there is a relator, the relator can continue to pursue the case separately.

**Pfizer Inc. (September 2009) - \$2.3B for Bextra, Geodon, Zyvox, Lyrica**

Alleged improper marketing activities of an anti-inflammatory (Bextra) for off-label uses and dosages which the government alleged FDA has specifically declined to approve, and for promotion of an anti-psychotic (Geodon), antibiotic (Zyvox), and anti-epileptic (Lyrica) for uses that were not alleged to be not medically accepted indications and thus covered under government health care programs.

**Eli Lilly (January 2009) - \$1.4B for Zyprexa**

Alleged improper marketing activity of adult schizophrenia/bipolar drug included promoting adverse event of weight loss as a benefit; promoting product to population in which disease rarely occurs (elderly); using medical reprints – where clinical results were mixed – to demonstrate drug's effectiveness for unapproved indications.

**Cephalon (September 2008) – \$425M for Actiq, Gabitril, Provigil**

Alleged improper marketing activity included promoting products for unapproved indications; calling on doctors who normally would not prescribe products; training reps to prompt doctors into off-label conversations; encouraging off-label promotion through compensation and bonus structure; explaining to doctors how to document their off-label use so as to receive reimbursement from insurers who did not pay for off-label uses.

**Bristol-Myers Squibb (Sept. 2007) – \$515M for Abilify, Serzone (civil only)**

Alleged improper marketing activity included promoting Abilify (anti-psychotic for adult schizophrenia and bipolar disorder) for pediatric use and dementia; sales reps calling on inappropriate call points such as child psychiatrists and nursing homes.

**Purdue Frederick Co., Inc. (May 2007) – \$635M for OxyContin**

Felony case in the Western District of Virginia, Purdue allegedly marketed and promoted OxyContin as a less addictive pain medication, even though Purdue's own study indicated otherwise; sales reps trained how to significantly downplay abuse issues and addictive qualities of

drug when promoting to healthcare providers.

**Pharmacia (April 2007) – \$34.7M for Genotropin**

Felony case for alleged off-label promotion activity that included marketing human growth hormone to anti-aging physician specialists and for cosmetic use and athletic performance enhancement.

**InterMune (October 2006) – \$37M for Actimmune**

Malignant osteoporosis drug was allegedly promoted for the unapproved indication of idiopathic pulmonary fibrosis (IPF, a fatal lung condition), when Company's own clinical trial failed to establish the drug's efficacy for IPF.

**Schering-Plough Sales Corporation (August 2006) – \$435M for Temodar and Intron A**

Felony conspiracy case in which company made alleged false statements in response to an FDA inquiry into illegal promotional activities involving the use of Temodar as a first-line treatment for brain cancer, when it was only approved as a second-line treatment; and the use of Intron A, a Hepatitis C drug, in patients being treated for bladder cancer, an unapproved indication.

**Serono (October 2005) – \$704M for Serostim**

Serono redefined the indicator of AIDS wasting from weight loss (the pivotal study clinical endpoint) to lost Body Cell Mass (BCM); and to increase use of its drug, engaged in an alleged felony conspiracy to market non-FDA approved computer software that used BCM to diagnose AIDS wasting.

**Warner Lambert (May 2004) – \$430M for Neurontin**

Felony misbranding case due to prior FDCA violations that included allegations that company promoted its adult epilepsy-partial seizure drug for non-approved indications (e.g., pain, bipolar disorder, ALS, migraine, alcohol withdrawal, restless leg syndrome, spinal cord injury, monotherapy for epilepsy), despite the FDA's specific rejection of an application for monotherapy indication; improper use of organized consultant meetings, advisory boards, teleconferences and purportedly independent medical education programs to promote off-label use.

#### **IV. CLASS ACTIONS RESULTING FROM OFF-LABEL COMMUNICATION**

In addition to the significant resource drain and disruption caused by government investigations of alleged off-label promotion, a well-organized plaintiffs' bar, which coordinates closely with federal and state enforcement authorities, often brings parallel class action claims grounded in product liability, consumer fraud (individual and third-party payor), ERISA, securities violations, and RICO.

There are numerous defenses to these claims. These include the learned intermediary defense; the fact that off-label communications are not inherently fraudulent<sup>11</sup> and have certain First Amendment protections; that there is no private right of action to enforce federal regulations concerning off-label promotion;<sup>12</sup> that no causal connection exists between the alleged off-label promotion and the injury; that the case is not suitable for class certification, as common questions will not predominate over issues affecting individual plaintiffs;<sup>13</sup> or, in the context of medical devices, that federal law preempts suits where FDA has approved the labeling claims.<sup>14</sup>

Based on a combination of the above defenses, a number of parallel civil

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<sup>11</sup>See *U.S. ex rel Hess v. Sanofi*, 2006 U.S. Dist. Lexis 22449 (E.D. Mo. 2006).

<sup>12</sup>See *In re Epogen & Arasnep Off-Label Mktg. and Sales Practices Litig.*, 590 F. Supp. 2d 1282 (C.D. CA. 2008).

<sup>13</sup>See *In re Neurontin Mktg. Sales Practices & Prod. Liab. Litig.*, No. 04-10981, 2009 WL 1323835 (D. Mass. May 13, 2009).

<sup>14</sup>See *Riegel v. Medtronic Inc.*, 128 S. Ct. 998 (2008).

cases have been dismissed. For example, earlier this year, Philadelphia and Massachusetts state courts decertified class actions relating to off-label promotion of Neurotin, based on a lack of common issues in large part on off-label promotion claims.<sup>15</sup> In addition, in a 2008 case involving alleged off-label promotion of Seroquel, a Florida federal court ruled that plaintiffs failed to allege a causal connection between the alleged fraudulent marketing scheme and their injuries.<sup>16</sup> Finally, in a 2009 case involving alleged off-label promotion of Actimmune, a court dismissed the suit because the plaintiffs failed to plead facts showing ascertainable loss in direct relation to the alleged fraudulent activity, and that off-label marketing of an approved drug was inherently fraudulent.<sup>17</sup>

Notwithstanding these decisions a number of class action suits relating to off-label promotion of drugs have settled.<sup>18</sup>

## **V. BUT WAIT....DOESN'T FDA ALLOW FOR DISTRIBUTION OF OFF-LABEL REPRINTS?**

Despite the activity swirling around off-label promotion in the

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<sup>15</sup>See *In re Neurontin Mktg. Sales Practices & Prod. Liab. Litig.*, No. 04-10981, 2009 WL 1323835 (D. Mass., May 13, 2009); *Clark v. Pfizer*, No. 2004-1819 (Phila. Ct. Com. Pl., Feb 9, 2009).

<sup>16</sup>See *Ironworkers Local Union No. 68 v. AstraZeneca Pharm. LP*, 585 F. Supp 2d 1339 (M.D. Fla. 2008).

<sup>17</sup>See *In re Actimmune Mktg. Litig.*, No. Co 08-02376 WL 1139585 (N.D. CA. Apr. 28, 2009).

<sup>18</sup>See, e.g., *Carpenters & Joiners Welfare Fund v. SmithKline Beecham Corp.*, No. CV 04-3500 MJD/SRN, 2008 WL 4435734 (D. Minn. 2008) (Paxil settlement).

enforcement world, FDA continues to acknowledge that dissemination of information about off-label uses to healthcare practitioners, either in the office or in the surgical suite, is acceptable to advance medical science and protect patient health. FDA certainly continues to assert, through Warning Letters and industry meetings, that the FDCA does not allow off-label promotion.<sup>19</sup> Consequently, notwithstanding vocal congressional objections to an FDA policy allowing the dissemination of off-label reprints,<sup>20</sup> in January 2009 FDA issued a final guidance (“Reprint Guidance”) setting criteria for the distribution of reprints on off-label uses.<sup>21</sup>

The Reprint Guidance can be viewed by drug and device manufacturers as either an opportunity or a curse—it sets out a set of rigorous controls under which reprints discussing off-label uses of approved drugs or approved or cleared devices can be given affirmatively by field personnel to health care providers (“HCPs”).

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<sup>19</sup>See, e.g., Letter to Brian A. Markinson, CEO, King Pharmaceutical, Inc. from Thomas W. Abrams, Dir., Div. of Drug Marketing, Advertising, and Communications, CDER, Food and Drug Administration, dated March 24, 2008 (marketing materials allegedly improperly broadened indications for Avinza); see also reports of the stent industry meeting in which FDA identified concerns relating to the promotion by manufacturers of off-label uses of biliary stents through improper advertising, promotion and trade show activities, in Food and Drug Administration Reports from ODE Division, FY 2006 and FY 2007 ODE Annual Report.

<sup>20</sup>See Letter from the Hon. Henry A. Waxman, Chairman, U.S. House of Rep. Committee on Oversight and Government Reform, to the Hon. Dr. Andrew C. von Eschenbach, Commissioner of the Food and Drug Administration, Nov. 30, 2007.

<sup>21</sup>See Good Reprint Guidance for the distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices, Dept. of Health and Human Serv., Food and Drug Admin., Office of the Commissioner, Office of Policy Jan. 2009, available at: <http://www.fda.gov/oc/op/goodreprint.html>.

Under the Guidance, FDA has defined a “good reprint” to be a peer-reviewed scientific/medical journal article or reference publication published by a legitimate scientific organization with a qualified and independent editorial board, with a full disclosure policy on conflicts of interest. A good reprint is based on scientifically sound, adequate, and well-controlled clinical studies, e.g., historically controlled studies, pharmacokinetic/pharmacodynamic (PK/PD) studies and meta-analyses testing a specific hypothesis. For devices, the study can relate to significant non-clinical research. A good reprint is not false or misleading, i.e., it should not be called a definitive study if it is not, or be used if it has already been determined by FDA to not be adequate and well-controlled. Most importantly, it should not pose a significant risk to public health, if relied upon by HCPs. Letters to Editors, Abstracts, Phase I studies of healthy subjects or reference publications that do not discuss study data are not good reprints.

In addition to qualifying a reprint following the above criteria, FDA also requires companies to provide substantial disclosures with the reprint in order to ensure that the reader will understand its proper context; if this information is not given with the reprint, the presumption is that the reprint constitutes illegal promotion. These disclosures include: approved labeling; a comprehensive bibliography; any articles with contrary information about the off-label use; notice indicating that the use is unapproved; disclosures about the nature and amount of any financial interests by the author in the product or

the company, or any compensation received from the manufacturer for generating the report or performing the research; and all significant risks known to the manufacturer concerning the unapproved use discussed in the reprint.

There are a number of outstanding questions about these disclosure requirements which the guidance does not make clear. For example, with respect to the bibliography, how often should it be updated, and what is the extent of materials that should be on it? For the author-related disclosure, how far back should the company look to determine compensation? How detailed must the compensation information be, and do companies need to obtain the author's permission to reveal such information if it is not specifically allowed in the consulting contract? With respect to significant risk disclosure, there is no guidance on how to define significant risk (e.g., is it the same as applied to adverse event reporting requirements?), or on the appropriate or expected standard for company "knowledge" of such risks.

Consequently, although many companies view the new Reprint Guidance as an opportunity for outreach to HCPs, other companies believe that the burdens of compliance are so great and will increase the overall exposure to potential off-label promotion so significantly that they have decided not to affirmatively distribute any reprints.

## **CONCLUSION: BEST PRACTICES TO MITIGATE THE RISKS OF OFF-LABEL COMMUNICATION**

In light of the substantial risks of corporate and personal liability exposure from inappropriate off-label promotion, and the competing corporate objectives to educate HCPs about its drugs and devices, the following are some best practices that companies can take to mitigate this risk:

- Adequately train sales reps and managers to understand what is off-label promotion; test the effectiveness of materials and training through surveys.
- For device reps, make sure they understand how to provide technical assistance and support without promoting off-label uses; consider policies specifically applicable to the surgical suite.
- Compensate reps and managers in a way that does not incentivize off-label sales; reward good conduct; monitor sales numbers, review business and strategic plans.
- Audit sales and marketing personnel and materials frequently to determine compliance.
- Fully follow FDA's Reprint Guidance, and ensure the company has adequate controls, resources, and infrastructure to manage identification and distribution of off-label reprints.
- Ensure that traditional marketing materials are not viewed as a way to communicate otherwise impermissible messages to physicians and to the market.
- Do not use "scientific publications" as vehicles for marketing messages.
- Review CME grants closely to ensure they are properly independent and not a tool for off-label promotion.

- In the medical device context, balance the risk of providing technical support to physicians on off-label uses with the risk to patient safety of not providing technical support.