How Hard Should It Be to Imprison Someone for Telling the Truth?

FDA Advertising Regulation Enforcement

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The past two decades have seen a flurry of enforcement activity surrounding pharmaceutical companies' promotion of their drugs for uses other than those approved by the Federal Food and Drug Administration (FDA)—so-called "off-label" uses.[1] At the heart of these criminal prosecutions is the allegation that the advertisements of the medications at issue resulted in misbranding.[2] While several off-label advertisement defenses have focused on the advertising party's First Amendment rights,[3] these defenses have only been partially successful, since "commercial speech" is provided far less protection under the First Amendment than topics like political, scientific or purely opinion speech.[4]

I. Background: The FDA Regulatory Framework for Advertising

The Pharmaceutical Regulatory Scheme and FDCA Cases

When the government pursues a criminal prosecution under the Federal Food, Drug and Cosmetic Act (FDCA), the false or misleading message appears to be that the off-label use is, in fact, approved by the Food and Drug Administration (FDA).[5] Which uses are "on" and which are "off" label are a by-product of the following complicated FDA regulatory scheme.

After reviewing the clinical data submitted by a pharmaceutical company or drug manufacturer, FDA evaluates whether

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a "new drug" is safe and effective for its proposed uses. Absent a finding that the "new drug" meets those criteria, the sponsor of the "new drug" cannot market or distribute the drug in the United States. The process of getting a drug approved by FDA—the investigational new drug (IND) process—is costly and time-consuming. The IND process typically has three separate phases.[6]

"Phase I" trials evaluate the safety of the medication by studying the effect of the drug and are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness.[7] "Phase II" trials are designed to obtain preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition.[8] "Phase III" trials are intended to gather additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug.[9] Many drugs, like chemotherapy drugs for example, have deeply deleterious—sometimes even fatal—side effects, and part of the FDA approval process is weighing the potentiality for those side effects against the disease process the drug is designed to treat. The sponsor's goal at the end of the IND process is an approved New Drug Application (NDA).[10]

The FDCA generally prohibits manufacturers of new drugs or new devices from distributing products in interstate commerce for any use not set forth in the approved NDA.[11] Nevertheless, once an approved NDA exists, a healthcare professional may lawfully use or prescribe that product for any use, within the limits set by professional standards of practice, including off-label uses not set forth in the approved NDA.[12] For some conditions, an off-label use of a medication may reflect the standard of care.[13]

Therefore, in many cases health insurers, including the Federal government, will pay for off-label treatments.[14] Under FDA regulations, however, if the sponsor wants to market or promote the "new drug" for an off-label use, then FDA requires separate approval by FDA through the filing, for example, of an NDA deviation.[15] Consequently, while physicians may prescribe an approved drug for any purpose, sponsors may only market their drugs for uses set forth in the approved NDA.

In order to ensure that sponsors do not market their drugs for unapproved uses, FDA controls sponsors' promotional activities through an intricate series of regulations and statutes. Under the FDCA it is illegal to directly or indirectly distribute a product in interstate commerce that is "adulterated" or "misbranded."[16] The statute further mandates that an approved drug that is marketed for an unapproved use (whether in labeling or in another manner) is "misbranded" because the labeling of such drug does not include "adequate directions for use."[17]

A drug is "adulterated" if its labeling includes information regarding a use that FDA has not approved.[18] Furthermore, FDA regulations also provide "[a] n advertisement for a prescription drug … shall not be recommended or suggest any use that is not in the labeling accepted in such approved new-drug application or supplement."[19] FDA interprets "advertisement" "to include information other than labeling that originates from the same source as the product and that is intended to supplement or explain the product."[20] Consequently, in addition to drug labeling, FDA considers manufacturer speech concerning its products subject to its regulatory prohibitions on off-label promotion.

Pharmaceutical sponsors of approved drugs engage in standard advertising techniques, including mailing sales brochures to physicians and their offices, giving out "free samples" to prescribing physicians and putting advertisements in medical journals.[21] But they also maintain a network of sales representatives that utilize sophisticated technology, including data-mining and personal interviews, to monitor individual physicians' prescribing habits and target those physicians that they believe are under-utilizing their product or utilizing a competitor product instead.[22]

A fine line often exists between some pharmaceutical companies' marketing and research activities. Pharmaceutical companies often hire scientists and physicians, sometimes from high-profile academic institutions, to conduct or present the latest research about their products, or lead physician groups dedicated to creating standard uses of medications for particular conditions or diagnoses.[23]

II. *Caronia*, *Harkonen* and *Holloway*

In *United States v. Caronia*, the United States charged Alfred Caronia (Caronia), a sales representative for Orphan Medical, Inc. (Orphan), with violating Sections 331(a) and (k) of the FDCA. Sections 331(a) and (k) prohibit the introduction or causing the introduction into interstate commerce of any misbranded drug.

Caronia was a sales representative for Xyrem, a sleep inducing depressant, whose principal ingredient was

gamma-hydroxybutyrate (GHB).[24] Xyrem was first approved by FDA in July 2002 to treat patients with narcolepsy who experience episodes of cataplexy, a condition associated with weak and paralyzed muscles.[25] In November 2005, FDA approved Xyrem to treat excessive daytime sleepiness (EDS) in patients with narcolepsy. Xyrem is not approved for any other medical indications.

Abuse of Xyrem can lead to dependence and withdrawal symptoms as well as medical problems including seizures, coma and death. Due to FDA's concerns over Xyrem's potential serious risks, FDA required, prior to approval, that Xyrem's label include a "black box" warning.[26] In addition, distribution of Xyrem was restricted and subject to several conditions. For example, Orphan only distributed it through a single, centralized pharmacy, was required to provide physician and patient education, maintain a physician and patient registry, track prescription usage, and detail patient surveillance.

In April 2005 FDA's Office of Criminal Investigations, Special Prosecutions Staff, opened a criminal investigation of alleged off-label promotion of Xyrem. As part of its investigation, the government used a physician as an undercover cooperating witness to determine if the allegations were true. The government charged that on October 26, 2005, Caronia allegedly promoted several off-label uses of Xyrem including fibromyalgia, EDS, muscle disorders, chronic pain, and fatigue to its undercover witness.[27] The government further alleged that, on November 2, 2005, Caronia introduced to the undercover witness another Orphan-paid physician who also promoted Xyrem for off-label indications, including fibromyalgia, EDS, sleepiness, weight loss and chronic fatigue.[28]

Pursuant to its misbranding regulations, the U.S. government filed a two-count misdemeanor complaint against Caronia.[29] Count one alleged that, between March 2005 and March 2006, Caronia knowingly and intentionally conspired with others to misbrand a drug by marketing Xyrem for off-label uses in violation of 21 U.S.C. §§ 331(a), (k), 333(a)(1) and 18 U.S.C. § 371. Count two charged Caronia with a substantive violation of misbranding a drug while it was held for sale after shipment in interstate commerce, violating 21 U.S.C. §§ 331(k) and 333(a)(1).

Caronia moved to dismiss on several bases, including that the misbranding provisions of the FDCA violated the Free Speech Clause of the First Amendment.[30] The *Caronia* Court quickly rejected Caronia's first two arguments in support of his motion to dismiss.[31] But, the Court spent considerable analysis on Caronia's First Amendment argument as the constitutional issues raised by Caronia were "very much unsettled, not only in this circuit but nationwide."[32] Essentially, Caronia argued that the government cannot restrict truthful, non-misleading promotion by a pharmaceutical representative to a physician of the off-label uses of an FDA-approved drug.[33] He pointed out the legal inconsistency that prohibits a pharmaceutical manufacturer from promoting off-label uses to physicians and consumers, yet permits physicians to prescribe drugs for an off-label purpose, regardless of whether that purpose has been approved by FDA.[34]

The Court denied Caronia's argument that Sections 331(a) and (k) of the FDCA violated the First Amendment of the U.S. Constitution by restricting Caronia's freedom of speech.[35] After noting a recent trend among courts holding that FDA's off-label marketing restrictions were unconstitutional restrictions on commercial speech under the First Amendment, the Court rejected Caronia's argument, instead finding that, in this case, the FDCA's prohibition against off-label promotion was a reasonable fit for the government's interest in protecting the public health.[36]

In *United States v. Harkonen*, the United States has charged Scott Harkonen, an M.D. and C.E.O. of the small pharmaceutical company InterMune in California, with one count of wire fraud and one count of misbranding under section 331(a) of the FDCA.[37] Dr. Harkonen's company manufactures Actimmune (interferon gamma-1b), a medication designed to treat chronic granulomatous disease and severe, malignant ostepetrosis.[38] In October 2000, an article published in the *New England Journal of Medicine*, one of the preeminent medical journals in the world, suggested that Actimmune may also have anti-fibrotic properties for treating idiopathic pulmonary fibrosis (IPF).[39] The article was based on a tiny observational study of 18 patients in Austria.[40] In other words, the article noted an exciting observation that was potentially a coincidence, but potentially a breakthrough therapy.

Fibrosis is a description of progressive scarring that can occur in any bodily organ.[41] In IPF the lungs are slowly overcome with fibrosis.[42] No one knows what causes the fibrosis and, so far, there is no available treatment that stops or slows the progression. Thus, off-label use of Actimmune for IPF likely began shortly after the article was published in the *New England Journal of Medicine*. Dr. Harkonen and his company also quickly began a clinical trial to validate the observation in the Journal article, and make treating IPF an approved

use of Actimmune.[43] Two years later, in 2002, the study was completed.[44] The fibrosis of patients across the board had not improved significantly enough to conclude that Actimmune should become a standard therapy for IPF.[45] What it did find, however, was a slowing of the progression of the fibrosis for patients that had initially begun treatment in a less advanced stage of IPF.[46]

Based on the finding about the subgroup of patients with mild to moderate IPF that could potentially benefit from Actimmune, Dr. Harkonen sent out a press release touting the breakthrough to physicians and patients.[47] Harkonen also assisted and caused the dissemination, by a specialty pharmacy in Florida, of the press release and an accompanying letter to patients and doctors, describing the findings of the "preliminary data" and encouraging patients to use Actimmune early to treat IPF.[48] InterMune also began an internal program encouraging and tracking the sale of Actimmune for IPF and rewarding sales representatives for those sales in their region.[49] As part of the kick-off of this new program, InterMune sales representatives were given, inter alia, t-shirts promoting the use of Actimmune for IPF.[50]

In December of 2003, InterMune began a Phase II clinical trial of Actimmune in patients with early IPF.[51] In 2004, the Department of Justice (DOJ) began looking into allegations that InterMune marketed and promoted the sale of its drug Actimmune for the off-label use of treating IPF.[52] In 2007, the Phase II clinical trial was discontinued because of lack of demonstrated benefit to patients.[53] In March 2008, the DOJ indicted Harkonen for disseminating and causing to be disseminated information about Actimmune for the treatment of IPF with the intent to defraud and mislead, causing Actimmune to be misbranded.[54]

Harkonen moved to dismiss the charges arguing that the press release and other communications about Actimmune's effectiveness for treating IPF charged as disseminations should be excluded from evidence because they do not constitute impermissible "labeling" within the meaning of the FDCA and that releases and communications fall under speech protected by the First Amendment.[55] The court ruled on Harkonen's motion to dismiss, refusing to dismiss the indictment, but agreeing that the evidence relating to the T-shirt distribution should be excluded because the shirts do not constitute labeling under the FDCA.[56]

In *United States v. Holloway*, the United States charged Mary Holloway (Holloway), the regional sales manager for the Northeast Region at Pfizer, with violating sections 331(a), 333(a)(1), and 352(f) of the FDCA.[57] Sections 331(a), 333(a)(1), and 352(f) prohibit the introduction or delivery for introduction into interstate commerce of any misbranded drug.[58] The United States alleged that Holloway marketed the drug Bextra, which was FDA approved to treat the signs and symptoms of osteoarthritis, adult rheumatoid arthritis, and primary dysmenorrhea, for off-label uses and dosages to prevent blood clots known as deep vein thromboses (DTV) and to alleviate surgical pain.[59]

Holloway worked in pharmaceutical sales at Pfizer for more than two decades, earning glowing reviews and standing out as one of the few women at her level within the company.[60] In 2002, Ms. Holloway provided a $100,000 research grant to a consultant studying the effect of replacing narcotics with COX-2 inhibitors in patients that have had joint replacement surgery.[61] The basic theory behind the research was that Bextra has fewer sedative side effects than narcotics. Since one of the primary reasons joint replacement patients develop DVTs after surgery is that they spend too long after surgery not moving, the research demonstrated that providing them with a pain reliever like Bextra, instead of an opioid which has the side effect of increased drowsiness, tended to protect against DVTs.[62] Ms. Holloway prepared a "DVT Backgrounder" with this information, and had the consultant teach the science behind the message directly to her sales staff.[63] She also, in coordination with another Regional Manager, collected and presented a group of pain management protocols and standing orders that had been implemented by various healthcare institutions; in those protocols and standing orders, some of the uses of Bextra were off-label.[64] Ms. Holloway also forwarded to physicians in her sales region "Medical Inquiry Letters," describing on-label and off-label product usage and disease states.[65] These letters were prepared by healthcare professionals and scientists.[66]

The Specific Statements

In *Caronia*, the Government provided a transcript of two conversations between Mr. Caronia and a "cooperating physician" that it purports demonstrated Mr. Caronia's false statements.[67] But, as the transcript makes clear, Mr. Caronia "clearly state[d] that Xyrem's only indication is for narcolepsy."[68] Mr. Caronia did indicate that the company was actively researching the potential use of Xyrem for what were then off-label uses like, for example, fibromyalgia.[69] Repeatedly, Mr. Caronia directed questions about off-label uses to

Dr. Gleason, a licensed physician that was also engaged as a consultant.[70] The indictment itself explains that Gleason gave talks promoting Xyrem's off-label uses.[71] Mr. Caronia was responsible for introducing Dr. Gleason to other physicians.[72]

The specific representations Dr. Gleason was charged with making were that the "deep[er] sleep" made available by use of Xyrem benefited additional diseases other than narcolepsy.[73] Assuming, then, that these representations can be attributed to Mr. Caronia through the conspiracy charges brought against him, the false representations he is charged with making is that Xyrem has benefits for patients with diseases other than narcolepsy because the symptoms of those diseases are primarily caused by a lack of deep sleep.

In *Harkonen*, the Court addressed the scope of the false statements at issue. It found, in its Opinion addressing Harkonen's Motion to Dismiss, that

> labeling under the FDCA is construed expansively, such that it may encompass nearly every form of promotional activity, including package inserts, pamphlets, mailing pieces, fax bulletings, reprints of press releases, and all other literature that supplements, explains, or is otherwise textually related to the product.[74]

Applying this definition to the communications at issue in *Harkonen*, the Court found that the press release and accompanying letter sent by the pharmacy constituted "labeling," although the T-shirts distributed to company employees did not. The Court explained this was because the "distribution was internal to InterMune employees only and was not designed for use in the distribution and sale of the drug, nor did it otherwise serve the 'purposes of labeling' so as to 'supplement or explain' Actimmune's intended use."[75]

The specific representations at issue in *Harkonen*, then, were all interpretations of the 2000 and 2002 studies, and conclusions as to patient care drawn from them. They were limited to the press release and its accompanying letter, since the definition of "labeling" used by the Court would seem to preclude prosecution on the basis of any documents designed by the company for internal use only.[76]

In *Holloway*, the specific representations, thus, boiled down to summaries of the DVT research, hospital protocols and standing orders, the communications regarding the off-label uses that were disclosed outside the company.[77]

III. Constitutional Law: The First Amendment, *Central Hudson*, and Procedural Due Process

None of the statements at issue in *Caronia*, *Harkonen* or *Holloway* explicitly misrepresented FDA regulatory status of the usages allegedly promoted. None, however, were considered "scientific opinion," and therefore given full First Amendment protection, either. Instead, to the extent that they were scientific opinion offered by or on behalf of scientists, they were all alleged to have violated 21 CFR § 312.7(a), which reads:

> A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

Section 312.7(a), by its own terms, acknowledges that it has the potential to restrict the flow of information that is scientific in nature, but relies on a finding of commercial "intent" to restrict only those communications made with a promotional purpose. At root, then, the FDCA makes not specific communications illegal, but rather specific intentions.

Fitting this regulation within First Amendment case law, the intention requirement converts these communications from fully-protected opinion speech to the less-protected "commercial" speech. Scrutiny of "commercial" speech is based on the "Central Hudson," test, first established in *Central Hudson Gas v. Public Serv. Comm'n of New York*, 447 U.S. 557 (1980). When applying the Central Hudson test, a court must determine, as a threshold matter, whether the commercial speech concerns unlawful activity or is misleading.

If the statements in question are found to be unlawful or misleading in and of themselves, then they are not protected by the First Amendment and the inquiry stops. Based the on *Washington Legal Foundation* line of cases, the promotion of off-label uses of FDA approved drugs has generally not been, in and of itself, considered unlawful or misleading. Since physicians may lawfully prescribe drugs for off-label uses, physician statements

concerning off-label uses are generally not considered illegal.

This comports with FDA regulations, which do not prohibit physicians from communicating information about off-label uses to each other, since FDA does not have authority to regulate the practice of medicine itself.[78] The second prong of the *Central Hudson* test requires the court to evaluate whether the asserted government interest is substantial. There can be no question that the government has a substantial interest in promoting accurate information disclosure about pharmaceutical applications.

In the third step of its *Central Hudson* analysis, a Court must determine whether the particular regulation at issue directly advances this governmental interest. Finally, in the fourth prong of *Central Hudson* analysis, a Court must apply the "reasonable fit" test; it must determine whether the regulations at issue are more extensive than necessary to serve their purpose. If they are a "reasonable fit," the regulations will stand.

The Supreme Court has recognized that some advertisements are so inherently misleading that they can be held as such as a matter of law.[79] Yet subsequent Supreme Court case law suggests that the weakest protections lie against speech that is more "action" than pure speech itself. "Our cases teach that there is a difference of constitutional dimension between rules prohibiting appeals to the public at large … and rules prohibiting direct, personalized communication in a coercive setting."[80] First Amendment case law also appears much more likely to uphold disclosure requirements than regulations or statutes that prohibit specific speech.[81]

IV. Reliance in *Harkonen, Holloway* and *Caronia*

This evaluation of the actual effect of the off-label advertising is the key element missing in the FDCA prosecutions in *Caronia*, *Harkonen* and *Holloway*, and it should make these and other FDCA prosecutions suspect under the First, Fifth and Fourteenth Amendments of the U.S. Constitution. Off-label prescriptions are legal because FDA lacks legal authority over the practice of medicine and, from a policy perspective, because of deference to physicians' training and judgment regarding the best interests of their patients. The "audience" for pharmaceutical advertisements is particularly well-versed in exactly the field being addressed: medicine. In fact, physicians assume a heightened duty, even under product liability law, to understand and warn patients of the possible side effects of medications.[82] Even under the reduced protections of *Central Hudson*, commercial speech is protected to the extent that it is not false or misleading.

A. Caronia

In *Caronia*, the Court reached its decision by applying the *Central Hudson* test and determining that the "public interest" in promoting public health justified the restrictions on promotional advertising of off-label usages.[83] At the heart of this missing discussion was the Court's willful blindness to the fact that, in the regulatory system set up by the FDA, it is not the Courts that are in the position to determine the best interests of the patients. It is up to physicians and patients to make that determination.

The crux of the statements at issue in *Caronia* was that Xyrem would induce deeper sleep, which could itself assist in resolving the symptoms of several indications for which the medication was not approved.[84] FDA does not dispute that Xyrem induces deeper sleep. Nor does it aver that obtaining deeper sleep has no effect on patients afflicted with these other physical issues. It merely contends, essentially, that Xyrem has yet to prove this to the satisfaction of FDA. Since FDA regulations allow the use of prescription medications for off-label usages, however, the government implicitly acknowledges that it is not up to FDA to weigh the potential risks and benefits for these off-label uses for each patient. That determination is left up to the discretion of the treating physician and the patient. Thus, FDA has not identified what "harm" it is trying to protect against by restricting speech.

B. Holloway

The specific statements at issue in the Holloway case, the only ones that were communicated outside the company (and were therefore "promotional" as opposed to evidence of promotional intent), were the DVT research, hospital protocols and standing orders. There was no allegation that these communications were literally false, and no evidence proferred to suggest that they misled physicians. In fact, the hospital protocols and standing orders were drafted by practicing physicians that had already weighed the risks and benefits to their patients. Ms. Holloway's communications, which of course were absolutely made for promotional/commercial purposes, communicated the professional judgments made by one set of physicians to another set of physicians. As Ms. Holloway's case settled before it could be decided by a jury, the Court was never faced with the question of how the government could prove, beyond a reasonable doubt, that physicians—the only people in a position to actually rely on the communications—were misled by the statements.

C. Harkonen

Dr. Harkonen's trial is still pending, but all parties agree that the government is not required to introduce evidence of "reliance" in proving falsity.[85] The Court has already upheld the prosecution under *Central Hudson*, so presumably it is satisfied that the public good—including the health of the patients afflicted with IPF that have no other medication to even try to slow or stop the progression of their fibrosis—is advanced by the prosecution of off-label advertising.

V. Conclusion

The byzantine regulation of pharmaceutical sales has evolved into a danger to patient care and a threat to physician autonomy. The lost middle between "scientific opinion" and "promotional communication" is "in the best interests of the patient." If FDA is going to strictly regulate this admittedly commercial speech, the prosecutors enforcing the regulations should at least be required to prove the substance of the communications as they are understood by physicians, who with patients make the determinations regarding medical care and the best interests of the patients.

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1 For example, on Jan. 15, 2009 Eli Lilly and Company agreed to pay a $800 million civil settlement for its off-label promotional activities concerning its drug Zyprexa.

2 *See* FDCA, 21 U.S.C. §§ 331, 333 (2008).

3 *See e.g.* Washington Legal Foundation v. Friedman, 13 F. Supp.2d 51 (D.D.C. (1998)) (holding that FDA's guidance restricting dissemination of reprints and medical articles discussing off-label uses of drugs violated the First Amendment as unconstitutional restriction on commercial speech); Thompson v. Western States Medical Center, 535 U.S. 357 (2002) (holding that it was improper for Congress and FDA to bar the advertising of "compounded" drugs.); and United States v. Caputo, 517 F.3d 935 (7th Cir. (2008)) (stating in dicta that some parts of the FDCA relating to off-label promotion may be unconstitutional at least as applied in some circumstances).

4 *See* Florida Bard v. Went for It, Inc., 515 U.S. 618, 634 (noting the "subordinate position" of commercial free speech among First Amendment values).

5 Government's Memorandum for Entry of Plea and Sentencing at 2–3, United States v. Eli Lilly, (E.D.Pa. (2009)) (explaining that only FDA approved drugs can be distributed and marketed in interstate commerce, implying that off-label advertisements are inherently claiming FDA approval), also *available at* http://www.usdoj.gov/usao/pae/News/Pr/2009/jan/lillygovtmementrypleasent.pdf.

6 *See* 21 CFR §§ 312.20–312.38 (2008).

7 *Id*. at § 312.21.

8 *Id*.

9 *Id*.; *See* the Center for Drug Evaluation and Research (CDER) Handbook: http://www.fda.gov/cder/handbook/. (this link did not work for me).

10 Similar procedures and restrictions apply to biologics. *See* 42 U.S.C. § 262. In the case of biologics, the sponsor must obtain a biologics license or approved BLA. *Id.* However, the same restrictions on off-label promotion apply. *Id.* For purposes of this article, the term "drug" includes an approved biologic.

11 21 U.S.C. §§ 355, 352(o), 351(f)1(B), 331(a) and (d).

12 *Guidance for Industry on 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*; *Availability*, 74 Fed. Reg. 1694 (Jan. 13, 2009) (the "Good Reprint Practices Guidelines"). The Good Reprint Practices Guidelines are *available at* http://www.fda.gov/cder/guidance/ (Jan. 2009). Good Reprint Practices Guidelines at page 2.

13 74 Fed. Reg. 2881, 2882 (Jan. 16, 2009).

14 *Id*.

15 *See generally* 21 C.F.R. Pt. 312.

16 21 U.S.C. §§ 351, 352 (2002).

17 21 U.S.C. § 352(f). A drug that is marketed to the public for an off-label indication or use does not contain "adequate directions for use" because such use and related information were not included in the FDA-approved labeling for the drug.

18 21 U.S.C. § 351.

19 21 C.F.R. § 202.1(e)(i)(a).

20 Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074, 64,076 (Dec. 3, 1997).

21 *See*, *e.g.*, Kemper & Hood, *Does Pharmaceutical advertising affect journal publication about dietary supplements?*, BMC Complementary and Alternative Medicine, V. 4 (Apr. 9, 2008).

22 *See* Carlat, *Dr. Drug Rep*, The NY Times, (Nov. 25, 2007); however, the United States Department of Justice (DOJ) and the Office of Inspector General (OIG), United States Department of Health and Human Services (HHS) is taking a close look at these practices. *See Prosecutors Plan Crackdown on Doctors Who Accept Kickbacks*, The NY Times, (Mar. 4, 2009).

23 *Id*.

24 U.S. v. Caronia, Superseding Indictment (Jul. 25, 2007) at ¶1.

25 *Id*. at ¶2.

26 A black box warning (also sometimes called a black label warning or boxed warning) is a type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. 21 C.F.R. § 201.57(c)(1).

27 U.S. v. Caronia, Superseding Indictment at ¶12 and 24(e).

28 *Id*. at ¶24(f).

29 On July 13, 2007, Orphan pled guilty to felony misbranding in connection with the off-label promotion of Xyrem and agreed to pay more than $20 million in fines.

30 Caronia, 576 F.Supp.2d at 393.

31 First, Caronia argued that the allegations in the indictment actually establish that he did not misbrand Xyrem within the meaning of 21 U.S.C. §331(k) because he administered adequate warnings to the cooperating witness physician. Caronia claims that regardless for what purpose Xyrem is prescribed, it is administered in the same manner and dosage, and therefore the black box warning satisfied the FDCA's branding requirements. The Court rejected this argument as "utterly without merit" based on the FDCA's "intended use" regulations, which prohibit off-label promotion of a drug regardless of what directions the manufacturer or representative provided for that use. The court also rejected Caronia's argument that, even accepting the factual allegations of the information as true, he did not conspire to misbrand Xyrem under either 21 U.S.C. § 331(a) or (k), because the cooperating witness physician never had any intention of prescribing Xyrem for off-label use. The Court rejected this argument because 21 U.S.C. §331(k) only requires the Government to prove that the defendant took some action with respect to the drug that resulted in the drug being misbranded not that the drug was actually used for an off-label purpose. *Caronia*, 576 F.Supp.2d at 391-393.

32 *Id*. at 394.

33 *Id*. at 393.

34 *Id*.

35 U.S. v. Caronia, 576 F. Supp.2d 385 (E.D.N.Y. (2008)).

36 *Id*. at 401.

37 Memorandum & Order at 1–2, United States v. Harkonen, No. C 08-00164 MHP.

38 *Id*.

39 *Id*. at 3–4.

40 *Id*. at 3.

41 See Dox, Eisner, Melloni, and Melloni, Attorney's Illustrated Medical Dictionary f15 (West Publishing Company 1997).

42 Memorandum & Order at 3–4, United States v. Harkonen, No. C 08-00164 MHP.

43 *Id*. at 3.

44 *Id*.

45 *Id*.

46 *Id*. at 3–4.

47 *Id*.

48 Memorandum & Order at 4, United States v. Harkonen, No. C 08-00164 MHP.

49 Defendant's Motion in Limine re: "Labeling" and to Exclude Protected First Amendment Speech or, in the Alternative, to Dismiss the Indictment

50 *Id*.
51 *Id*. at 3.
52 *Id*. at 2.
53 *Id*. at 3.
54 *Id*.
55 *Id*. at 5.
56 *Id*. at 17.
57 Plea Agreement at 1, United States v. Holloway.
58 31 U.S.C. §§ 331(a), 333(a)(1), and 352(f).
59 Plea Agreement at 3, United States v. Holloway.
60 Sentencing Memorandum of Mary Holloway, p. 2.
61 Holloway sentencing memorandum, p. 4.
62 Mary Holloway's Sentencing Memorandum, p. 4.
63 *Id*.
64 *Id*. at 7.
65 *Id*. at 9-10.
66 *Id*.
67 United States v. Caronia, 576 F. Supp. 2d 385, 389–90(E.D.N.Y. (2008)). Another allegation against Mr. Caronia and the physician with whom he allegedly "conspired" is that they provided instructions to other physicians to use inaccurate diagnosis codes in order to obtain insurer payment for off-label uses of Xyrem. Indictment, Dkt. No. 28, ¶ 17. These actions were cited as bases for charges of healthcare fraud, but are not addressed here.
68 Third Memorandum of Law in Support of the Dismissal of Charges Against Defendant Alfred Caronia, Dkt. No. 72, p. 6.
69 *Id*. at 7.
70 *Id*.
71 Indictment, ¶ 12
72 *Id*.
73 *Id*. at ¶12–14.
74 U.S. v. Harkonen, No. C 08-00164 at 16 Mem. & Order, (N.D. Ca. (June 3, 2009)) (slip op.).
75 *Id*. at 18.
76 Although, as the Court makes clear, documents designed for internal use only could be introduced as evidence of a broader corporate plan to promote off-label uses.
77 Holloway pled guilty and was sentenced to parole and a $75,000 fine without going to trial, so we cannot know for certain which specific averments would have been at issue in a jury trial. Based on the rulings in, inter alia, Harkonen, however, one could assume that the communications solely internal to Pfizer, while potentially probative of the intent behind the communications disclosed outside the company, would not have been the "false and misleading" statements that were themselves the basis for the prosecution.
78 *See*, *e.g.*, 21 U.S.C. § 396.
79 Ohralik v. Ohio State Bar Assn., 436 U.S. 447, 464 (1978).
80 Tennessee Secondary School Athletic Assoc. v. Brentwood Academy, 551 U.S. 291, 296 (2007) (citations omitted).
81 Zauderer v. Office of Disciplinary Counsel of Supreme Court of Ohio, 471 U.S. 626, 651 (1985).
82 *See*, *e.g.*, Ebel v. Eli Lilly & Co, No. 08-40170, 2009 U.S. App. LEXIS 6710 (5th Cir. (Mar. 30, 2009)) (unpub. op.), Knipe v. Smithkline Beecham, 583 F. Supp. 2d 602, n. 13 (D.N.J. (2009)), Misouria v. Eli Lilly & Co., 04-MD-1596, 2009 U.S. Dist. LEXIS 57215, (E.D.N.Y. (June 24, 2009)).
83 U.S. v. Caronia, 576 F.Supp.2d 385, 398 (E.D.N.Y. (2008)).
84 Third Memorandum of Law in Support of the Dismissal of Charges Against Defendant Alfred Caronia, Dkt. No. 72, at 5.
85 USA's Reply to the Defendant's Response to the USA's Motion in Limine, Dkt. No. 149, p. 5.

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