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## Off-Label Promotion: Government Theories of Prosecution and Facts That Drive Them

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# Off-Label Promotion: Government Theories of Prosecution and Facts That Drive Them\*

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The Department of Justice (DOJ) and the U.S. Attorneys' Offices enforce the criminal laws which, among other things, prohibit pharmaceutical or medical device manufacturers from engaging in schemes to defraud or intentionally disseminating false and misleading information. In recent years, they have also undertaken to criminally prosecute companies and individuals who promote approved drugs for off-label uses—despite the fact that there is not a statute or meaningful body of case law that clearly criminalizes this conduct.<sup>1</sup> Thus, the government is investigating and prosecuting the off-label promotion of approved drugs, in effect undertaking a series of novel and aggressive prosecutions, using a virtually untested legal formulation.

In addition to the legal issues attendant to these prosecutions, there is also a troubling tension between such aggressive enforcement in an unclear legal environment and the public interest served by the dissemination of scientific information concerning off-label uses for approved prescription drugs or medical devices. As discussed at length in other chapters of this book, off-label use of approved drugs and devices ensures that patients receive the best available medical care, and industry plays a critical role in disseminating this information.

It is well accepted as a matter of public policy that it is legal for a doctor to prescribe a drug for off-label uses and that it is likewise legal for a company to sell a drug to a doctor, knowing that the doctor may use the drug for an off-label use. Thus, “[t]he Department [of Justice] recognizes that once a drug has been approved by the Food and Drug Administration (FDA) for a medical condition, a healthcare practitioner may lawfully prescribe the drug for any use, regardless of whether FDA has determined that drug to be safe and effective for that use.”<sup>2</sup>

More than just being legally permissible, the off-label use of approved drugs is an indispensable component of effective medical treatment. The American Medical Association (AMA) has recognized that “[u]p-to-date, clinically appropriate medical practice at times requires the use of pharmaceuticals for ‘off-label’ indications

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<sup>1</sup> See, e.g., *Underwood v. Rhone-Poulenc Rorer Pharm.*, 890 So.2d 429, 431 (Fla. App. 2004) (“Although authority is sparse, we conclude that nothing in the FDCA actually prohibits manufacturers from promoting off-label uses.”); *Long v. Rhone-Poulenc Rorer Pharm.*, 1999 WL 680867, at \*3 (N.D. Ohio Feb. 23, 1999) (finding “no clear public policy against off-label promotion”).

<sup>2</sup> Letter from Peter D. Keisler, Assistant Attorney General, U.S. Department of Justice, to David Price, Senior Vice President, Legal Affairs, Washington Legal Foundation (Oct. 5, 2004) *citing* Robert D. McCallum, Jr., Esq., Associate Attorney General, U.S. Department of Justice, Department of Justice Update Regarding the Prosecution of Pharma, Biotech and Device Cases, Speech at The Pharma, Biotech and Device Colloquium, Princeton University (June 9, 2004).

as distinct from the specific approved indication(s) from the U.S. Food and Drug Administration . . . .”<sup>3</sup> FDA “acknowledges that off-label uses of drugs by prescribers is often appropriate and may represent the standard of practice.”<sup>4</sup> It has also acknowledged that, “the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert . . . .”<sup>5</sup>

Similarly, the courts and Congress have also emphasized the important role in effective medical treatment played by off-label use. As the Supreme Court has said, off-label use “is an accepted and necessary corollary of the FDA’s mission to regulate in this area without directly interfering with the practice of medicine. . . . Off-label use is widespread in the medical community and often is essential to giving patients optimal medical care, both of which medical ethics, FDA, and most courts recognize.”<sup>6</sup> In 1997, Congress enacted 21 U.S.C. § 396 which explicitly provides that “[n]othing in [the Food Drug and Cosmetic Act] shall be construed to limit or interfere with the authority of a healthcare practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate healthcare practitioner-patient relationship,” in effect preempting any effort to limit the ability of physicians to prescribe FDA-approved products for off-label uses.

In order for physicians to make appropriate choices about new off-label uses, it is, of course, essential that they be properly educated about them. The drug industry plays a critical role in advising the medical profession and the public about these advances. Drug companies have both the economic interest and the resources to provide the continuing medical education (CME) that the profession needs to stay current with the appropriate uses of both old and new medications. Industry involvement guarantees the prompt dissemination of information to the medical community. It is, after all, industry that often has the most profound and earliest knowledge about new developments in the drugs that it markets. As the AMA has recognized, “[i]t is imperative that physicians have access to accurate and unbiased information about unlabeled uses of prescription drugs. . . . Dissemination of independently derived scientific information about unlabeled uses by manufacturers to physicians can help physicians have access to the latest, scientifically credible information.”<sup>7</sup>

With these public policies in mind, this chapter will focus on how the scientific exchange of information and off-label promotion are treated under FDA regulations and the Federal Food, Drug, and Cosmetic Act (FDCA), with some attention to the role of the False Claims Act. We will then review recent criminal cases, and how they were resolved, to gain insight into where the law on off-label communications may be headed.

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<sup>3</sup> AMA House of Delegates, Resolution 820 (Sept. 21, 2005), *available at* [www.ama-assn.org/meetings/public/interim05/820i05.doc](http://www.ama-assn.org/meetings/public/interim05/820i05.doc).

<sup>4</sup> Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, Lecture to Drug Information Association, A Shift in the Regulatory Approach (June 23, 1997), *available at* <http://www.fda.gov/cder/present/diamontreal/regappr/sld005.htm>.

<sup>5</sup> Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16,503, 16,503 (Aug. 15, 1972).

<sup>6</sup> *Buckman Co. v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 350-51 (2001) (in part quoting James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 *FOOD & DRUG L.J.* 71, 72 (1998)).

<sup>7</sup> Summaries and Recommendations of Council on Scientific Affairs Reports, 1997 AMA Annual Meeting, *available at* <http://www.ama-assn.org/ama1/pub/upload/mm/443/csa-97.pdf>.

## I. THE FALSE CLAIMS ACT AND OFF-LABEL PROSECUTIONS

The emergence of government investigations and prosecutions of off-label promotion is based in large part on the expanding use of the False Claims Act (FCA),<sup>8</sup> which prohibits the filing of false claims for payment by the federal government.<sup>9</sup> The FCA, also known as the Qui Tam Statute,<sup>10</sup> allows private citizens—often referred to as relators or whistle-blowers—to sue FCA violators on behalf of the government.

Qui tam suits under the FCA are initially filed under seal while DOJ investigates the relator's allegations and decides whether to intervene. If DOJ chooses to intervene, it takes over the litigation.<sup>11</sup> Even if DOJ declines intervention, the relator may choose to litigate the case on his or her own. The case has a much greater chance of success, however, if DOJ intervenes because of its authority over contracting and Medicare matters. The reward—or the incentive—for successful relators is typically between 15 to 30 percent of total government recovery, in addition to attorneys' fees and costs.

In the context of off-label promotion in the pharmaceutical industry, the typical qui tam suit under the FCA will allege that a drug manufacturer induced, by promoting off-label use(s) of a drug, the filing of a fraudulent claim for reimbursement from a governmental entity, often Medicare or Medicaid. The recent upsurge in such claims has undoubtedly exposed drug manufacturers to enormous new costs and risks. Indeed, in the past few years, numerous drug manufacturers have paid settlements in the range of hundreds of millions to even billions of dollars as a result of off-label promotion allegations brought by qui tam relators.

Once a potential cause of action has been brought to the attention of the federal government, it has the option of investigating the case as a civil or a criminal matter. Although the FCA's counterpart at 18 U.S.C. § 287 (Criminal FCA) imposes criminal liability for false claim submissions to the government,<sup>12</sup> it appears that the government declines to use the Criminal FCA in the off-label arena because the "false claims" theory is too attenuated for use in a criminal prosecution. Instead, criminal investigations of alleged off-label promotion are often conducted based on the provisions of the FDCA, 21 U.S.C. §§ 331 *et seq.*, which, *inter alia*, sets forth prohibited acts, penalties, and related provisions.

In terms of civil FCA cases, it is interesting to note two divergent recent developments. On the one hand, a number of courts have recently dismissed FCA qui tam complaints in the face of Federal Rule of Civil Procedure 12(b)(6) motions to dismiss where the complaint failed to allege the actual submission of a specific false claim to the government. For example, recently, in *U.S. ex rel. Roop v. Hypoguard*

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<sup>8</sup> 31 U.S.C. §§ 3729 *et seq.*

<sup>9</sup> The FCA provides for liability for triple damages and a \$5,500 to \$11,000 penalty per claim for anyone who knowingly submits or causes the submission of a false or fraudulent claim to the federal government. *Id.* § 3729(a).

<sup>10</sup> "Qui tam" is shorthand reference to the Latin phrase "qui tam pro domino rege quam pro seipso," which means, "he who sues for the king as for himself." The FCA/Qui Tam Statute was enacted during the Civil War to thwart fraudulent suppliers to the Union military at a time when the war made it difficult for the government to investigate and prosecute the fraud itself.

<sup>11</sup> DOJ does not intervene in just any case. In fact, less than 25 percent of qui tam suits result in intervention by DOJ.

<sup>12</sup> 18 U.S.C. § 287 provides: "Whoever makes or presents to any person or officer in the civil, military, or naval service of the United States, or to any department or agency thereof, any claim upon or against the United States, or any department or agency thereof, knowing such claim to be false, fictitious, or fraudulent, shall be imprisoned not more than five years and shall be subject to a fine in the amount provided in this title."

*USA, Inc.*,<sup>13</sup> the Eighth Circuit held that the relator's First Amended Complaint "failed to cure deficiencies in the initial Complaint" because it "did not plead with particularity the details of any false Medicare reimbursement claim presented to, or paid by, the United States or its agent. . . ."<sup>14</sup>

On May 20, 2009, however, President Obama signed into law the Fraud Enforcement and Recovery Act (FERA), which, among other things, revises the civil liability provisions of the FCA. These revisions will significantly expand the scope of the FCA, enabling the government and qui tam relators to pursue wrongdoing related to a federal program, regardless of whether there is actually a false claim made to the government. Recovery against FCA defendants will undoubtedly be easier due to these FCA revisions, which provide that, among other things: 1) liability can attach even if the alleged false claim is presented to a private intermediary and not directly to the government; 2) liability can attach even where the defendant did not have specific intent to defraud the government; 3) the definition of "claim" is broadened to include any request or demand for money, whether or not the government has title to that money or property; and 4) the statute of limitations for the government will "relate back" to the date of the relator's original complaint, meaning that the time spent by the government investigating the relator's allegations prior to intervention cannot be used as a basis for a statute-of-limitations defense.

Although a civil investigation and resolution under the FCA can result in massive fines for a company or an individual, a companion criminal investigation brings other investigative and punitive tools to bear. For example, a criminal investigation allows the government to collect evidence using the full panoply of criminal investigative tools such as the grand jury, search warrants, and the like. A company that is criminally convicted can face mandatory exclusion from Medicare and state healthcare programs.<sup>15</sup> Because this sort of sanction is a literal death knell for many pharmaceutical companies, even the threat of a criminal prosecution can be a powerful incentive for a company to resolve pending civil and criminal investigations on terms favorable to the government simply to avoid the risk of exclusion. Further, resolutions of criminal investigations can often include additional large sums of money in the form of criminal fines and the implementation of corporate integrity agreements which can afford the government leverage over these companies for years to come. Thus, the investigative tools available for a criminal investigation, the additional potential sanctions, and the always terrifying threat of exclusion and the leverage that it brings, all make a companion criminal investigation an attractive option to the government once it has determined to pursue an FCA complaint.

## II. THE FDCA AS A BASIS FOR CRIMINALLY PROSECUTING OFF-LABEL PROMOTION

The government's theories of criminal prosecution to address allegations of off-label marketing are premised on both the "new drug" (21 U.S.C. § 331(d)) and "misbranding" (21 U.S.C. § 331(a)) provisions of the FDCA.<sup>16</sup> A discussion of each follows.

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<sup>13</sup> 559 F.3d 818, 825-26 (8th Cir. 2009).

<sup>14</sup> See also U.S. ex rel. Hopper & Hutto v. Solvay Pharm., Inc., 590 F. Supp. 2d 1352, 1359, 1361 (11th Cir. 2008) (observing that "in *qui tam* actions like this one, a False Claims Act count must, in order to satisfy Rule 9(b)'s particularity requirement, allege a false claim that was actually submitted to the government") (citing *Mitchell v. Beverly Enterprises, Inc.*, 248 Fed. Appx. 73, 2007 WL 2551404 (unpub. dec.), *reh'g en banc denied*, 255 Fed. Appx. 504 (11th Cir. 2007); U.S. ex rel. *Atkins v. McInteer*, 470 F.3d 1350, 1356 n.10 (11th Cir. 2006); *Corsello v. Lincare, Inc.*, 428 F.3d 1008 (11th Cir. 2005), *cert. denied*, 127 S. Ct. 42 (2006); U.S. ex rel. *Clausen v. Laboratory Corp. of America, Inc.*, 290 F.3d 1301 (11th Cir. 2002), *cert. denied*, 537 U.S. 1105 (2003). See also United States ex rel. *Rost v. Pfizer, Inc.*, 507 F.3d 720 (1st Cir. Mass. 2007).

<sup>15</sup> 42 U.S.C. § 1320a-7.

<sup>16</sup> 21 U.S.C. §§ 301 et seq.

### A. *Unapproved “New Drug”*

The introduction of an unapproved new drug into interstate commerce is prohibited by 21 U.S.C. § 331(d). To prove a misdemeanor violation of the new drug provision, the government must prove the following beyond a reasonable doubt:

- that the defendant introduced a drug into interstate commerce, and
- that the drug qualified as a “new” drug.

To allege a felony, the government would also have to prove that the defendant acted with the intent to defraud or mislead.

For purposes of the FDCA, the term “new drug” is a defined term with a statutory definition that distinguishes a “new drug” from a “drug.”<sup>17</sup> The FDCA defines a “new drug”<sup>18</sup> as: “(1) Any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . .”<sup>19</sup> To sustain a charge that a drug manufacturer violated the “new drug” provision of the FDCA, the government must show that the company distributed “labeling” that “accompanied” the drug and that the labeling “prescribed, recommended or suggested” the drug for an unapproved use.

By the definition, whether a substance qualifies as a “new drug” is determined by its labeling.<sup>20</sup> If a drug is not accompanied by “labeling” that “prescribes, recommends or suggests” the drug for an unapproved use then the drug is not a “new drug” for purposes of the act and the “new drug” provisions of the act will not be a basis for criminal liability.

Because new drug status turns on labeling, it is necessary to determine what materials constitute labeling. The FDCA defines “labeling” as “all labels and other written, printed, or graphic matter: (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.”<sup>21</sup> The statutory definition of labeling encompasses only written materials and this construction is supported by the case law.<sup>22</sup>

Not all written information about off-label uses is labeling simply because it is disseminated by a manufacturer. If it were, the criminal laws would be violated each and every time a company disseminated information about off-label uses—a prac-

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<sup>17</sup> In pertinent part, the FDCA defines “drug” as “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals. . . and articles (other than food) intended to affect the structure or any function of the body of man or other animals. . . .” 21 U.S.C. § 321(g)(1)(B) and (C).

<sup>18</sup> 21 U.S.C. § 321(p).

<sup>19</sup> 21 C.F.R. § 310.3 then, in pertinent part, states that “[t]he newness of a drug may arise by reason (among other reasons) of . . . [t]he newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body.” 21 C.F.R. § 310.3(h)(4). A new drug must be approved prior to its being affirmatively marketed.

<sup>20</sup> 21 U.S.C. § 321(p).

<sup>21</sup> 21 U.S.C. § 321(m).

<sup>22</sup> See, e.g., *V.E. Irons, Inc. v. United States*, 244 F.2d 34, 39 (1st Cir. 1957) (labeling includes all literature used in the sale of food and drugs, whether or not it is shipped into interstate commerce along with the article); *Washington Legal Found. v. Friedman (WLF I)*, 13 F. Supp. 2d 51, 55 (D.D.C. 1998) (labeling includes package insert and “nearly every form of drug company promotional activity, including booklets, pamphlets, mailing pieces, bulletins, and all literature that supplements, explains, or is otherwise textually related to the product”).

tice that is common, lawful, and sanctioned by FDA. Rather it is clear—under the statute, under FDA guidance, and under First Amendment analysis—that written materials disseminated by third-party providers independent of the company, or fair and balanced materials disseminated by the company in response to unsolicited requests, are not labeling. This was recognized by FDA in its 1997 Guidance which explicitly stated that while “promotional labeling” ordinarily includes any written materials disseminated by a manufacturer, it does not generally include “the materials [that] are prepared and disseminated by the [third-party] provider for educational purposes, or the materials [that] are disseminated by the company in response to an unsolicited request . . . .”<sup>23</sup> Indeed, as discussed further below, FDA in its recent “Good Reprint Practices” Guidance (issued in January 2009) has indicated support for the dissemination of balanced, scientific materials concerning off-label uses, though subject to certain conditions.<sup>24</sup>

Even if scientific materials could lawfully constitute labeling, the labeling would still need to have “accompanied” the product to establish this element of the statute. “Accompanying” is not defined in the FDCA itself or in any applicable regulation. “[T]he definitive test of whether literature can be said to accompany an article and thus constitute labeling within the meaning of the Act”<sup>25</sup> was set forth in *Kordel v. United States*.<sup>26</sup> In *Kordel*, the Supreme Court stated:

One article or thing is accompanied by another when it supplements or explains it, in the manner that a committee report of the Congress accompanies a bill. No physical attachment is necessary. It is the textual relationship that is significant.<sup>27</sup>

In its decision, the Court further stated:

In this case the drugs and the literature had a common origin and a common destination. The literature was used in the sale of the drugs. It explained their uses. Nowhere else was the purchaser advised how to use them.

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<sup>23</sup> 1997 Guidance, 62 Fed. Reg. 64,074, 64,091 (Dec. 3, 1997). Note that there is case law that suggests that under certain circumstances, third-party materials distributed by a manufacturer can become labeling if the materials are used to promote a product. Each of these cases, however, was decided before the 1997 FDA Guidance and none undermines the proposition that scientific literature authored by third parties or summarized by a company in a fair, balanced, and comprehensive way does not constitute labeling, so long as the materials are separate from the marketing or promotional function. Rather, these cases involve third-party statements that were excerpted and included in promotional materials used to market the product. *See, e.g., V.E. Irons, Inc. v. United States*, 244 F.2d 34, 40 n.6 (1st Cir. 1957) (where quotes from third party were excerpted for use in promotional literature used by the company to market the natural vitamin products, writings of other authors can become the labeling of the dispenser “so long as these writings are quoted with approval” by the dispenser); *United States v. 353 Cases Mountain Mineral Water*, 247 F.2d 473, 478 (8th Cir. 1957) (labeling where pamphlets were printed to promote the sale of water and were “useful for no other purpose”); *United States v. Diapulse Mfg. Corp.*, 389 F.2d 612, 616 (2d Cir. 1968) (in device case, scientific literature can constitute labeling where it supplements or explains the device); *United States v. Sene X. Eleemosynary Corp.*, 479 F. Supp. 970, 980 (S.D. Fla. 1979) (advertising materials “incorporating” newspaper articles and third-party publications were “labeling”). The import of these cases is that third-party literature can become labeling based on how it is used by the company manufacturing or distributing the product.

<sup>24</sup> *See* FDA’s 2009 Guidance entitled “Good Reprint Practices 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,” 74 Fed. Reg. 1694 (Jan. 13, 2009).

<sup>25</sup> *United States v. Article of Drug Consisting of 47 Bottles*, 320 F.2d 564, 568 (3d Cir. 1963).

<sup>26</sup> 335 U.S. 345 (1948).

<sup>27</sup> *Id.* at 350.

It constituted an essential supplement to the label attached to the package. Thus the products and the literature were interdependent . . . .<sup>28</sup>

The Court further recognized that “[t]he . . . literature in the present case was designed for use in the distribution and sale of the drug, and it was so used . . . ,” and further, that “the booklet and drugs were . . . interdependent; they were parts of an integrated distribution program.”<sup>29</sup>

Courts applying the *Kordel* formulation have consistently recognized that the hallmark of “labeling” that “accompanies” a product is the overt use of the labeling to promote the product to the ultimate consumer.<sup>30</sup> In terms of assessing whether a product and particular literature are part of an “integrated distribution program,” a number of courts have at least suggested that finding the product and literature to be part of an integrated distribution program is necessary, although perhaps not alone sufficient to establish that the literature accompanied the product.<sup>31</sup> Further, the concept of an “integrated distribution program” seems to encompass the idea that the information contained in the literature must be textually related and supplemental to the product at issue.<sup>32</sup>

Finally, First Amendment considerations lead to the same conclusion as the statutory analysis, a factor that undoubtedly bears on FDA’s recognition in the 1997 Guidance that such independent scientific material is not “labeling.” As the court recognized in *Washington Legal Foundation v. Friedman (WLF I)*,<sup>33</sup> it is “beyond dispute” that—outside the context of off-label promotion—“CME seminars, peer-reviewed medical journal articles and commercially available medical textbooks merit the highest degree of constitutional protection.”<sup>34</sup> It cannot be, the court reasoned, that the same is “inherently misleading” or otherwise outside the realm of speech protected by the First Amendment when the drug manufacturer is the sponsor, but be an important contribution to scientific thought when sponsored by anyone else.<sup>35</sup>

For a new drug prosecution to be successful, the government must also prove that there was labeling that “prescribed, recommended, or suggested” off-label uses.<sup>36</sup>

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<sup>28</sup> *Id.* at 348.

<sup>29</sup> *Id.* at 350.

<sup>30</sup> *See, e.g.,* *United States v. 250 Jars, Etc. of U.S. Fancy Pure Honey*, 218 F. Supp. 208, 211-12 (E.D. Mich. 1963) (literature was mailed “in order to promote the sale of the seized honey”); *United States v. 24 Bottles*, 338 F.2d 157, 159 (2d Cir. 1964) (literature not labeling because not used, among other things, to promote the sale of the product); *United States v. 353 Cases*, 247 F.2d 473, 478 (8th Cir. 1957) (literature “accompanied” product because, among other things, the literature had been printed for the purpose of promoting the product).

<sup>31</sup> *See, e.g.,* *United States v. Guardian Chem. Corp.*, 410 F.2d 157, 161 (2d Cir. 1969) (literature and product do not have to ship together as long as the distribution of the drug and the brochures are parts of an “integrated distribution program”); *Founding Church of Scientology of Washington D.C. v. United States*, 409 F.2d 1146, 1157 (D.C. Cir. 1969) (interpreting *Kordel* to hold that “accompanying” requires that literature be “designed for use in the distribution and sale of” the product and that the two must be “parts of an integrated distribution program”).

<sup>32</sup> *See, e.g., 47 Bottles*, 320 F.2d at 568 (finding “integrated distribution program” given “textual relationship and supplemental nature of the literature” to the drug); *Alberty Food Products Co. v. United States (Alberty I)*, 185 F.2d 321, 325 (9th Cir. 1950) (interpreting *Kordel* to hold that integrated distribution program requires literature to be “an essential supplement to the label attached to the package containing the drug” and finding no integrated distribution program where advertising too remote to product).

<sup>33</sup> 13 F. Supp. 2d 51, 74 (D.D.C. 1998).

<sup>34</sup> 13 F. Supp. 2d at 62.

<sup>35</sup> *Id.* at 67.

<sup>36</sup> 21 U.S.C. § 321(p)(1).

The meaning of “recommended, prescribed and suggested” is rarely discussed in the case law, perhaps because the phrase so readily lends itself to a common-sense interpretation. The words “recommend,” “prescribe,” and “suggest” by definition connote a sense of proactive advocacy. In other words, a fair reading of the language of the statute compels the conclusion that written materials must go beyond the objective reporting of scientific information to constitute literature that “prescribes, recommends or suggests” for purposes of the statute, even if the reported information is generally favorable.

## B. *Misbranding*

The FDCA prohibits the introduction of misbranded drugs into interstate commerce.<sup>37</sup> For the government to prove a misdemeanor violation of this statutory provision, it would have to prove the following beyond a reasonable doubt:

- that the defendant introduced a drug into interstate commerce, and
- that the drug was misbranded.

In addition, to allege a felony violation, the government would also have to prove that the defendant acted with the intent to defraud or mislead.<sup>38</sup>

In terms of proving that the drug was misbranded, the government has generally identified two provisions of the misbranding statute, sections 352(a) and 352(f), that it believes it can use to prosecute the off-label promotion of drugs and medical devices. Pursuant to these statutory provisions, a drug is deemed “misbranded” under the FDCA if its “labeling” bears “inadequate directions for use,” 21 U.S.C. § 352(f), or if its “labeling” is “false or misleading,” 21 U.S.C. § 352(a). A discussion of each provision follows.

### 1. *Inadequate Directions for Use*

In a prosecution for off-label promotion based on the “inadequate directions for use” provision of the misbranding statute, the government would likely rely on 21 C.F.R. § 201.5, which defines “adequate directions for use” as “directions under which the layman can use a drug safely and for the purpose for which it is intended.” Thus, according to the government’s prosecution theory, an analysis of “adequate directions for use” under the misbranding statute requires an examination of the drug’s “intended use.”<sup>39</sup>

The “intended use” of a drug can be determined from a wide range of sources, including the oral representations of a drug company or its sales agents.<sup>40</sup> Indeed, the federal regulations provide an extraordinarily broad definition of “intended uses”:

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<sup>37</sup> 21 U.S.C. § 331(a).

<sup>38</sup> *See, e.g.*, *United States v. Arlen*, 947 F.2d 139, 143 (5th Cir. 1991).

<sup>39</sup> This position is supported by case law. *See, e.g.*, *United States v. Article of Drug*, 362 F.2d 923, 925 (3d Cir. 1966) (“Whether labeling contains ‘adequate directions for use’ of an article necessarily depends upon what it is intended to be used for.”); *Alberty Food Products v. United States*, 194 F.2d 463, 463-64 (9th Cir. 1952) (affirming that misbranding occurs when a drug’s labeling fails “to enumerate the disease conditions for which said drug is intended and offered to the public.”).

<sup>40</sup> *See, e.g.*, *United States v. Article*, 409 F.2d 734, 739 (2d Cir. 1969) (“It is well settled that the intended use of a product may be determined from its label, accompanying labeling, promotional material, advertising and any other relevant source.”) (citations omitted).

The words “intended uses” or words of similar import in §§ 201.5 . . . refer to the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons’ expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. . . . But if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.<sup>41</sup>

Therefore, if any conduct by a manufacturer or its sales agents, including oral statements, suggests an intent that its drug product be used off label, then the drug would arguably be misbranded under section 352(f) because the drug’s labeling would not have “adequate directions” for such off-label use.<sup>42</sup>

It should be noted that there is a very untested, but interesting argument that properly distributed prescription drugs are exempt from 21 U.S.C. § 352(f), the “adequate directions for use” provision of the misbranding statute. “[P]rescription drugs were exempted from the requirements of [§ 352](f).”<sup>43</sup> If true, a criminal prosecution based on the sale of a prescription product could not be based on section 352(f).

Under 21 U.S.C. § 352(f), a drug is deemed to be misbranded “[u]nless its labeling bears . . . adequate directions for use . . . .” However, under 21 U.S.C. § 353, captioned “Exemptions . . . for certain drugs,” there are two relevant exemptions, which, taken together, exempt prescription drugs prior to the time they are dispensed if certain conditions are met and then, after dispensing, if certain additional conditions are met. Specifically, section 353(b)(2) provides that prescription drugs are exempt from section 352(f):

if the drug bears a label containing the name and address of the dispenser, the serial number and date of the prescription or of its filling, the name of the prescriber, and, if stated in the prescription, the name of the patient, and the directions for use and cautionary statements, if any, contained in such prescription.<sup>44</sup>

In other words, as long as the pharmacist or other dispenser of a prescription puts the *prescriber’s* directions (if there are any) on the label, no other directions for use are required. This is consistent with the statute’s focus on giving directions for use to the patient, not to the physician. Prior to being dispensed by the phar-

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<sup>41</sup> 21 C.F.R. § 201.128.

<sup>42</sup> A possible counterargument to this “intended use” prosecution theory is that it improperly relies on agency regulations that the statute does not authorize. One can argue that by declaring that a drug is misbranded for failing to provide adequate directions for all of its “intended” uses under 21 C.F.R. §§ 201.5 and 201.128, FDA has radically broadened the scope of the misbranding offense to criminalize conduct that Congress never intended to criminalize. Indeed, under § 201.128, a manufacturer commits misbranding if it merely “knows” that a drug is being used off-label.

<sup>43</sup> Pharm. Mfrs. Ass’n v. FDA, 484 F. Supp. 1179, 1186 (D. Del. 1980), *aff’d* 634 F.2d 106, 108 (3d Cir. 1980).

<sup>44</sup> 21 U.S.C. § 353(b)(2).

macist, the drug need bear only the symbol "Rx only." As 21 U.S.C. § 353(b)(4) provides, "a [prescription drug] shall be deemed to be misbranded if at any time prior to dispensing the label of the drug fails to bear, at a minimum, the symbol 'Rx only.'"

These statutory provisions seem to establish that prescription drugs are exempt from the "adequate directions for use" prong of the misbranding statute if, prior to being dispensed, the drug bears the "Rx only" designation specified in section 353(b)(4) and if, after being dispensed, the prescription label bears the prescriber's directions for use (if any) as specified by section 353(b)(2). Alternatively, the language of section 353(b)(2) can be read to mean that prescription drugs are wholly exempt from the "adequate directions for use" prong of the misbranding statute so long as the label of the drug, once prescribed, bears the designated information.

In 1976, consistent with the idea that the statutory language exempts prescription drugs from the "adequate directions for use" prong of the misbranding statute, FDA defined "adequate directions for use" in its regulations as "directions under which the layman can use a drug or device safely and for the purposes for which it is intended . . . ." <sup>45</sup> The regulation goes on to state expressly that there is no need to include directions for use when the drug is used under the supervision of a physician:

[d]irections for use may be inadequate because, among other reasons, of omission, in whole or in part, or incorrect specification of: (a) Statements of all conditions, purposes, or uses for which such drug is intended . . . ; except that such statements shall not refer to conditions, uses, or purposes for which the drug can be safely used only under the supervision of a practitioner licensed by law and for which it is advertised solely to such practitioner. <sup>46</sup>

Thus, the regulation seems to require labeling for all intended uses, but excludes intended uses for prescription drugs, so long as those drugs are advertised only to physicians. <sup>47</sup>

There is also federal case law that supports the proposition that section 352(f) was enacted to provide adequate directions for use and warnings against use by a layman, not a physician, and recognizes an unqualified exemption for prescrip-

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<sup>45</sup> 21 C.F.R. § 201.5.

<sup>46</sup> *Id.*

<sup>47</sup> Even prior to the enactment of this regulation, FDA had evidenced a very consistent understanding that the "adequate directions for use" provision of section 352(f) applied only to drugs purchased directly by the consumer. In the immediate aftermath of the passage of the statutory amendment, FDA enacted a new implementing regulation that reflected the same understanding. Passed in 1952, the agency's original post-Durham-Humphrey regulation defining the adequate directions for use requirement specifically provided that statements of intended use which, if deficient, could give rise to a violation of that requirement could *not* include statements relating to prescription drugs. *See* 17 Fed. Reg. 6818 (July 25, 1952) (codified in 21 C.F.R. § 1.106(a)(1) (1952 Cum. Supp.)) ("such statements shall not refer to conditions, uses, or purposes for which the drug or device can safely be used only under the supervision of a practitioner licensed by law and for which it is advertised solely to such practitioner"). Similarly, in a subsection of the original regulation entitled "Exemption for prescription drugs," FDA made clear that prescription drugs need not bear adequate directions for use as long as they were labeled with the standard caution that they could only be dispensed upon prescription. 21 C.F.R. § 1.106(b)(2) & (3) (1952 Cum. Supp.); *see also Guardian Chem. Corp.*, 410 F.2d at 160 n.2 ("Regulations promulgated by the Secretary under the Act (21 C.F.R. § 1.106(b)) exempt from the requirement of § 352(f)(1) that the labeling set forth adequate directions for use for a drug which comes within § 353(b)(1), *i.e.*, a prescription drug, provided that its label bears the cautionary legend quoted above.").

tion drugs. For example, in *Pharmaceutical Manufacturers Association v. Food and Drug Administration*,<sup>48</sup> the plaintiffs challenged an FDA regulation that required certain warning information to be provided to women who were prescribed drugs that contained estrogen, alleging that, pursuant to 21 U.S.C. § 353(b)(2), FDA did not have statutory authority to require patient packaging inserts for prescription drugs. The court held that “prescription drugs were exempted from the requirements of [Section 352](f) in 1951” through the enactment of section 353(b)(2), explaining that “the 1951 exemption of prescription drugs from the requirement of [Section 352](f) was enacted with the idea that prescribing physicians would be the primary source of adequate directions for use and adequate warning against misuse or overuse.”<sup>49</sup>

These cases reflect the view that Congress wholly exempted all prescription drugs from the requirement that drugs bear adequate directions for lay use and therefore support the notion of an “absolute exemption.” There is another line of cases, however, which takes a narrower view of the exemption based solely on the application of 21 U.S.C. § 353(b)(2). As discussed above, section 353(b)(2) is the particular clause of the prescription drug exemption that requires that the prescriber’s directions for use be included on the prescription label at the time the drug is dispensed to the consumer. Under this second approach, a prescription drug is not exempt from the misbranding provision pursuant to section 353(b)(2) until the time it is actually dispensed to a consumer, presumably because there can be no labeling sufficient to satisfy section 353(b)(2) until the drug has actually been dispensed.<sup>50</sup>

A holding that section 353(b)(2) does not exempt prescription drugs until the time they are dispensed is not inconsistent with the position that section 353(b), read in its entirety, nonetheless exempts prescription drugs from the “adequate instructions for use” provision of the misbranding statute through section 353(b)(4). To the extent section 353(b)(2) is read to cover only from the time a drug is dispensed forward, section 353(b)(4) must then be understood to apply to the time period prior to the drug being dispensed. In other words, section 353(b)(4) seems to insulate prescription drugs from a charge of misbranding prior to the time a drug is dispensed so long as it bears the “Rx only” label and is properly distributed.<sup>51</sup>

## 2. False and Misleading Information

In addition to a drug being deemed misbranded based on inadequate directions for use as discussed above, under the FDCA, a drug can, alternatively, be deemed

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<sup>48</sup> 484 F. Supp. 1179 (D. Del. 1980), *aff’d* 634 F.2d 106, 108 (3d Cir. 1980).

<sup>49</sup> *Id.* at 1185. *See also* United States v. Vital Health Products, Ltd., 786 F. Supp. 761, 768 (E.D. Wis. 1992) (“Title 21 U.S.C. § 353(b) exempts prescription medications from the definition of ‘misbranded,’ because the burden of providing information to the customer has been shifted from the manufacturer to the prescribing physician”).

<sup>50</sup> *See, e.g.*, In re Canadian Import Antitrust Litigation, 385 F. Supp. 2d. 930, 934 (D. Minn. 2005) (pharmacist exemption described in section 353(b)(2) not effective until moment drugs are dispensed); United States v. An Article of Drug (*BIFLAV-C-2*), 292 F. Supp. 346, 348 (C.D. Cal. 1968) (concluding without analysis that “[u]nder 21 U.S.C. § 353(b)(2), drugs dispensed on prescription are exempt from certain labeling requirements of the [FDCA] if specified conditions are met, but this exemption becomes effective only at the time such drugs are actually dispensed on prescription”).

<sup>51</sup> *See, e.g.*, *Guardian Chem. Corp.*, 410 F.2d at 161 (“If [the drug] could safely be administered only with a doctor’s prescription, then under § 353(b)(4) its label had to bear the statutory ‘Caution.’ . . . If, on the other hand [the drug] was not something which could be dispensed only by a physician, then under § 352(f) its labeling, *i.e.*, its label and the ‘accompanying’ brochures, were required to state adequate directions for use.”).

“misbranded” if its labeling bears false and misleading information. Under section 352(a), a drug is deemed misbranded “[i]f its labeling is false or misleading in any particular.” This requires the government to prove the existence of “labeling”<sup>52</sup> that is “false or misleading.” The FDCA sets forth certain factors to be considered in determining whether a drug’s labeling is misleading:

If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in light of such representations or material with respect to consequences which may result from the use of the articles to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.<sup>53</sup>

It should be noted that “labeling” that makes efficacy claims for unapproved uses is not necessarily “false or misleading” under section 352(a) as a matter of law.<sup>54</sup> Instead, it appears that whether any such labeling is “false or misleading” under section 352(a) is a question of fact.<sup>55</sup>

In the context of prescription drug labeling provided to prescribers, the sophisticated knowledge of the physician audience could make it difficult to prove that anyone was misled. “The falsity or misleading character of a label or of labeling or of advertising is to be measured by its significance as read by those to whom it appeals.”<sup>56</sup> As the *WLF I* court said in dismissing FDA concerns about physicians

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<sup>52</sup> See *supra* notes 20 and 22 and accompanying text.

<sup>53</sup> 21 U.S.C. § 321(n).

<sup>54</sup> See *United States v. Sene X Eleemosynary Corp.*, 479 F. Supp. 970, 980 (S.D. Fla. 1979) (efficacy claims for drugs’ unapproved uses found to be misleading only after defendants failed to rebut government’s expert testimony that drugs were ineffective for unapproved uses indicated in labeling); *United States v. 47 Bottles*, 320 F.2d 564, 570-71 (3d Cir. 1963) (labeling affirmed as misleading where court below weighed conflicting expert testimony to conclude that drug was ineffective for uses claimed in the labeling).

In *Sene X*, the government brought an action to enjoin the defendants from promoting and distributing its “GH-3” prescription drug products for unapproved uses such as arthritis and diabetes treatment as indicated in the drugs’ labeling. 479 F. Supp. at 972-74. The government alleged that the drugs had been distributed in violation of the FDCA in that they were 1) unapproved “new drugs” under section 321(p), 2) misbranded due to “false or misleading” labeling under section 352(a), and 3) misbranded due to inadequate directions for use under section 352(f). *Id.* at 972. The court first held that the unapproved GH-3 drugs were “new drugs” because the government had introduced sufficient expert testimony to meet its burden of demonstrating that the drugs were “not generally recognized as safe and effective by qualified experts for use as promoted by the defendants.” *Id.* at 977.

The court then held that GH-3’s labeling was “false or misleading” under section 352(a) because the “[d]efendants offered no testimony to rebut that of [the government’s experts] that there is no clinical proof . . . which establishes that GH-3, or any similar procaine product, is effective for any indicated use.” *Id.* at 980. Thus, the fact that GH-3’s labeling made efficacy claims for unapproved uses did not mean that it was “false or misleading” under section 352(a) as a matter of law. Instead, the section 352(a) allegation raised a question of fact that required the government to introduce expert testimony to prove that the labeling was “false or misleading.” *Id.*

<sup>55</sup> See *47 Bottles*, 320 F.2d at 571 (“Whether or not labeling is false or misleading in any particular is a question of fact for determination by the trial judge in the absence of a jury.”); *United States v. Vital Health Products, Ltd.*, 786 F. Supp. 761, 767, 775 (E.D. Wis. 1992) (where drugs’ labeling made efficacy claims for unapproved uses, “[w]hether or not [the labeling] is misleading is a question of fact”).

<sup>56</sup> *United States v. Vitamin Indus., Inc.*, 130 F. Supp. 755, 767 (D. Neb. 1955)..

being misled, “physicians are a highly educated, professionally-trained and sophisticated audience.”<sup>57</sup> Given this audience, the threshold for finding information false or misleading should be very high.<sup>58</sup>

### C. *Intent to Defraud or Mislead*

To prove felony liability based on alleged violations of either the “new drug” or “misbranding” provisions of the FDCA or even under traditional mail and wire fraud theories, the government must prove an additional element—that the drug manufacturer acted with the specific “intent to defraud or mislead.”<sup>59</sup> Even willful violations of the FDCA are not necessarily felonies. As the Fifth Circuit has observed:

While every conscious or willful violation of § 331 will carry a misdemeanor penalty, it will not always subject the violator to a felony sentence. To subject the defendant to a felony sentence requires the government to establish not only that the violation was willful but that it was committed with the specific intent to defraud or mislead an identifiable government agency.<sup>60</sup>

A felony conviction pursuant to section 333(a)(2) “requires knowledge of the misbranding and proof of specific intent to mislead or defraud connected to the misbranding violation.”<sup>61</sup> The same is true for violations of the “new drug” provision. Thus, to prove a felony violation of either the “new drug” or “misbranding” provisions of the FDCA, the government must prove beyond a reasonable doubt not only that the defendant knew the drug was either an unapproved new drug or misbranded,<sup>62</sup> but also that the defendant acted with the specific intent to defraud or mislead.

In analyzing this issue of whether a defendant had the specific intent to defraud or mislead FDA, courts have stated or strongly suggested that the government must prove that the defendant was taking active steps to mislead or defraud the agency. In *United States v. Arlen*,<sup>63</sup> the Fifth Circuit affirmed the defendant’s felony conviction for misbranding because his actions “went beyond mere willfulness and constituted active deception of the FDA.”<sup>64</sup> Indeed, the defendant “rented a private postal box under a fictitious name, and used phone names and addresses

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<sup>57</sup> 13 F. Supp. 2d at 63.

<sup>58</sup> See *United States v. Caputo*, 288 F. Supp. 2d 912, 921 (N.D. Ill. 2003) (where defendants promoted off-label use to physicians, sophistication of audience precluded finding that off-label promotion was inherently misleading).

<sup>59</sup> 21 U.S.C. § 333(a)(2).

<sup>60</sup> *United States v. Arlen*, 947 F.2d 139, 143 (5th Cir. 1991).

<sup>61</sup> *United States v. Mitcheltree*, 940 F.2d 1329, 1351 (10th Cir. 1991).

<sup>62</sup> See, e.g., *United States v. Haas*, 171 F.3d 259, 267 (5th Cir. 1999) (affirming felony conviction because, among other things, jury was not unreasonable in disbelieving that defendant did not have knowledge of illegality); *United States v. Hiland*, 909 F.2d 1114, 1128 (8th Cir. 1990) (observing that one “could not have acted with the intent to defraud or mislead absent,” among other things, “knowledge [that the drug] was ‘misbranded’”).

<sup>63</sup> 947 F.2d 139 (5th Cir. 1991).

<sup>64</sup> *Id.* at 143.

when mailing steroid packages. These were active steps taken to avoid detection and regulation by the FDA.<sup>65</sup>

In sum, the government's theories of prosecution for the off-label promotion of approved drugs effectively puts a drug manufacturer in a difficult position. The government has suggested and threatened that a drug manufacturer could be prosecuted for introducing a new drug into commerce for an indication not supported in its labeling; or it could be prosecuted for failing to include adequate directions for use in its labeling; or it could be prosecuted for having labeling containing false or misleading statements. Under this statutory formulation, a manufacturer is always at risk of being accused of committing a crime if it discusses off-label uses. If the manufacturer provides adequate directions for off-label use in its labeling, it could be committing the crime of illegally introducing a "new drug" into commerce, because the off-label use has not been approved by FDA.<sup>66</sup> Alternatively, if it fails to include such information in its labeling, then it could be selling a drug in commerce without adequate directions for use.<sup>67</sup> Considered from the most conservative perspective, the government's approach to off-label promotion can be understood to prohibit any and all manufacturer-sponsored speech about off-label uses—this despite the value of off-label prescribing as more fully discussed above. Further, the restrictions on speech inherent in the government's current legal formulations raise significant First Amendment issues.

### III. THE FIRST AMENDMENT OVERLAY

In a very fundamental way, the conduct at issue when thinking about prosecutions for the off-label promotion of approved drugs is the dissemination of information—a form of speech. Whether the dissemination of scientific information is viewed to be pure speech or commercial speech, it is indisputably protected by the First Amendment. In the current legal framework, there is no statute that specifically makes off-label promotion a crime. Meanwhile, because there is really nothing in the FDCA or FDA's regulations that defines the contours of what information about off-label uses can lawfully be communicated to the medical community, there is no statutory line between what is truthful speech that is not actionable versus what is truthful speech that is prohibited. The First Amendment implications are obvious and known to FDA.

In October 1996, FDA published two guidance documents entitled *Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data*

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<sup>65</sup> *Id.* at 144. See also *United States v. Andersen*, 45 F.3d 217, 219 (7th Cir. 1995) (finding defendants liable under section 333(a)(2) on the basis that 1) they failed to register their drug business with FDA, and 2) they actively "attempted to conceal their drug business from the FDA by coding and disguising information on invoices" and "rerouting shipments"); *United States v. Bradshaw*, 840 F.2d 871, 873 (11th Cir. 1988) (affirming felony conviction under section 333(a)(2) because defendant "took various actions to avoid detection," such as using false names, moving from state to state frequently, and hiring surrogates to deliver products).

It must be noted that in *Hiland*, 909 F.2d 1114 (8th Cir. 1990), the court used a less stringent standard for imposing felony liability under section 333(a)(2). In affirming the defendants' convictions under the felony provision, the *Hiland* court found no error with the trial court's "willful blindness" jury instruction. *Id.* at 1130. Accordingly, the government may argue that felony liability under section 333(a)(2) attaches if a person is merely "willfully blind" to a section 331 violation. There does not appear to be any other reported decision, however, that accepts the "willful blindness" standard to impose felony liability under section 333(a)(2).

<sup>66</sup> 21 U.S.C. § 355(a).

<sup>67</sup> 21 U.S.C. § 352(f).

and Guidance for Industry Funded Dissemination of Reference Texts.<sup>68</sup> Neither guidance purported to give complete meaning to what truthful speech the agency considered appropriate. And of course, neither had the force of law. Rather, like all agency guidances in this area, each prominently stated that it reflected only the agency's "current thinking" and that "this guidance does not create or confer any rights on any person and does not operate to bind FDA in any way. . . ."<sup>69</sup>

Then, in December 1997, FDA issued its Final Guidance on Industry-Supported Scientific and Educational Activities,<sup>70</sup> which was proclaimed as the product of the agency's efforts to "strike a proper balance between the need for industry-supported dissemination of current scientific information and the need to ensure that promotional activities by industry meet the requirements of the law."<sup>71</sup> This Guidance also represented only the agency's "current thinking" and prominently stated that it did "not operate to bind FDA or the industry."<sup>72</sup> The 1997 Guidance provided that: "Manufacturers of drugs and devices are not permitted to promote unapproved products or unapproved uses of approved products, either directly or indirectly, such as through industry-supported scientific and educational activities."<sup>73</sup>

Nonetheless, FDA acknowledged the importance of off-label uses and recognized that "promotional labeling" did not generally include materials disseminated by an independent provider for educational purposes or those disseminated by the company itself in response to an unsolicited request:

Written, printed, or graphic materials containing product information and disseminated by, or on behalf of, a product manufacturer are generally viewed as promotional labeling. If, on the other hand, the materials are prepared and disseminated by the [CME] provider for educational purposes, or the materials are disseminated by the company in response to an unsolicited request, this would *not* generally be considered as a possible indication of company influence.<sup>74</sup>

Thereafter, the Washington Legal Foundation brought a lawsuit against FDA challenging the agency's restrictions on the dissemination of off-label information by drug companies on First Amendment grounds. The district court ruled that the 1996 and 1997 FDA guidance documents were unconstitutional under the First Amendment.<sup>75</sup> The court noted that off-label prescriptions "constitute the most effective treatment available for some conditions." For that reason, it explained, "the open dissemination of scientific and medical information regarding these treatments is of great import."<sup>76</sup> Recognizing that the government's interest in preventing the dissemination of "misleading information" was "well-intentioned," the court nonetheless found that as a consequence "a great deal of truthful information will also be embargoed. In this case, the truthful information may be life saving information, or information that makes a life within a debilitating condition

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<sup>68</sup> 61 Fed. Reg. 52,800, 52,801 (Oct. 8, 1996).

<sup>69</sup> *Id.* at nn.1-2.

<sup>70</sup> 62 Fed. Reg. 64,074 (Dec. 3, 1997) (hereinafter 1997 Guidance).

<sup>71</sup> *Id.* at 64,074.

<sup>72</sup> *Id.* at 64,094 n.1.

<sup>73</sup> *Id.* at 64,081.

<sup>74</sup> *Id.* at 64,091 (emphasis added); *see also id.* at 64,099 (same).

<sup>75</sup> Washington Legal Found. v. Friedman (*WLF I*), 13 F. Supp. 2d 51, 74 (D.D.C. 1998).

<sup>76</sup> *Id.* at 56.

more comfortable.”<sup>77</sup> Accordingly, the court found the restrictions in the guidance documents unconstitutional. They were “more extensive than necessary to serve the asserted government interest and . . . they unduly burden important speech.”<sup>78</sup>

Soon after the court rendered its decision in *WLF I*, the Food and Drug Modernization Act of 1997 (FDAMA) was passed. FDAMA amended FDCA expressly to identify as a “prohibited act”—violation of which would subject a manufacturer to criminal penalties—“the dissemination of information” in violation of section 360aaa of FDCA (or section 401 of FDAMA).<sup>79</sup> At the same time, section 360aaa expressly allowed drug companies to disseminate certain information about off-label use under specified conditions.<sup>80</sup> The court in *WLF II* promptly ruled that FDAMA was unconstitutional for the same reasons as the guidances.<sup>81</sup> The statute barred truthful speech about off-label uses protected by the First Amendment. Accordingly, the *WLF II* court amended its *WLF I* order “to explicitly declare unconstitutional and unenforceable the FDAMA and its implementing regulations.”<sup>82</sup>

On appeal, FDA, faced with the likelihood that the appeals court would invalidate its first-ever effort to criminalize “the dissemination of information” by pharmaceutical manufacturers, beat a strategic retreat. Although on its face FDAMA outlawed truthful speech that did not fit within its exceptions, 21 U.S.C. § 331(z), FDA abandoned this position in court, asserting—in a binding stipulation—that neither the guidance nor FDAMA “provides the FDA with independent authority to regulate manufacturer speech.”<sup>83</sup> In other words, FDA agreed that FDAMA and the 1997 Guidance “established nothing more than a ‘safe harbor’ ensuring that certain forms of conduct would not be used against manufacturers in misbranding and ‘intended use’ enforcement actions based on pre-existing legislative authority.”<sup>84</sup> In response, WLF stated that it no longer had a constitutional objection to FDAMA or the 1997 Guidance in light of the representations made by FDA. Accordingly, the court dismissed FDA’s appeal and vacated the district court’s decisions and injunctions “insofar as they declare the FDAMA and the CME Guidance unconstitutional.”<sup>85</sup>

At FDA’s urging, the *WLF III* court left the agency a small amount of wiggle room. The court noted that “arguably promotional conduct” could be “evidence in a misbranding or ‘intended use’ enforcement action,”<sup>86</sup> but that a manufacturer “may still argue that the FDA’s use of a manufacturer’s promotion of off-label uses as evidence in a particular enforcement action violates the First Amendment.”<sup>87</sup> FDA thereafter explained its thinking, acknowledging that it could not criminalize truthful speech:

[T]he statute and guidance create no per se bar or prohibition to dissemination of truthful, nonmisleading information about unapproved new uses

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<sup>77</sup> *Id.* at 73.

<sup>78</sup> *Id.* at 74.

<sup>79</sup> 21 U.S.C. § 331(z).

<sup>80</sup> 21 U.S.C. § 360aaa.

<sup>81</sup> *Washington Legal Found. v. Henney (WLF II)*, 56 F. Supp. 2d 81, 84 (D.D.C. 1999).

<sup>82</sup> *Id.* at 87.

<sup>83</sup> *Washington Legal Found. v. Henney (WLF III)*, 202 F.3d 331, 336 (D.C. Cir. 2000).

<sup>84</sup> *Id.* at 335.

<sup>85</sup> *Id.* at 337.

<sup>86</sup> *Id.* at 336 (emphasis in original).

<sup>87</sup> *Id.* at 336 n.6.

of approved medical products. . . . [T]his potential evidentiary use is the only consequence of those practices.<sup>88</sup>

Soon thereafter, the U.S. Supreme Court's decision in *Thompson v. Western States Medical Center* effectively removed whatever wiggle room FDA thought it retained.<sup>89</sup> In *Western States*, the court found unconstitutional another provision of the FDCA, which barred licensed pharmacists from promoting drug compounding services. Drug compounding is the process by which a pharmacist combines ingredients—often, FDA-approved drugs—to create a new medication tailored to the needs of an individual patient. As with off-label uses, FDA has recognized the value of drug compounding and permits the activity, but sought to restrict the large-scale manufacture of unapproved drugs by banning advertising about compounding services.

The Supreme Court recognized, as it said in *Virginia State Board of Pharmacists v. Virginia Citizens Consumer Council, Inc.*, that the First Amendment commands the assumption that physicians will make the best decisions “only if they are well enough informed, and that the best means to that end is to open the channels of communication rather to close them.”<sup>90</sup> “If the First Amendment means anything, it means that regulating speech must be a last—not first—resort.”<sup>91</sup>

The Court completely rejected the concept that doctors could not be counted on to exercise appropriate medical judgment about unapproved medications. In language equally applicable to doctors' ability to appropriately prescribe drugs off label, the Court said, “if it is appropriate for the statute to rely on doctors to refrain from prescribing compounded drugs to patients who do not need them, it is not clear why it would not also be appropriate to rely on doctors to refrain from prescribing compounded drugs to patients who do not need them in a world where advertising was permitted.”<sup>92</sup>

Taken together, the outcomes of the *WLF* litigation and the Supreme Court's decision in *Western States* leave FDA on thin ice in attempting to impose criminal sanctions for the dissemination of truthful scientific information by drug manufacturers. Even FDA's equivocal reference to the “evidentiary” use of truthful speech runs smack into the Supreme Court's insistence that, where there is a public benefit to commercial speech, the least restrictive—and clearest—lines must be drawn.

In January 2009, in response to the September 2006 sunset of FDAMA section 401 (that FDA conceded was nothing more than a “safe harbor” for manufacturers that disseminate scientific information), FDA released its final guidance on “Good Reprint Practices,” which appears to indicate some newfound—but limited—support by the agency for drug manufacturers' dissemination of balanced, scientific materials concerning off-label uses, though subject to certain conditions.<sup>93</sup> Recognizing “the important public health and policy justification supporting dissemination of truthful and non-misleading medical journal articles . . . and publications on

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<sup>88</sup> Letter from Margaret M. Dotzel, Associate Commissioner for Policy, FDA, to Daniel J. Popeo, Esq. and Richard A. Samp, Esq., Washington Legal Foundation, at 6 (Jan. 28, 2002); see also FDA's *Federal Register* Notice at 65 Fed. Reg. 14,286 (Mar. 16, 2000).

<sup>89</sup> 535 U.S. 357 (2002).

<sup>90</sup> 425 U.S. 748, 765 (1976).

<sup>91</sup> 535 U.S. at 373.

<sup>92</sup> *Id.* at 376.

<sup>93</sup> Good Reprint Practices 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, 74 Fed. Reg. 1694 (Jan. 13, 2009).

unapproved uses of approved drugs,” FDA’s “Good Reprint Practices” guidance provides two significant changes from the prior regulatory regime: 1) manufacturers are no longer limited to providing information about new uses for which they will apply for a new indication, and 2) manufacturers are no longer required to submit their scientific materials to FDA for approval prior to dissemination.<sup>94</sup>

While these two changes indicate some FDA support for manufacturers’ dissemination of scientific materials, it should be noted that the “Good Reprint Practices” guidance merely represents the agency’s “current thinking on this topic” rather than any formal rulemaking or regulation. Further, FDA stated in the guidance that its “legal authority to determine whether distribution of medical or scientific information constitutes promotion of an unapproved ‘new use,’ or whether such activities cause a product to violate the FD&C Act has not changed.”<sup>95</sup> Unsurprisingly, FDA did not elucidate how its “legal authority” would comport with the First Amendment.

As matters now stand, the standoff is unresolved in court. The Supreme Court is on record as highly skeptical of laws that regulate conduct through broad prohibitions on speech. Meanwhile, FDA continues to assert an interest in regulating in this area, but it has not undertaken any formal rule-making or even clarifying regulations that would define the boundaries between permissible and impermissible conduct in the off-label arena. To further complicate matters, on July 28, 2008, at the request of Senator Chuck Grassley, the United States Government Accountability Office (GAO) issued a report on “FDA’s Oversight of the Promotion of Drugs for Off-Label Uses” (GAO-08-835). The report found that FDA “oversees drug promotion for off-label uses by reviewing promotional materials that drug companies submit to the agency” but that “it is unable to review all submissions because of the volume of materials it receives” and is “hampered by the lack of a system that consistently tracks the receipt and review of submitted materials.”<sup>96</sup> The GAO further stated that [a]lthough the agency conducts additional monitoring and surveillance to detect violations that could not be identified through a review of submitted materials, the extent and variety of promotional activities make it difficult for FDA to monitor these in a comprehensive manner.<sup>97</sup>

Overall, the best that can be said for the legal climate surrounding the off-label area is that the government is aggressive; FDA interested, but perhaps overwhelmed or unsure of how to proceed in the current climate; and Congress unimpressed with FDA, although unwilling or unable to pass legislation that would clarify the legal landscape.

#### IV. THE GOVERNMENT’S EVIDENCE IN OFF-LABEL PROMOTION CASES

As the above discussion shows, the government has available a variety of legal theories and remedies—criminal, civil, and administrative—when bringing enforcement actions against manufacturers for off-label marketing. Because certain off-label conduct is permissible under the First Amendment, the line between prohibited off-label promotion and permissible off-label education is murky at best. The federal government does not pursue every conceivable case of off-label promotion. And

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<sup>94</sup> Note that despite these changes, most of the guidance is substantially similar to the previous regulatory regime. *See id.*

<sup>95</sup> *Id.* at 1694.

<sup>96</sup> GAO-08-835, at 1.

<sup>97</sup> *Id.* at 13.

of the federal enforcement cases to date, one size does not fit all. Some cases have involved civil and administrative allegations only; others have included the full range of criminal, civil, and administrative charges. Of the cases including criminal charges, some have involved felony charges; others, only misdemeanors.

Each case presents its own unique facts. Discerning why one case has a different outcome than the next is difficult, because of the many factors that determine a case's outcome. The government's public filings in these cases are often quite detailed, and reveal a fair amount about practices the government seems to find most problematic. While by no means perfect guides, these filings can assist both the company caught up in its own off-label investigation to evaluate its exposure, and the company seeking to avoid an investigation altogether to implement proactive compliance measures.

What follows is a discussion of some (but not all) of the government's off-label enforcement cases. The discussion is organized around eight focal points of a typical off-label investigation. They are: 1) the ratio of a drug's off-label sales to the drug's total sales; 2) the manufacturer's conduct surrounding the drug approval process with FDA—including whether formal clinical trials were sought and approved by FDA; 3) company statements about research results for a drug's off-label uses; 4) the role, if any, for off-label sales in company business plans; 5) the sales force's direct interaction with physicians on everything from educational information to reimbursement information; 6) the company's use of scientific articles, abstracts, and studies of off-label uses; 7) the company's involvement in CME and other educational programs on off-label uses; and 8) the company's financial payments to physicians. This list is by no means exhaustive. We discuss below how the government mines these eight areas for individual pieces of evidence, hoping in the end to paint an overall picture of corporate intent to promote a drug's off-label use in a deceptive or misleading manner.

#### *A. The Proportion of Sales Revenue from Unapproved Indications*

A significant factor in any off-label investigation is how drug sales revenues for approved indications compare with revenues from unapproved indications. Suppose sales due to approved uses are small relative to sales due to unapproved indications. Suppose further that money budgeted for and spent on the company's promotional activities exceeds anticipated revenues from approved indications alone. In these circumstances, one arguably can infer that the company intends all along to market and sell the drug for unapproved uses. The flip side, of course, is that sales revenues for unapproved uses are insignificant relative to revenues for approved uses, and the company's anticipated revenues from sales for approved uses fully justify the budgets to promote those uses. In that situation, physicians' independent decisions to prescribe for off-label uses may account for the off-label sales of a company otherwise promoting only approved uses. Against that backdrop, the government has a harder time painting a clear picture of corporate intent to promote a drug's off-label use.

Several enforcement cases illustrate the significance of the amount of off-label sales relative to on-label sales. In May 2004, Warner-Lambert (and its corporate parent, Pfizer Inc.) agreed to pay \$430 million to resolve Warner-Lambert's criminal and civil exposure for off-label promotion of Neurontin, a drug approved in December 1993 as adjunctive therapy for epilepsy; i.e., as a secondary medication

for use along with another, primary medication.<sup>98</sup> Through its Parke-Davis division, Warner-Lambert promoted Neurontin for unapproved uses, including treatment of pain and psychiatric conditions such as bipolar disorder and anxiety. Warner-Lambert pled guilty to one count of introduction of Neurontin as a new drug intended for unapproved uses, and one count of introduction of a misbranded drug—both misdemeanor violations of the FDCA.<sup>99</sup> The government, however, charged them as felonies, not because Warner-Lambert committed the offenses with the intent to defraud or mislead, but because it committed them having previously been convicted of a separate FDCA violation, a fact which automatically converts a misdemeanor violation into a felony.<sup>100</sup>

Warner-Lambert's own sales data cast an ominous cloud over its conduct. In 1994, the year Warner-Lambert began to market Neurontin, sales for off-label uses accounted for 1.5 percent of all Neurontin sales; by 2002, sales for unapproved uses made up 94 percent of total sales.<sup>101</sup> Under this type of cloud, isolated pieces of incriminating evidence appeared all that more damaging. For example, the government recovered a particularly harmful tape-recorded voice message from the manager of the company's medical liaisons in the northeastern United States urging them to promote Neurontin's unapproved uses, including for pain and as monotherapy:

So what we need to do is focus on Neurontin. When we get out there, we want to kick some ass on Neurontin, we want to sell Neurontin on pain. All right? And monotherapy and everything that we can talk about, that's what we want to do. 'Cause I'm embarrassed. I don't know if you guys are embarrassed. But I'm embarrassed about where we are with Neurontin. We've got to take it into our own hands and really kick some ass on it, all right? Let's do it up.<sup>102</sup>

Against the backdrop of the dramatic growth in Neurontin's off-label sales as a percentage of total Neurontin sales, the manager's statements became much harder to explain away as an unrepresentative, isolated instance.

The government's case against InterMune, Inc., for its off-label promotion of Actimmune provides a second example of the significance of off-label sales relative to total sales. In October 2006, InterMune agreed to pay nearly \$37 million to resolve criminal and civil allegations of off-label marketing.<sup>103</sup> Actimmune's approved use was for the treatment of chronic granulomatous fibrosis and severe, malignant osteopetrosis—diseases that affect a very small patient population.

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<sup>98</sup> "Drug Maker to Pay \$430 Million in Fines, Civil Damages," 38 FDA CONSUMER (July-August 2004), available at [http://www.fda.gov/fdac/features/2004/404\\_w1.html](http://www.fda.gov/fdac/features/2004/404_w1.html). See also Settlement Agreement, available at <http://www.usdoj.gov/civil/foia/elecread/2004/Pfizer%20Inc.%202004.pdf>.

<sup>99</sup> Judgment in a Criminal Case, United States v. Warner-Lambert Co., LLC, No. 04-10150 (D. Mass. filed June 7, 2004). The government specifically charged violations of 21 U.S.C. § 331(d) and § 355(a) (introduction of an unapproved new drug) and § 331(a) and § 352(f)(1) (introduction of a misbranded drug in that Neurontin's "labeling lacked adequate directions" for the unapproved uses for which the drug was intended).

<sup>100</sup> See 21 U.S.C. § 333(a)(2).

<sup>101</sup> Sentencing Memorandum of the United States at 13, United States v. Warner-Lambert Co. LLC, No. 04-10150 (D. Mass. filed June 2, 2004).

<sup>102</sup> *Id.* at 11.

<sup>103</sup> Press Release, U.S. Department of Justice, Biopharmaceutical Firm InterMune to Pay U.S. over \$36 Million for Illegal Promotion and Marketing of Drug Actimmune (Oct. 26, 2006), available at [http://www.usdoj.gov/opa/pr/2006/October/06\\_civ\\_728.html](http://www.usdoj.gov/opa/pr/2006/October/06_civ_728.html).

The government's investigation revealed, however, that the "vast majority" of the company's Actimmune sales were attributable to prescriptions to treat idiopathic pulmonary fibrosis (IPF), a debilitating, fatal lung disease for which there was no FDA-approved treatment.<sup>104</sup> As in the case of Neurontin, the government could easily paint an overall picture of corporate intent to sell Actimmune for unapproved uses, in part, because they accounted for such a significant portion of the drug's total sales. Rather than plead guilty, InterMune resolved the felony misbranding charge against it by reaching a deferred prosecution agreement with the government.<sup>105</sup>

The government's investigation of Cephalon for off-label promotion of Gabitril also focused on evidence of an increase in prescriptions attributed to off-label promotion. FDA approved Gabitril as an anti-seizure drug for adjunctive therapy for partial seizures in adults and children 12 years and older. Four years after initial new drug application (NDA) approval, Cephalon allegedly re-launched Gabitril to take advantage of a growing market among psychiatrists, who would treat for anxiety, insomnia, and pain, rather than neurologists, who likely would prescribe for the drug's only approved anti-seizure use.<sup>106</sup> As a result of the successful re-launch, Cephalon tracked a rise in psychiatrists' prescriptions from 8,065 in 2000 to 49,922 in 2001.<sup>107</sup> The government also discovered that Cephalon sales reports showed that Gabitril sales increased from \$24.6 million in 2001 to \$87.3 million in 2004. Sales also similarly increased for two other drugs under investigation for off-label promotion: Actiq, another pharmaceutical prescribed for relief of breakthrough pain, had sales increase from \$50.1 million in 2001 to \$550.4 million in 2006; Provigil, a pharmaceutical prescribed for narcolepsy, had sales increase from \$146.2 million in 2001 to \$691.7 million in 2006.<sup>108</sup> This evidence allowed the government to depict a dramatic increase in prescriptions and sales as correlated to Cephalon's off-label promotional practices. In September 2008, Cephalon agreed to pay \$425 million and enter into a guilty plea for misdemeanor distribution of Gabitril, Actiq, and Provigil.<sup>109</sup>

## B. *The NDA Approval Process*

In search of evidence of a company's knowledge and intent to promote off-label uses, the government will look back at least as far as the company's NDA submission to FDA for the drug in question. The NDA submission and discussions surrounding it will normally illuminate what the company believed, as of the submission, it could demonstrate with respect to the efficacy and safety of the drug. The government will then compare the company's conduct in seeking approval of the drug with its conduct in marketing the drug post-approval. Did the company sell the drug for indications whose approval the company never sought, or sought

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<sup>104</sup> Deferred Prosecution Agreement at Attachment A, *United States v. InterMune, Inc.*, No. 06-0707 (N.D. Cal. filed Dec. 4, 2006).

<sup>105</sup> *Id.* The government charged specifically that InterMune, with intent to defraud and mislead, promoted Actimmune for an unapproved use, the result of which was misbranding of the drug within the meaning of 21 U.S.C. § 352(f)(1), in that its labeling did not bear adequate directions for use, all in violation of 21 U.S.C. § 331(k) and § 333(a)(2).

<sup>106</sup> Government's Sentencing Memorandum at 12, *United States v. Cephalon, Inc.* (E.D. Pa. filed Sept. 2, 2009); Information at ¶ 9 (E.D. Pa. filed Sept. 29, 2009).

<sup>107</sup> Government's Sentencing Memorandum at 12, *Cephalon*.

<sup>108</sup> *Id.* at 14.

<sup>109</sup> Press Release, U.S. Department of Justice, Biopharmaceutical Company, Cephalon, to Pay \$425 Million & Enter Plea to Resolve Allegations of Off-Label Marketing (Sept. 29, 2009), available at <http://www.usdoj.gov/opa/pr/2008/September/08-civ-860.html>.

but failed to obtain? If the answer is “yes,” then the government will infer that the company fully understood the limitations on the drug’s “intended use,” but went ahead and promoted off-label uses anyway. For example, in the Warner-Lambert case, while the company allegedly decided for business reasons not to seek approval of Neurontin for treatment of psychiatric conditions (such as bipolar disorder) or for treatment of pain, it promoted those uses anyway.<sup>110</sup>

Similarly, in its case against Schering-Plough Corporation, the government contended that the company deliberately chose not to seek FDA’s approval to use Intron A to treat superficial bladder cancer, even though the company had supported various studies of that use. The company, according to the government, wanted to avoid the costs of the approval process, as evidenced by one executive’s comment: “why buy the cow when you can get the milk for free.”<sup>111</sup> In other words, why incur the significant costs of obtaining approval for the off-label uses, if the company can successfully promote those uses without approval? A Schering-Plough subsidiary, Schering Sales Corporation, pled guilty to the felony charge of conspiracy to make material false statements to federal agencies, some of which were allegedly intended to conceal from FDA the extent of Schering Sales’ off-label promotion of Intron A and Temodar, another cancer drug.<sup>112</sup>

*United States v. Caputo*, a medical device case, provides another example of government review of the approval process to look for evidence of criminal intent under the FDCA.<sup>113</sup> There, the government successfully prosecuted the chief executive officer (CEO) and the chief compliance officer of AbTox Inc., a company that sold sterilizers of medical equipment. AbTox applied for and obtained clearance from FDA to sell its small sterilizer for use only with solid stainless-steel medical instruments. However, the company had no intention of selling the small sterilizer for the approved uses, and instead marketed a large, unapproved sterilizer for unapproved uses. The defendants continued marketing the large sterilizer, even after notice by the FDA that doing so constituted off-label promotion. The defendants asserted that their conduct was protected by the First Amendment. On appeal, the Court side-stepped the issue whether a seller of drugs or medical devices has a constitutional right to promote off-label uses. The Court concluded that AbTox had no authority to market the large sterilizer for any use.<sup>114</sup> Thus, the First Amendment was not implicated, as it would have been had AbTox obtained approval to sell the large sterilizer.

FDA has indicated that it will not only inquire into past conduct in the approval process, but also into whether a company chose to evade the costs of FDA approval of supplemental uses of drugs and devices that have demonstrated some efficacy or even promise, through off-label use. No investigation to date focuses more on this issue than the current indictment of a medical device company and several of its executives. The government recently charged Synthes, a medical device manufacturer, with criminal violations of the FDCA.<sup>115</sup> While there are multiple alleged violations based upon contact with physicians, the government’s ire was invoked by

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<sup>110</sup> Information at ¶¶ 8-18, *Warner-Lambert Co., LLC* (filed May 13, 2004).

<sup>111</sup> Government’s Redacted Sentencing Memorandum at 20, *United States v. Schering Sales Corp.*, No. 06-10250-PBS (D. Mass. filed Jan. 15, 2007).

<sup>112</sup> Press Release, U.S. Department of Justice, Schering to Pay \$435 Million for the Improper Marketing of Drugs and Medicaid Fraud (Aug. 29, 2006).

<sup>113</sup> 517 F.3d 935 (7th Cir. 2008). The United States Supreme Court denied the petition for writ of certiorari. *Caputo v. United States*, 129 S. Ct. 94 (2008).

<sup>114</sup> *Id.* at 940-41.

<sup>115</sup> Indictment, *United States v. Norian Corp. et al.*, No. 09-00403 (E.D. Pa. filed June 16, 2009).

what it perceived as an end-run around FDA's repeated admonition that the use of Synthes's bone cement in combination with another compound for treatment of vertebral compression fractures required FDA-approved clinical trials. The government alleges that Synthes conducted "market research" studies in lieu of clinical trials. These studies are alleged to have revealed a significant risk of death, even though they were not approved by FDA. Rather than withdrawing the product from the market for such off-label use, the government contends that Synthes continued to conduct "research" that was tantamount to an unapproved clinical trial. While the facts of this case are yet to unfold through any defense presented, it shows the focus on FDA's approval process is still paramount. Indeed, the facts of any case where it looks as if unapproved clinical trials were conducted on patients where a significant risk of death existed appears not only unlawful under the FDCA, but also suggests the spectre of uncontrolled studies on human patients reminiscent of allegations of patients' rights violations dating back over half a century. While this depiction may not be accurate, it is a picture that the government will try to paint and it may lead to the filing of parallel civil cases.<sup>116</sup>

### *C. False or Misleading Statements About Research Results or Reports*

The government also scrutinizes carefully a company's statements about studies of its drug for a particular off-label use. Here, the government looks for false or misleading statements about the outcome of a study. Such evidence can be particularly helpful to prove the company's intent to defraud or mislead—an essential element of felony violations of either the "new drug" or "misbranding" provisions of the FDCA and also of any mail or wire fraud charge.

The InterMune case provides a dramatic example of the government's focus on alleged misrepresentations overstating research results. There, the company conducted a two-year, Phase III clinical trial of Actimmune for the treatment of IPF to determine whether the drug extended the time to disease progression or death. The primary endpoint for the drug's efficacy was progression-free survival, along with several secondary endpoints, including overall patient survival. According to the government, the clinical trial's data failed to establish statistical significance on the primary endpoint agreed upon between InterMune and FDA. FDA's medical review staff told InterMune officials that, in view of the inconclusive test results, it was unlikely to approve Actimmune for IPF without further study of the drug's effectiveness.

The next day, the company issued a press release announcing, among other things, that the Phase III data demonstrated a "survival benefit of Actimmune in IPF," a claim the government alleged was false and misleading because it falsely portrayed the clinical trial as establishing that Actimmune helped IPF patients live longer. The company repeated this claim in communications with pulmonologists and in a direct letter to IPF patients. The allegedly false statements about the clinical trial results were at the heart of both the government's criminal information in October 2006, charging InterMune with a felony misbranding violation of the FDCA, and the subsequent criminal indictment in March 2008, charging InterMune's former

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<sup>116</sup> See, e.g., *The Baffling Death of a Gene-Trial Patient*, THE PHILADELPHIA INQUIRER (Oct. 1, 1999).

CEO with wire fraud and a felony misbranding violation.<sup>117</sup> In the case against the former CEO, the government alleged that the interstate, electronic transmission of the false and misleading press release was the necessary wire communication in furtherance of the fraud scheme to induce physicians to prescribe and patients to take Actimmune to treat IPF.<sup>118</sup> Similarly, the government alleged that with intent to defraud and mislead, the CEO disseminated the false and misleading press release, thereby causing Actimmune to be misbranded, in violation of 21 U.S.C. § 331(k), § 333(a)(2), and § 352(a).<sup>119</sup>

A statement need not be false to support an inference of fraudulent intent. A material omission will suffice. Thus, for example, suppose some studies support an unapproved use, but others do not. During a sales call, a physician asks the sales representative about the unapproved use, thereby opening the door to some permissible off-label discussion. The sales representative mentions only the favorable studies. The government would likely claim that the representative's material omission of the unfavorable studies transforms an otherwise accurate, permitted statement about off-label use into misleading promotion of that use.

This was the situation presented in the prosecution of Mary Holloway, a sales manager who allegedly engaged in the off-label promotion of Bextra. FDA approved Bextra to treat symptoms of osteoarthritis, adult rheumatoid arthritis, and primary dysmenorrhea. FDA declined to approve Bextra for general acute pain, for the preemption of surgery pain, or for opioid sparing.<sup>120</sup> Two studies showed that the use of injectable Bextra in coronary artery bypass graft surgeries was linked to an excess or significant increase in adverse cardiovascular events.<sup>121</sup> FDA sent a letter to Pfizer, which Holloway received, stating its safety concerns when using Bextra for acute pain. The government alleged that Holloway asked Pfizer managers not to share FDA's letter with sales representatives and that she also directed sales staff not to disclose the adverse studies.<sup>122</sup> Holloway pled guilty to a misdemeanor count of misbranding and was sentenced to 24 months' probation and a \$75,000 fine.

Similarly, in the Synthes indictment, it is alleged that the company failed to reveal pilot study test results on the safety of its bone cement.<sup>123</sup> The company and key employees are also alleged to have failed to submit timely and complete medical device reports to physicians using its cement for off-label use.<sup>124</sup> The government alleges that this failure is a direct violation of the FDCA and its criminal provisions.

### *D. Business Plans That Depend on "Growing" the Off-Label Market*

A company's business and marketing plans are an obvious place to look for evidence of corporate intent to promote off-label usage of a drug. These plans tend to reflect the corporate mindset at relatively high levels of the company. The government routinely reviews them, both to develop direct evidence of corporate intent and to rebut any claim that individual sales representatives, who promoted

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<sup>117</sup> Information, *United States v. InterMune, Inc.*, No. 06-0707 (N.D. Cal. filed Oct. 26, 2006); Indictment, *United States v. W. Scott Harkonen*, No. 08-0164 (N.D. Cal. filed Mar. 18, 2008).

<sup>118</sup> Indictment at ¶ 26, *W. Scott Harkonen*.

<sup>119</sup> *Id.* at ¶ 28. At the time of publication, the charges against the former CEO were pending. On September 29, 2009, a jury found the former CEO guilty of the count for wire fraud, but acquitted on the misbranding charge.

<sup>120</sup> Information at ¶ 14, *United States v. Holloway* (D. Mass. filed Mar. 30, 2009).

<sup>121</sup> *Id.* at ¶¶ 17, 19.

<sup>122</sup> *Id.* at ¶¶ 18, 24.

<sup>123</sup> Indictment at ¶ 86, *Norian Corp.*

<sup>124</sup> *Id.* at ¶ 87.

a drug's off-label usage to physicians, were rogue employees acting outside the corporate reservation.

Business plans have figured prominently in the government's descriptions of its evidence of off-label marketing in cases brought to date. The government's case in December 2005 against Eli Lilly and Company for its off-label promotion of Evista is a good example. FDA had approved Evista as a drug therapy to prevent osteoporosis in postmenopausal women. FDA had not approved the drug as therapy to reduce the risk of breast cancer and cardiovascular disease. When Evista sales languished in its first year on the market, Eli Lilly, according to the government, expanded its sales pitch to include the unapproved uses.<sup>125</sup> Instead of focusing on Evista's approved use only, the company began to emphasize the drug's "3 combined benefits" for postmenopausal women; namely, reducing the risks of osteoporosis (the approved use) and breast cancer and cardiovascular disease (the unapproved uses).

The government found support for its theory in various company business plans. For example, one described the change in emphasis as "3 combined benefits versus Osteoporosis only."<sup>126</sup> Another identified one of the company's strategic marketing objectives as follows: "Build PMH [postmenopausal health] market by driving urgency to prevent PMH risks," and by "[l]everag[ing] national advocacy efforts to create and build market as defined by osteoporosis, cardiovascular disease and breast cancer."<sup>127</sup> This language in the business plans went a long way toward undermining any defense claim that a sales representative, who marketed all three uses, instead of the approved use only, acted without the company's authority. Eli Lilly pled guilty to a single misdemeanor charge of misbranding Evista (its labeling lacked adequate directions for the intended, unapproved uses) in violation of the FDCA.<sup>128</sup> The company agreed to pay a total of \$36 million to resolve its criminal and civil exposure.<sup>129</sup>

Business plans also figured somewhat prominently in the Schering-Plough case. The government claimed that Schering-Plough, through a subsidiary, improperly induced physicians to prescribe Intron A and Temodar for unapproved uses—the former for superficial bladder cancer and the latter for certain brain tumors and brain metastases. According to the criminal charge to which the subsidiary pled guilty, the company's "marketing department provided the sales force a plan of action that targeted off-label sales...."<sup>130</sup> The company then required the sales force "to create business plans that emphasized detailed promotional goals to obtain off-label sales."<sup>131</sup> The subsidiary evaluated and compensated its sales force "by their success in achieving sales in unapproved uses."<sup>132</sup>

In March 2008, in an offshoot of the InterMune investigation, the government indicted the former CEO on separate felony charges of wire fraud and misbranding with intent to defraud and mislead in violation of the FDCA.<sup>133</sup> The indictment

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<sup>125</sup> Information at ¶ 19, *United States v. Eli Lilly & Co.*, No. 05-0206 (S.D. Ind. filed Dec. 21, 2005).

<sup>126</sup> *Id.* at ¶¶ 20, 22.

<sup>127</sup> *Id.* at ¶ 22.

<sup>128</sup> Press Release, U.S. Department of Justice, *Eli Lilly and Company to Pay U.S. \$36 Million Relating to Off-Label Promotion* (Dec. 21, 2005).

<sup>129</sup> *Id.*

<sup>130</sup> Information at ¶ 32, *Schering Sales Corp.* (filed Aug. 29, 2006).

<sup>131</sup> *Id.*

<sup>132</sup> *Id.*

<sup>133</sup> Indictment, *W. Scott Harkonen*.

alleges, among other things, that the CEO promoted Actimmune for its off-label use to treat IPF by establishing sales goals for Actimmune, and then, to meet those goals, directing sales staff to call on pulmonologists to sell Actimmune for treatment of IPF.<sup>134</sup>

Plans to grow the off-label market for one drug to replace waning revenues of another drug were significant to the government in the Eli Lilly-Zyprexa investigation. FDA approved Zyprexa for treatment of schizophrenia and acute manic episodes associated with Bipolar I Disorder.<sup>135</sup> The government argued that the evidence showed Eli Lilly decided to broaden its efforts to promote and sell Zyprexa, including for off-label uses, to compensate for lost revenue from the popular antidepressant drug Prozac.<sup>136</sup>

### E. Sales Approaches to Physicians

The sales representative is a drug company's principal conduit between business planning and actual sales. The sales representative's interchange with physicians is thus a focal point of any government investigation of off-label promotion. The legal backdrop for the government's review is FDA guidance. While the guidance does not have the force of law, it nonetheless is an FDA pronouncement allowing a drug manufacturer to disseminate accurate information in response to a physician's unsolicited inquiry about an off-label use. Thus, the government looks for evidence of sales representatives initiating off-label discussions with physicians, rather than awaiting the physician's unsolicited inquiry. Some companies have required their sales representatives to maintain notes of their sales calls on physicians. The government combs through these notes, searching for evidence of a sales representative's repeated initiation of off-label topics during sales calls.

The government is also on the alert for a sales representative's subtle, indirect methods to circumvent FDA guidance. For example, in the case against Eli Lilly for its off-label promotion of Evista, the government alleged that the company had trained its sales representatives "to prompt or bait questions by doctors in order to promote Evista" for unapproved uses.<sup>137</sup> Similarly, the government alleged that the company had encouraged sales representatives to send unsolicited medical letters to doctors to promote Evista's unapproved uses, because, as one sales manager wrote in an email, they "go beyond... what we are able to discuss with our customers."<sup>138</sup> In *Holloway*, the government alleged that Pfizer manager Mary Holloway instructed her sales force to send out unsolicited "medical inquiry" letters to physicians who wrote many prescriptions for the competitor drug Vioxx.<sup>139</sup> The letters were written as if they were responses to the physicians' inquiries. The government found evidence of more sophisticated methods of off-label marketing, including the promotion of drugs through pathways and protocols. The government alleged that Holloway had her assistant circulate an electronic template of a hospital-wide pain management pathway that provided for administration of Bextra for unapproved uses and at unapproved dosages.<sup>140</sup> Holloway also allegedly instructed her sales representatives

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<sup>134</sup> *Id.* at ¶ 21.

<sup>135</sup> Information at ¶ 15, *United States v. Eli Lilly & Co.* (E.D. Pa. filed Jan. 15, 2009).

<sup>136</sup> Government's Memorandum for Entry of Plea and Sentencing at 13, *United States v. Eli Lilly & Co.* (E.D. Pa. filed Jan. 15, 2009).

<sup>137</sup> Information at ¶ 28, *Eli Lilly & Co.*

<sup>138</sup> *Id.* at ¶ 27.

<sup>139</sup> Information at ¶ 39, *Holloway*.

<sup>140</sup> *Id.* at ¶ 28.

to send examples of written protocols that called for unapproved uses and dosages of Bextra in certain surgical and pain management settings.<sup>141</sup>

Telling physicians how to use certain diagnostic codes to obtain reimbursement for off-label uses is another tactic that has drawn the government's attention. In the case against Cephalon, the government alleged that the company instructed sales representatives to coach physicians on what diagnostic codes to record in their documentation so that insurers would pay for off-label uses.<sup>142</sup> According to the government, Cephalon instructed its sales force to advise doctors to use the diagnostic code for idiopathic hypersomnia when prescribing Provigil (approved for daytime sleepiness associated with narcolepsy, excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder) to treat fatigue, because insurers and payers like Medicaid would not reimburse for Provigil if prescribed for the off-label indication of fatigue.<sup>143</sup>

Touting increased reimbursements for off-label uses was also alleged by a relator in a recently unsealed qui tam complaint against Boston Scientific Corporation and Guidant Corporation. The relator alleged that the companies promoted their microwave ablation products for off-label uses by "marketing the spread" between the high reimbursement for atrial fibrillation procedures using their products and the low cost of the procedures.<sup>144</sup> The marketing brochure targeted hospitals and advised that designation of microwave surgical ablation as a stand-alone procedure would result in a significantly higher Medicare reimbursement.<sup>145</sup>

Companies that hire medical professionals to do what the companies perceive sales representatives cannot under FDA guidance also attract the government's attention. In the Warner-Lambert case, for example, the government alleged that the company used "medical liaisons" from its Medical Affairs department to promote Neurontin's unapproved uses. In the company's view, medical liaisons (but not sales representatives) could respond to off-label questions asked by physicians. Nevertheless, the medical liaisons, according to the government, did not simply respond to inquiries, but actually "initiated off-label promotions by raising off-label subjects."<sup>146</sup> The government did not allege that the medical liaisons made false or misleading statements about Neurontin's off-label uses. Thus, their alleged conduct appears to have fallen into the murky waters between protected and prohibited speech.

The government suggested, however, that the medical liaisons had a deceptive air about them. They allegedly succeeded in accessing physicians (whom sales representatives had been unable to access), because they gave the appearance of persons with a scientific background whose corporate function was not sales, when, in fact, company management viewed them "first and foremost, as a highly useful marketing tool."<sup>147</sup>

A more egregious example (at least according to government allegations) of a company's use of medical professionals to promote off-label sales is *United States v. Gleason*. There, the government alleged that Orphan Medical, Inc., a subsidiary of Jazz Pharmaceuticals, Inc., hired Gleason, a psychiatrist, to help promote off-

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<sup>141</sup> *Id.* at ¶ 29.

<sup>142</sup> Information at ¶ 16, *Cephalon*.

<sup>143</sup> *Id.*

<sup>144</sup> First Amended Complaint at ¶ 88, *United States ex rel. Doe v. Boston Scientific Corp. et al.* (N.D. Ill. filed July 10, 2009).

<sup>145</sup> *Id.* at ¶ 94.

<sup>146</sup> Sentencing Memorandum of the United States at 28, *Warner-Lambert Co., LLC*.

<sup>147</sup> *Id.* at 30.

label uses of Xyrem, a drug approved to treat two narcolepsy-related disorders.<sup>148</sup> The federal government had classified Xyrem as a “date rape” drug used in sexual assaults, and considered it a drug subject to recreational abuse. Gleason allegedly gave many talks around the country to groups of physicians to promote Xyrem’s unapproved uses.<sup>149</sup> The government alleged specifically that Gleason made “deceptive and misleading” representations to physicians, including that Xyrem was not a “date rape” drug, had only minor side effects, and was safe for people of all ages, including children.<sup>150</sup>

In July 2007, Orphan Medical pled guilty to a felony misbranding charge. The government specifically charged that the company, with intent to defraud and mislead, introduced into interstate commerce a misbranded drug under 21 U.S.C. § 352(f), in that the company marketed Xyrem for unapproved uses, knowing that its labeling lacked adequate directions for and adequate warnings against those uses, in violation of 21 U.S.C. §§ 331(a) and 333(a)(2).<sup>151</sup> The parent company, Jazz Pharmaceuticals, entered into a nonprosecution agreement with the government. The companies agreed to pay a total of \$20 million to resolve their criminal and civil liability.<sup>152</sup> In April 2006, the government indicted Gleason on felony misbranding charges and healthcare fraud.<sup>153</sup> In a plea deal, the government later filed a misdemeanor misbranding charge against Gleason,<sup>154</sup> and his sentencing is pending.<sup>155</sup>

The government also examines whether the sales force calls on physicians whose practices are consistent with the drug’s unapproved uses. If the physician has little or no use for a drug’s approved use, but a strong interest in its unapproved uses, then the government will try to infer from the sales representative’s unsolicited call an intention to promote the drug’s off-label uses. The government’s case in September 2007 against Bristol-Myers Squibb Company for off-label promotion of its drug Abilify provides a good example. Abilify is an atypical, anti-psychotic drug approved by FDA to treat adults with schizophrenia or bipolar disorder—not children, nor geriatric patients suffering from dementia-related psychosis. As evidence of the company’s intention to promote Abilify’s off-label use in children, the government cited the company’s direction of its sales force to call upon child psychiatrists and other pediatric specialists.<sup>156</sup> The theory is as follows: because the targeted physicians only see children, the company must have off-label use in mind when calling on them to sell Abilify.

Similarly, Bristol-Myers Squibb allegedly created a sales force to call almost exclusively on nursing homes providing long-term care, where dementia-related psychosis (an unapproved use) is far more prevalent than schizophrenia or bipolar

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<sup>148</sup> Information, *United States v. Orphan Medical, Inc.*, No. 07-531 (E.D.N.Y. filed July 13, 2007).

<sup>149</sup> Superseding Indictment at ¶ 12, *United States v. Peter Gleason et al.*, No. 06-229 (E.D.N.Y. filed July 25, 2007).

<sup>150</sup> *Id.* at ¶ 14.

<sup>151</sup> Press Release, U.S. Attorney’s Office, Eastern Dist. of New York, Jazz Pharmaceuticals, Inc. Agrees to Pay \$20 Million to Resolve Criminal and Civil Allegations in “Off-Label” Marketing Investigation (July 13, 2007), available at <http://www.usdoj.gov/usao/nye/pr/2007/2007jul13a.html>.

<sup>152</sup> *Id.*

<sup>153</sup> Superseding Indictment, *Gleason*. Gleason has raised various defenses, including that his presentations to physicians were protected speech under the First Amendment. Motion to Dismiss Counts One and Three of the Indictment, *Gleason* (filed Mar. 1, 2007).

<sup>154</sup> Superseding Misdemeanor Information (filed Aug. 8, 2008).

<sup>155</sup> Since the original publication of this piece, the Court sentenced Gleason to one year of probation.

<sup>156</sup> Press Release, U.S. Department of Justice, Bristol-Myers Squibb to Pay More Than \$515 Million to Resolve Illegal Drug Marketing and Pricing (Sept. 28, 2007), available at [http://www.usdoj.gov/opa/pr/2007/September/07\\_civ\\_782.html](http://www.usdoj.gov/opa/pr/2007/September/07_civ_782.html).

disorder (the approved uses).<sup>157</sup> Obviously, a company can counter that because nursing homes are likely to have some patients whose diagnoses coincide with a drug's approved use, the company has every reason to call upon them. The government will, nevertheless, look for internal documents and other evidence showing that the company's resources devoted to nursing homes are disproportionate to relatively small patient populations having the approved diagnosis. Such evidence, in combination with a company's internal tracking of off-label prescriptions at nursing homes, tends to show that a company's nursing home initiative is driven by off-label sales.

Bristol-Myers Squibb paid \$515 million to resolve civil FCA and other civil and administrative liability for a variety of allegedly illegal drug marketing and pricing practices, one of which involved off-label promotion of Abilify.<sup>158</sup> The company did not have to plead guilty to or otherwise resolve criminal charges. In its press release announcing the resolution, the government noted that, prior to the government's investigation, the company had taken steps to modify its physician "call lists" to reduce the potential for off-label marketing.<sup>159</sup>

In another example of physician-targeted tactics, Lilly developed two sales teams—one for primary care physicians and one for physicians treating the elderly. The long-term care sales force, charged with promoting Zyprexa (approved for treatment of schizophrenia and bipolar disorder) to nursing homes and similar facilities, grew from 15 to 160 representatives in less than a year.<sup>160</sup> Sales staff were told to seize "A Golden Opportunity" and focus on behavioral symptoms rather than on FDA-approved indications.<sup>161</sup> Lilly trained its primary care physician sales representatives to similarly promote Zyprexa by focusing on symptoms. The government alleged that Lilly created patient profiles, including a fictitious patient called "Martha," who exhibited dementia symptoms like agitation.<sup>162</sup> Lilly allegedly trained primary care physician sales representatives to lead their pitches with the "Martha" profile, which was a very successful tool for promoting Zyprexa. Lilly agreed to pay a record \$1.415 billion in criminal fines, forfeiture, and to settle FCA violations.<sup>163</sup>

#### F. *The Use of Scientific Articles, Abstracts, and Studies*

The government often scrutinizes the sales force's handling of scientific articles, abstracts, and studies on off-label topics. Under FDA guidance, a company presumably has some leeway to discuss these materials and to make them available to physicians who ask about them. The government's firm position, however, is that a sales representative has no business getting into these materials unless asked. The government even views suspiciously the sales representative who carries off-label articles along to the initial sales call.<sup>164</sup>

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<sup>157</sup> *Id.*

<sup>158</sup> *Id.*

<sup>159</sup> *Id.*

<sup>160</sup> Government's Memorandum for Entry of Plea and Sentencing at 13, *Eli Lilly*.

<sup>161</sup> *Id.* at 13-14.

<sup>162</sup> Information at ¶ 26, *Eli Lilly & Co.*

<sup>163</sup> Press Release, U.S. Attorney's Office, Eastern Dist. of Pennsylvania, Pharmaceutical Company Eli Lilly to Pay Record \$1.415 Billion for Off-Label Drug Marketing (Jan. 15, 2009).

<sup>164</sup> Michael K. Loucks, *The Off-Label Nightmare: What Happens When the Feds Come A'Calling*, REGULATORY FOCUS, May 2008.

In the investigation into Eli Lilly for off-label promotion of Zyprexa, the government found evidence that sales staff were directed to commence sales calls with physicians by discussing a study reprint that showed low-dose Zyprexa was effective in treating agitation, aggression, and psychosis in the population of elderly patients with Alzheimer's disease.<sup>165</sup> The government contended that the use of the one study in isolation was misleading because other Eli Lilly studies had different results that showed, among other things, Zyprexa was no more efficacious in treating Alzheimer's than a placebo or other drugs.<sup>166</sup> Sales representatives were also encouraged to induce physicians to ask unsolicited questions about another study that suggested Zyprexa was an effective treatment for dementia (not an FDA-approved indication).<sup>167</sup>

The government also places under the microscope the sales representative's handling of off-label materials in response to a physician's inquiry about them. In the case against Eli Lilly for off-label promotion of Evista, for example, the government highlighted the company's alleged mishandling of an article reprinted from the *Journal of the American Medical Association* on the drug's effectiveness in reducing the risk of breast cancer in postmenopausal women—an off-label use of the drug. According to the government, the company, in training on how to present the reprint to physicians, instructed its sales force to hide the reprint's disclosure page.<sup>168</sup> That page disclosed that the reprint's authors were either employees or paid consultants of Eli Lilly, and that, according to Evista's prescribing information, its effectiveness in reducing the risk of breast cancer had not yet been established.<sup>169</sup> By presenting the article in this misleading light, the company allegedly intended to promote Evista's unapproved use as therapy to reduce the risk of breast cancer.<sup>170</sup> The government did not allege, however, that the company acted with the "intent to defraud or mislead" necessary to convert the misdemeanor offense of misbranding into a felony.

### G. CME Seminars and Conferences on Off-Label Uses

Under FDA guidance, promotional labeling does not generally include materials disseminated by an independent provider of medical education. The key word for the government is "independent." In off-label cases, the government looks for evidence of the manufacturer's undue influence on purportedly "independent" medical education, and views such influence as evidence of the company's intention to promote off-label use. The government's position is evident from congressional testimony of Lewis Morris, Chief Counsel to the Inspector General of the U.S. Department of Health and Human Services in February 2007. Identifying "abusive practices that provide false and misleading information about the safety or efficacy of products for non-approved uses," Mr. Morris included the following:

Sponsoring purportedly objective "independent" medical education events designed to discuss off-label uses. In fact, the manufacturer provides exten-

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<sup>165</sup> Government's Memorandum at 14-15, *Eli Lilly & Co.*

<sup>166</sup> *Id.* at 16.

<sup>167</sup> *Id.* at 16-17.

<sup>168</sup> Complaint for Permanent Injunction at ¶ 31, *United States v. Eli Lilly & Co.*, No. 05-1884 (S.D. Ind. filed Dec. 21, 2005).

<sup>169</sup> *Id.*

<sup>170</sup> *Id.*

sive subjective input about the topics, speakers, content, and participants of these events.<sup>171</sup>

Or, as another government enforcement official posed the government's concern: does the physician learn about a study of a drug's off-label use only because he or she attends a company-engineered CME program, without realizing (because the company conceals) that the company paid for and organized the program, and controlled the speaker topics and the invitation list?<sup>172</sup>

The Warner-Lambert case highlights these concerns. According to the government, internal marketing documents showed that the company viewed CME as an effective promotional program for Neurontin's off-label uses. The government uncovered evidence that the company influenced the content of supposedly "independent CME programs," even though the programs disclaimed any such influence.<sup>173</sup> Through its subsidiary, Warner-Lambert partnered with a vendor to furnish an "independent" medical education program designed to promote Neurontin's off-label use for pain. Warner-Lambert established a financial relationship with the vendor, and transferred drug company employees to work for the vendor. They participated in all stages of planning the off-label program. The vendor presented the program to thousands of physicians across the country, each time representing that the program materials met Accreditation Council for Continuing Medical Education guidelines for accreditation—in effect, a representation that Warner-Lambert did not control the program and that all financial affiliations had been disclosed. Neither Warner-Lambert nor the vendor, according to the government, ever disclosed Warner-Lambert's control over the program, the financial relationship between Warner-Lambert and the vendor, or Warner-Lambert's financial payments to the program's physician speakers. All of this, the government said, demonstrated that Warner-Lambert knew the CME programs were "unlawful promotional activities."<sup>174</sup>

#### H. *Paid Consultants, Advisory Boards, and Honoraria*

Off-label enforcement cases often involve a manufacturer's payments to or perks for physicians. Not unique to off-label cases, these financial benefits are problematic. The federal healthcare program's anti-kickback statute makes it a felony for anyone knowingly and willfully to pay remuneration to any person to induce him or her to order or arrange for an item for which payment may be made in whole or in part under a federal healthcare program.<sup>175</sup> In other words, payments to a physician to induce him or her to prescribe a particular drug to be paid for under a federal healthcare program are illegal remuneration. The anti-kickback statute does not differentiate between a drug's approved and unapproved uses.

The government in off-label investigations routinely looks for evidence of a manufacturer's payments to physicians to prescribe off-label uses of the company's drug. The government highlights these payments as evidence of illegal promotion,

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<sup>171</sup> "Allegations of Waste, Fraud and Abuse in Pharmaceutical Pricing: Financial Impacts on Federal Health Programs and the Federal Taxpayer," Testimony Before the House Oversight and Government Reform Committee, Feb. 9, 2007, at 6.

<sup>172</sup> See Loucks, *supra* note 163 at 30.

<sup>173</sup> Sentencing Memorandum of the United States at 40-42, *Warner-Lambert Co., LLC*.

<sup>174</sup> *Id.* at 42.

<sup>175</sup> 42 U.S.C. § 1320a-7b(b).

even in cases where the payments themselves do not give rise to separate criminal charges under the anti-kickback statute. Examples include:

- (1) Bristol-Myers Squibb's payment of "illegal remuneration in the form of consulting arrangement fees to physicians to induce them to prescribe Abilify" for unapproved uses<sup>176</sup>;
- (2) Warner Lambert's payment of extravagant expenses (trips, hotels, and dinners) for physicians to attend consultant or advisory meetings and speaker bureau trainings at which company representatives presented information on Neurontin's unapproved uses<sup>177</sup>;
- (3) Schering-Plough's facilitation of off-label sales "through the provision of substantial budgets for advisory boards (some of which were nothing more than an opportunity to present off-label messages), speakers, entertainment (including lavish entertainment in exchange for prescriptions), and preceptorships to assist in obtaining off-label sales"<sup>178</sup>;
- (4) Cell Therapeutics' use of sham "consulting agreements" to pay physicians \$500 to \$1,000 to attend dinners or conferences on Trisenox's off-label uses in treating certain cancers and speakers' fees to reward physicians who wrote large numbers of prescriptions for Trisenox for off-label uses<sup>179</sup>;
- (5) Cephalon's regular sending of doctors to lavish resorts for "consultant" meetings to hear discussions about off-label uses of its drugs.<sup>180</sup>

Occasionally, the government views these payments as sufficiently egregious to warrant their own separate anti-kickback charges. A prominent example is the case against Serono, S.A, a Swiss company, in October 2005. Serono and its U.S. subsidiaries agreed to pay a staggering \$704 million to resolve multiple allegations of illegal marketing of Serostim, a drug used to treat wasting caused by acquired immunodeficiency syndrome (AIDS).<sup>181</sup> Serono Laboratories, one of the subsidiaries, agreed to plead guilty to two separate, felony conspiracy counts: one to violate the FDCA by introducing into interstate commerce adulterated medical devices with intent to defraud or mislead; the other to violate the anti-kickback statute by knowingly and willfully paying illegal remuneration to physicians to induce them to write prescriptions for Serostim (for which payments were made by the federal Medicaid program). The first count pertained to the off-label marketing aspect of the case—introducing an unapproved medical device used to diagnose AIDS wasting with the intent to defraud physicians.

The second count pertained to the illegal kickback aspect of the case. The company allegedly targeted physicians, who were high prescribers of Serostim, and offered each one an all-expenses paid trip (travel, hotel, some meals, and entertainment) to a medical conference in Cannes, France, in exchange for the physician's writing

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<sup>176</sup> Press Release, *supra* note 155.

<sup>177</sup> Sentencing Memorandum of the United States at 27, *Warner-Lambert Co., LLC*.

<sup>178</sup> Government's Redacted Sentencing Memorandum at 24, *Schering Sales Corp.*

<sup>179</sup> Press Release, United States Dep't of Justice, Cell Therapeutics, Inc. to Pay United States \$10.5 Million to Resolve Claims for Illegal Marketing of Cancer Drug (Apr. 17, 2007), available at [http://www.usdoj.gov/opa/pr/2007/April/07\\_civ\\_258.html](http://www.usdoj.gov/opa/pr/2007/April/07_civ_258.html).

<sup>180</sup> Information at ¶ 18, *Cephalon*.

<sup>181</sup> Press Release, United States Dep't of Justice, Serono to Pay \$704 Million for the Illegal Marketing of AIDS Drug (Oct. 17, 2005), available at [http://www.usdoj.gov/opa/pr/2005/October/05\\_civ\\_545.html](http://www.usdoj.gov/opa/pr/2005/October/05_civ_545.html).

up to an additional 30 prescriptions.<sup>182</sup> With the cost per course of treatment per prescription at \$21,000, each physician who wrote an additional 30 prescriptions added \$630,000 to the company's revenue. According to the allegations, the company offered the all-expenses paid trip directly in exchange for prescriptions—a classic quid pro quo kickback. This is in contrast to indirect payments, such as some of the payments described in the above cases. For example, a company's payment for a physician to attend an advisory board meeting or a conference to discuss a drug's off-label use is not directly in exchange for writing additional prescriptions. Nevertheless, the company's purpose may be indirectly to induce the physician to write more off-label prescriptions by educating him or her on the drug's off-label uses. The anti-kickback statute is quite broad, and covers both direct and indirect payments to induce prescriptions for off-label use.

In April 2005, the government charged two former vice-presidents and two former regional sales directors of Serono Laboratories with criminal anti-kickback violations. Following a two-and-one-half week trial in federal court in Boston, the jury returned verdicts of not guilty on all four individuals after deliberating for less than three hours.<sup>183</sup>

## V. CONCLUSION

Government enforcement against off-label marketing has been remarkably aggressive despite uncertainty concerning the legal underpinnings of the theories of prosecution. The government's financial recoveries from pharmaceutical and medical device companies have been significant, particularly given that they rest, at least in part, on novel, largely untested theories of civil and criminal liability.

Under the civil False Claims Act, the government's theory that the pharmaceutical company's off-label marketing to a physician causes the physician to write an off-label prescription, which in turn causes a pharmacy to submit a false claim for payment to a federal healthcare program, requires several leaps of logic, none of which have been fully tested in the courts—and certainly not under the recent amendments to the FCA.

Similarly, the government's criminal theories under the FDCA raise as many questions as they answer. The unlawful introduction of an unapproved "new drug" requires proof that the drug is accompanied by "labeling," as that term is used under the statute, that promotes an unapproved use, which would not seem to encompass oral statements made by sales representatives. Moreover, as the statute, FDA's guidance interpreting the statute, and the First Amendment make clear, certain written information about a drug's off-label use is protected speech and cannot support a criminal prosecution for introduction of an unapproved, new drug.

As for the unlawful introduction of a misbranded drug due to labeling that bears "inadequate directions for use," prescription drugs may be exempt from this prohibition altogether. Further, in a prosecution for introduction of a misbranded drug due to false or misleading labeling, not all claims about a drug's efficacy for unapproved uses are necessarily "false or misleading" within the meaning of 21 U.S.C. § 352(a). And in any criminal prosecution for off-label promotion, the First

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<sup>182</sup> Information at ¶ 73, *United States v. Serono Laboratories, Inc.*, No. 05-10282 (D. Mass. filed Oct. 17, 2005).

<sup>183</sup> Ross Kerber, *Jury Acquits 4 in Serono Kickback Case*, BOSTON GLOBE (May 4, 2007), available at [http://www.boston.com/business/globe/articles/2007/05/04/jury\\_acquits\\_4\\_in\\_serono\\_kickback\\_case](http://www.boston.com/business/globe/articles/2007/05/04/jury_acquits_4_in_serono_kickback_case).

Amendment provides (as *Caputo* reminds us) a certain layer of protection still undefined by the courts.

In these uncharted waters, rather than raise legal challenges to the government's theories, many companies will sail grudgingly for the safe harbors of civil settlements, deferred prosecution agreements, and other comparable resolutions. They at least enable the company to move out from under the government cloud and to continue in business. No company today wants to become the next Arthur Andersen—winning a legal battle in the U.S. Supreme Court, having long since lost the survival war before its legal claims were ever fully heard. These companies will have to continue to monitor the government's enforcement cases carefully, looking for signals on how best to avoid prosecution or to minimize any damage if and when the government knocks on the company's door. Certain patterns of company activity are closely monitored by the government and often form the factual predicates for an investigation, or worse, an indictment. The government's focus on various such patterns has evolved more over the past year and will likely continue to do so, particularly with the recent changes in the political administration. For example, direct interactions between a company's sales and marketing team and practicing physicians have been a recent focus. As practices in the industry have changed in response, FDA focus appears to have shifted to clinical trials, emerging markets, and reimbursement, which may well direct or re-direct the focus of DOJ. Following and predicting this changing landscape should form the guideposts for corporate compliance.

Meanwhile, for legal relief, companies will likely have to look to criminal prosecutions of individuals, or civil FCA cases in which the relators go it alone because the government declines to intervene. In criminal cases against individuals, the prospect of stiff jail sentences often gives defendants the incentive to litigate to the fullest. While civil FCA recovery against defendants will likely be easier due to the recent amendments to the FCA, a relator's chance of recovery will still decline precipitously in cases where the government declines to intervene. Civil FCA cases and criminal prosecutions involving individuals are the venues where defendants are most likely to challenge the government's theories vigorously and where courts may lend some clarity to this consequential yet muddled area of law.