

# “Off-Label” Is “In”

## The Growing Trend of Pharmaceutical Prescriptions for Non-FDA Approved Purposes

*By Daniel S. Wittenberg and Brendan M. Ford, of Snell & Wilmer L.L.P.*

### I. Drugs Approved for Reducing Seizures and Depression Are Reducing Waistlines:

#### An Introduction to “Off-label” uses

Can antidepressants lighten people’s weight as well as their moods? According to a recent Wall Street Journal article, the answer is yes.<sup>1</sup> The article profiled Sally Krawczyk, a California woman who was prescribed antiseizure medications and antidepressants for weight loss. Ms. Krawczyk — who did not suffer from either seizures or depression — reportedly lost 135 pounds in 18 months. Ms. Krawczyk’s story is not unique, however. The article goes on to state that prescription drugs designed to treat Attention Deficit Hyperactivity Disorder (ADHD), depression, epilepsy, diabetes, sleep disorders, smoking, and opiate overdoses are increasingly being prescribed for weight loss.

These newest weapons in America’s ongoing battle of the bulge are but the latest chapter in the ongoing discussion and debate over off-label use, defined by the Food and Drug Administration (FDA) as “use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labeling.”<sup>2</sup> Off-label use raises several important questions: how prevalent is the trend? Is it legal? To what extent are physicians and drug manufacturers exposed to civil liability for off-label use? This article will address these issues.

### 2. Reported Data on Off-Label Use

Off-label use is prevalent in modern medicine. “Prescriptions for off-label uses of drug products may

account for more than 25% of the approximately 1.6 billion prescriptions written each year, with some recent estimates running as high as 60%.”<sup>3</sup> Certain categories of drugs — particularly those involving the central nervous system — are prone to off-label use. According to a University of Georgia study, “75 percent of antidepressant recipients, 80 percent of anticonvulsant recipients, and 64 percent of antipsychotic recipients received at least one of these medications off-label.”<sup>4</sup> Cancer and AIDS are treated extensively with off-label drugs: 65% of all anticancer drug use is off-label, more than 80% of AIDS patients’ treatment include at least one off-label drug, and more than 40% of all drugs prescribed for AIDS treatment are prescribed off-label.<sup>5</sup> Pediatric treatment is almost entirely off-label; more than 80% of drugs prescribed for children include orphaning clauses, FDA-mandated disclaimers on pediatric use due to the lack of clinical studies involving children.<sup>6</sup>

### 3. Off-Label Use: A Legal Overview

The Food, Drug and Cosmetics Act (FDCA)<sup>7</sup> governs the distribution of prescription medications in interstate commerce. Under the FDCA, new pharmaceutical drugs cannot be distributed through interstate commerce unless the drug’s sponsor proves to the FDA’s satisfaction that the drug is safe and effective for each of its intended uses.<sup>8</sup> “Absent state regulation, once a drug has been approved by the FDA, doctors may prescribe it for indications and in dosages other than those expressly approved by the FDA.”<sup>9</sup> Importantly, “[o]ff-label use does not violate federal law or FDA regulations because the FDA regulates the market-

ing and distribution of drugs in the United States, not the practice of medicine, which is the exclusive realm of individual states.” Notably, several states have statutorily authorized off-label use.<sup>11</sup>

The FDA itself acknowledges that off-label use is permitted: “Neither the FDA nor the Federal government regulate the practice of medicine. Any approved product may be used by a licensed practitioner for uses other than those stated in the product label. Off-label use is not illegal, but means that the data to support that use have not been independently reviewed by the FDA.”<sup>12</sup> A number of courts have confirmed that neither the FDCA nor the FDA “govern medical practice or the legality of a physician’s off-label use of prescription drugs and medical devices.”<sup>13</sup>

As the U.S. Supreme Court stated, the FDA is “charged with the difficult task of regulating the marketing and distribution of medical devices without intruding upon decisions statutorily committed to the discretion of health care professionals.”<sup>14</sup> On the one hand, the FDA prohibits manufacturers from marketing and promoting drugs for off-label uses.<sup>15</sup> On the other hand, physicians are free to prescribe drugs for off-label uses. A key principle in understanding this distinction is the FDA’s “practice-of-medicine policy.” This policy “recognizes that that physicians may, if their medical judgment so dictates, prescribe (but not promote) an approved drug for an unapproved use without violating the Act.”<sup>16</sup> The “practice-of-medicine policy is based on FDA’s long-standing policy of not interfering with the practice of medicine. Most off-label uses of prescription drugs are prescribed by a physician. FDA has made a policy judgment that, because of the involvement of a doctor, FDA will not generally interfere with these off-label uses.” The U.S. Supreme Court indirectly cited the practice-of-medicine policy when it described off-label usage as “an accepted and necessary corollary of the FDA’s mission to regulate

in this area without directly interfering with the practice of medicine.”<sup>18</sup> Indeed – perhaps to further emphasize the policy — the FDCA was amended in 1997, adding that “[n]othing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.”<sup>19</sup>

#### **4. Off-Label Use in Medical Malpractice Cases**

##### **a. In General**

For the reasons set forth above, prescribing pharmaceuticals for “off-label” purposes is not negligence per se; as some commentators have noted, “[t]he pace of medical discovery invariably runs far ahead of FDA’s regulatory machinery, and off-label use is frequently ‘state-of-the-art treatment.’”<sup>20</sup> Indeed, as one American Medical Association official stated, “[i]n some cases, if you didn’t use the drug in the off-label way, you’d be guilty of malpractice.”<sup>21</sup> In short, “[i]t is undisputed that the prescription of drugs for unapproved uses is commonplace in modern medical practice and ubiquitous in certain specialties.”<sup>22</sup>

##### **b. Potential Liability In Cases with Poor Scientific Support?**

While the decision to prescribe a drug for off-label purposes is not illegal, a physician may still be liable in malpractice. As one court explained, “the decision whether to use a drug for an off-label purpose is a matter of medical judgment, not of regulatory approval. By analogy, the off-label use of a medical device is also a matter of medical judgment and, as such, subjects a physician to professional liability for exercising professional medical judgment.”<sup>23</sup>

Most of the medical malpractice claims involving off-label use are “informed consent” cases, in which the plaintiff alleges that the physician breached a duty to disclose the nature of the

proposed treatment, as well as the risks, probable results, and alternatives.<sup>24</sup> More specifically, the plaintiff typically claims that the physician's failure to disclose the "off-label" nature of the proposed treatment violates informed consent rules.<sup>25</sup> Plaintiffs have had little success with "informed consent" claims based on off-label use; the vast majority of courts have determined that the physician has no duty to obtain the patient's informed consent for off-label uses, and have thus adjudicated such claims in the physicians' favor.<sup>26</sup>

One area of potential concern for physicians is the increasing evidence suggesting that many off-label uses lack scientific support. A recent study by the Stanford Prevention Research Center found that 21 percent of the prescriptions for the 160 most common drugs (an estimated 150 million prescriptions) were for off-label use.<sup>27</sup> Notably, 15% of those prescriptions — or 75% of off-label use — were prescribed for uses that lacked scientific support, according to the study's authors.<sup>28</sup> The FDA has cautioned physicians that

Good medical practice and the best interests of the patient required that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use of firm scientific rational and on sound medical evidence, and to maintain records of the product's use and effects."<sup>29</sup>

The quality of medical evidence in support of a particular drug's off-label use can vary widely. As Dr. Mark Fendrick, professor of internal medicine at the University of Michigan School of Medicine in Ann Arbor stated, "[t]he science for off-use can range from very carefully done rigorous trial that

are available in peer-reviewed literature but not submitted the FDA, to anecdotal evidence with no real scientific basis."<sup>30</sup> Without scientific support, physicians' ability to justify off-label uses may come under increasing scrutiny, and may expose them to potential malpractice claims.

## 5. Off-Label Use: The Drug Manufacturer's Perspective

As noted earlier, drug manufacturers may not market or promote drugs for off-label uses.<sup>31</sup> According to the FDA, permitting sponsors to promote off-label uses "would diminish or eliminate incentive to study the use and obtain definitive data; could result in harm to patients from unstudied uses that actually lead to bad results, or that are merely ineffective; would diminish the use of evidence-based medicine; [and] could ultimately erode the efficacy standard."<sup>32</sup> In 1997, the FDA relaxed the rules on off-label promotion, and provides certain new off-label disclosure requirements, including but not limited to:

1. The manufacturer has filed an application with the FDA for this new use;
2. The clinical studies for the new use were published in a scientific journal or other peer-reviewed publication, or a medical reference text;
3. The manufacturer conducted research, or used another manufacturer's research with permission;
4. Within 60 days of dissemination, the manufacturer submits to the FDA:
  - a. The proposed disseminated materials;
  - b. All clinical trial data related to the new use; and
  - c. A disclaimer that the information concerns a use that is not approved by the FDA.<sup>33</sup>

Violations of these rules can result in serious civil and criminal penalties. Most recently, at the end of August 2006, it was reported that Schering-Plough

agreed to pay \$435 million to settle federal civil and criminal charges that it illegally promoted several drugs, including Temador (for treating types of brain cancer that it was not then approved) and Intron A (a hepatitis and cancer drug for superficial bladder cancer).<sup>34</sup> Schering advised the FDA that the “off-label” promotions during 2001 to 2003 were isolated incidents. But, the government alleged that they were part of a national plan in which Schering salespeople were trained in off-label sales tactics including, allegedly, “illegal remuneration” to doctors and “sham advisory boards” and “lavish entertainment” and were paid for doing so.<sup>35</sup>

Drug manufacturer Serono settled similar charges last year involving its AIDS drug Serotism and in 2004, Warner-Lambert (now owned by Pfizer), also settled similar claims.<sup>36</sup>

On May 14, 2004, Warner-Lambert “agreed to plead guilty and pay more than \$430 million to resolve criminal charges and civil liabilities in connection with its Parke-Davis division’s illegal and fraudulent promotion of unapproved uses for one of its drug products[.]”<sup>37</sup> The government claimed that Warner-Lambert engaged in a number of improper tactics to market Neurontin for off-label purposes, including:

1. Encouraging sales representatives to provide one-on-one sales pitches to physicians about off-label uses of Neurontin;
2. Making false and misleading statements about Neurontin’s off-label uses;
3. Hiring medical liaisons to falsely promote themselves as experts on a particular disease in order to promote off-label uses for Neurontin;
4. Paying exorbitant consulting fees to physicians to attend presentations about Neurontin’s off-label uses;
5. Encouraging sales representatives to provide call-in numbers to doctors to hear about off-label uses of Neurontin;
6. Sponsoring “independent medical education” courses on off-label uses for Neurontin, with extensive Warner-Lambert input in topics, speakers, and content; and
7. Planting people in the audience at “independent medical education” to ask questions that highlighted the off-label benefits of the drug.<sup>38</sup>

In addition to the Department of Justice’s civil and criminal allegations, Warner-Lambert’s alleged tactics in promoting Neurontin spawned a slew of lawsuits from consumers, insurers, and other third party payees. Recently, insurers filed a RICO claim against Warner-Lambert (now owned by Pfizer) under the federal RICO statute. The MDL Court allowed some of the claims to survive Pfizer’s motion to dismiss, thereby subjecting Pfizer to significant potential damages.<sup>39</sup>

## 6. Conclusion

Off-label uses are an important part of modern medicine, and are often the first line of medical treatment for various conditions, including pediatric disease, AIDS, and cancer. Although physicians are entitled to prescribe FDA-approved medicines for unapproved purposes, physicians should be aware of the scientific evidence (or lack thereof) supporting an off-label use, or risk serious consequences, including malpractice claims. Drug manufacturers must be aware of the often fine line that exists between appropriate and inappropriate sales, marketing, and promotion activities, or risk significant criminal and/or civil exposure. In sum, off-label use is a controversial issue, with strong policy, medical, and economic arguments on both sides of the debate. Drug manufacturers, physicians, and the federal government must continue to work together to strike a balance between the freedom, innovation, and cost-effectiveness that off-label use provides, while still being mindful of the safety, efficacy, and evidence-based medicine goals that FDA regulations promote.

- <sup>1</sup> Elizabeth Bernstein, A New Breed of 'Diet' Pills, Wall St. J., Aug. 22, 2006, at D1.
- <sup>2</sup> Janet Woodcock, M.D., A Shift In The Regulatory Approach, <http://fda.gov/cder/present/diamontreal/regappr/sld003.htm>.
- <sup>3</sup> James M. Beck & Elizabeth D. Azari, FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions, 53 Food & Drug L.J. 71, 80 (1998) (internal quotes and citations omitted).
- <sup>4</sup> Medical News Today, UGA Researchers Find High Rates of off-label prescriptions: Antidepressant, Anticonvulsant, and Anti-psychotic Drugs, <http://medicalnewstoday.com/medicalnews.php?newsid=48087>.
- <sup>5</sup> Beck & Azari, supra, at 80, fns. 74 & 76.
- <sup>6</sup> Id. at 80, fn. 81.
- <sup>7</sup> 21 U.S.C. §§ 301-397.
- <sup>8</sup> See 21 U.S.C. § 355(a) and (d); see also U.S. ex rel. Franklin v. Parke-Davis, 147 F.Supp.2d 39, 44 (D.Mass. 2001).
- <sup>9</sup> Planned Parenthood Cincinnati Region v. Taft, 444 F.3d 502, 505 (6th Cir. 2006).
- <sup>10</sup> Id.
- <sup>11</sup> Beck & Azari, supra, at 76, fn.56 (citing state statutes).
- <sup>12</sup> U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Oncology Tools: A Short Tour, <http://fda.gov/cder/cancer/tour.htm>.
- <sup>13</sup> Baker v. Smith & Nephew Richards, Inc., 1999 WL 811334, \*7 (Tex. Dist.Ct.,1999); see also Staudt v. Froedtert Mem'l Lutheran Hosp., 580 N.W.2d 361, 363 (Wisc.App.1998); Femrite v. Abbott Northwestern Hosp., 568 N.W.2d 535, 542 (Minn.App. 1997); Klein v. Biscup, 673 N.E.2d 225, 231 (Ohio App. 1996); In re Litig Orthopedic Bone Screw Prod. Liab., 1996 WL 107556, at \*3, 1996 U.S. Dist. LEXIS 2825, LEXIS slip op. at \*10 (E.D.Pa. Mar. 8, 1996); Weaver v. Reagen, 886 F.2d 194, 198 (8th Cir.1989); United States v. Evers, 453 F.Supp. 1141, 1149-50 (M.D.Ala.1978), aff'd, 643 F.2d 1043 (5th Cir.1981); 21 U.S.C. § 906; 59 Fed.Reg. 59820, 59821 (FDA Nov. 18, 1994).
- <sup>14</sup> Buckman Co. v. Plaintiffs' Legal Cmte., 531 U.S. 341, 350 (2001).
- <sup>15</sup> 21 U.S.C. § 331(a) and (d); U.S. ex rel. Franklin v. Parke-Davis, 147 F.Supp.2d 39, 44 (D.Mass. 2001); see also Washington Legal Foundation v. Henney, 202 F.3d 331, 333 (D.C.Cir. 2000) (drug manufacturers "misbrands" a drug when labeling includes non-FDA approved uses).
- <sup>16</sup> 61 FR 44619, 45182 (Aug. 28, 1996) (citing 37 FR 16503 (Aug. 15, 1972)).
- <sup>17</sup> Id.
- <sup>18</sup> Buckman Co. v. Plaintiffs' Legal Cmte., 531 U.S. 341, 350 (2001).
- <sup>19</sup> Food and Drug Administration Modernization Act of 1997, 111 Stat. 2296 (Nov. 21, 1997); 21 U.S.C. § 396.
- <sup>20</sup> Richardson v. Miller, 44 S.W.3d 1, 13, fn. 11 (Tenn. Ct. App. 2000).
- <sup>21</sup> Beck & Azari, supra, at 80, fns. 73 and 82; see also Richardson, 44 S.W.3d at 13, fn.11 ("In some circumstances, an off-label use of a particular drug or device may even define the standard of care.")
- <sup>22</sup> Washington Legal Foundation v. Henney, 202 F.2d 331, 333 (D.C. Cir. 2000).
- <sup>23</sup> Klein v. Biscup, 673 N.E.2d 225, 231 (Ohio App. 1996)
- <sup>24</sup> Beck & Azari, supra at 87, fn. 128-130 (citing state cases and statutes).
- <sup>25</sup> See, e.g., Southard v. Temple Hospital, 781 A.2d 101 (Pa. 2001); Blazoski v. Cook, 787 A.2d 910 (N.J.Super. 2002); Sita v. Long Island Jewish-Hillside Medical Center, 22 A.D.3d 743, 744 (N.Y.A.D. 2005); Beck & Azari, supra, at 91-99 (discussing the informed consent doctrine under Pennsylvania, Tennessee, and California state law)
- <sup>26</sup> Id.
- <sup>27</sup> Rita Rubin, Study: Off-label drugs often prescribed, [http://www.usatoday.com/news/health/2006-05-08-offlabel-drugs\\_x.htm](http://www.usatoday.com/news/health/2006-05-08-offlabel-drugs_x.htm).
- <sup>28</sup> Id.
- <sup>29</sup> U.S. Food and Drug Administration, Off-Label and Investigational Use of Marketed Drugs, Biologics, and Medical Devices, <http://www.fda.gov/oc/ohrt/irbs/offlabel.html> (emphasis added).
- <sup>30</sup> Forbes.com, 'Off-Label' Prescription Drug Use Common, <http://www.forbes.com/forebeslife/health/feeds/hscout/2006/05/08/hscout532598.html>.
- <sup>31</sup> 21 U.S.C. § 331(a) and (d); U.S. ex rel. Franklin v. Parke-Davis, 147 F.Supp.2d 39, 44 (D.Mass. 2001); see also Washington Legal Foundation v. Henney, 202 F.3d 331, 333 (D.C.Cir. 2000) (drug manufacturers "misbrands" a drug when labeling includes non-FDA approved uses).
- <sup>32</sup> Janet Woodcock, M.D., A Shift In The Regulatory Approach, <http://fda.gov/cder/present/diamontreal/regappr/sld006.htm>.
- <sup>33</sup> Food and Drug Modernization Act of 1997, 111 Stat. 2296, 2356-2365; 21 U.S.C. § 360aaa et seq.
- <sup>34</sup> Julie Schmit, Schering-Plough to Pay \$435M Settlement, [http://usa-today.com/money/industries/health/drugs/2006-08-29-schering-settles\\_x.htm](http://usa-today.com/money/industries/health/drugs/2006-08-29-schering-settles_x.htm)
- <sup>35</sup> Id.
- <sup>36</sup> Id.
- <sup>37</sup> U.S. Department of Justice, Warner-Lambert to Pay \$430 Million to Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion, [http://www.usdoj.gov/opa/pr/2004/May/04\\_civ\\_322.htm](http://www.usdoj.gov/opa/pr/2004/May/04_civ_322.htm).
- <sup>38</sup> Id.
- <sup>39</sup> In re Neurontin Marketing, Sales Practices and Products Liability Litigation, 433 F.Supp.2d 172 (D.Mass. 2006)

Daniel S. Wittenberg is a partner with Snell & Wilmer, L.L.P. in Denver, Colorado. His practice is concentrated in defending medical device, pharmaceutical and consumer product companies in product liability litigation as well as representing businesses in commercial litigation. Dan's email is [dwittenberg@swlaw.com](mailto:dwittenberg@swlaw.com).

Brendan M. Ford is an associate with Snell & Wilmer, L.L.P. in the firm's Orange County, California office. His practice is concentrated in product liability litigation.

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