

**OFF LABEL PROMOTION OF PHARMACEUTICAL DRUGS
UNDER THE CARONIA AND AMARIN CASES**

Monica Marrero

OFF LABEL PROMOTION OF PHARMACEUTICAL DRUGS

UNDER THE CARONIA AND AMARIN CASES

I. Introduction

The Food and Drug Administration approval is necessary before a manufacturer can distribute a drug or medical device in the market. Congress amended the Federal Food Drug and Cosmetic Act (FDCA) by enacting the Drug Amendments of 1962.¹ The aforementioned require manufacturers to demonstrate that their drugs are both safe and effective for their intended uses before they are approved for distribution. Under the FDCA, a manufacturer may not introduce or deliver for introduction into interstate commerce any new drug that the FDA has not approved.²

The FDCA also prohibits the introduction or delivery for introduction into interstate commerce of a drug that is misbranded, even if FDA has approved the drug.³ The FDCA states that a drug or device is misbranded if its labeling is false or misleading in any particular.⁴ Labeling includes the label and any other written, printed, or graphic material that accompanies a device and any of its wrappers or containers.⁵ The labeling must include adequate directions for use of drugs and medical devices and any warnings necessary to protect the health of the user.⁶

A manufacturer seeking approval for a new drug must submit a detailed application to the FDA to demonstrate the drug's safety and efficacy and propose labeling for the drug.⁷ The average cost to develop a drug between 2000 to early 2010 was \$2.6 billion.⁸ The average time to develop a drug was more than ten years.⁹ The percentage of drugs entering clinical trials resulting in an approved medicine has been less than 12 percent.¹⁰ Therefore, the manufacturers invest a significant amount of money in research and development in order to create a new drug and to prove its safety and efficacy through clinical trials.

¹ Public Law 87-781, 76 STAT 780 [Provide US Code citation as well]

² 21 U.S.C. §§331(d), 355(a)

³ 21 U.S.C. §§331(a), 352

⁴ 21 U.S.C. §352 (a)

⁵ 21 CFR 1.3(b)

⁶ 21 U.S.C. §352 (f)

⁷ 21 U.S.C. §§355(b)

⁸ Pharmaceutical Research and Manufacturers of America. 2015 Pharmaceutical Industry Profile. Washington D.C. PhRMA April 2015 Page 35

⁹ Pharmaceutical Research and Manufacturers of America. 2015 Pharmaceutical Industry Profile. Washington D.C. PhRMA April 2015 Page 35

¹⁰ Pharmaceutical Research and Manufacturers of America. 2015 Pharmaceutical Industry Profile. Washington D.C. PhRMA April 2015 Page 37

FDA approval of a new drug application extends only to the uses prescribed, recommended, or suggested by the drug's FDA-approved "labeling".¹¹ Thus, if the manufacturer of an approved drug seeks to distribute "labeling" that prescribes, recommends, or suggests a new use not already generally recognized as safe and effective, the drug would be considered a "new drug"¹², and the manufacturer must obtain separate approval for the new use to avoid violating the FDCA.

FDA regulations state that a manufacturer that wants to promote an approved drug for a new use such as treatment for a new condition or another population must submit a supplemental new drug application. The drug must then undergo new clinical trials to demonstrate its safety and effectiveness for the new indication. Until the FDA has approved the new use, the manufacturer may not promote the drug for that use.¹³

The FDA's position is that a manufacturer who markets or promotes an off label drug risks criminal liability for "misbranding" under 21 U.S.C. § 331(a), which prohibits "the introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded." Misbranding carries a term of up to one year imprisonment and a fine of up to \$1,000 per occurrence¹⁴, but if the defendant either acted with "the intent to defraud or mislead" or is a repeat offender, a term of up to three years imprisonment and a fine of up to \$10,000 is authorized.¹⁵ Besides the potential misbranding charges under the FDCA, the off-label marketing can result into False Claims Act (FCA) lawsuits and has resulted in expensive greater penalties.¹⁶ The False Claims Act imposes liability on a person or corporation for knowingly presenting a false or fraudulent claim for payment to the United States.¹⁷ Off-label promotion by a drug manufacturer violates the False Claims Act because payment for off-label uses of prescription drugs by government funded healthcare programs such as Medicare and Medicaid is highly regulated and restricted. When drug manufacturers promote their drugs off-label and persuade physicians to write off-label prescriptions for their drugs to beneficiaries of Medicare and Medicaid, the government has argued that the drug manufacturer has allegedly caused the submission of false claims for reimbursement for the drug to the government.¹⁸

¹¹ 21 U.S.C. §321(p)

¹² 21 U.S.C. §321(p)

¹³ 21 U.S.C. §314.70

¹⁴ 21 U.S.C. § 333(a)(1)

¹⁵ id. § 333(a)(2)

¹⁶ Unlawful off-label drug promotion has been the subject of significant health care fraud enforcement efforts by the United States Department of Justice (DOJ) and the States' attorneys general using the Federal False Claims Act (FCA). 31 U.S.C. §§ 3729. The theory underlying these efforts is that, by promoting off-label uses that are not medically accepted, the manufacturers caused pharmacies to claim federal health program (e.g., Medicaid, Medicare) payment for drugs used in ways that are not covered by the federal health program. Most, if not all, State Medicaid programs exclude coverage for drugs that are used for off-label indications that are not medically accepted. Such use can, in principle, waste Medicaid funds on ineffective treatments. DOJ and State enforcement efforts have identified a wide range of deceptive practices by pharmaceutical manufacturers that promoted off-label uses of many prescription drugs. These practices have resulted in large monetary settlements under the FCA. Penalties include up to three times the amount of the damages plus an additional penalty of \$5,500 to \$11,000. Off Label Pharmaceutical Marketing: How to Recognize and Report It. <https://www.cms.gov/Medicare.../off-label-marketing-factsheet.pdf>

¹⁷ 31 U.S.C. §§ 3729

¹⁸ "Johnson & Johnson and Scios have agreed to pay the federal government \$184 million to resolve their civil liability for the alleged false claims to federal health care programs resulting from their off-label marketing of Natrecor". Department of Justice. Office of Public Affairs. November 4, 2013

Generally, drugs prescribed for off-label uses or dosages are eligible for reimbursement under certain circumstances. Medicare, Medicaid, and private insurers will cover off-label drug uses if they are included in major compendia, such as the American Hospital Formulary Service Drug Information and the United States Pharmacopeia Drug Information. The 1993 Omnibus Budget Reconciliation Act mandated that Medicare provide coverage for off-label uses of drugs in anticancer chemotherapy regimens if those uses were supported by designated compendia.¹⁹ State statutes generally require coverage on the basis of compendia listings, although some also require coverage based on articles in peer-reviewed journals.

FDA regulations incorporate the intended use. The term “intended use” refers to the objective intent of the persons legally responsible for the labeling of drugs.²⁰ This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives.²¹ The materials that may serve as proof of a manufacturer’s intended use include the promotional statements by the company or its representatives.²² “Off-label promotional statements could constitute evidence of an intended use of a drug that the FDA has not approved”.²³

A number of recent cases between pharmaceutical companies or representatives and the federal government have involved a novel legal argument that the truthful and non-misleading speech relating to an off label use is protected under the First Amendment of the United States Constitution.²⁴ “Where off-label prescribing is ineffective or ill-advised, the FDA has a legitimate, compelling interest in protecting the public health by ensuring that companies do not transmit false or misleading information, or otherwise encourage off-label prescribing when there is no underlying medical basis. But where the challenged off-label information is truthful, what is the public interest in forbidding it?”²⁵

In addition of criminal exposure under the FDCA for misbranding, drug manufacturers have increasingly been targeted in civil suits under the False Claims Act (“FCA”)²⁶ relating to alleged off-label promotion. These suits allege that off-label promotion caused false claims to be submitted to the federal government health care programs for non-covered and non-FDA-approved uses. In recent years, the government has brought FCA claims on this theory,

"Pfizer has agreed to pay \$1 billion to resolve allegations under the civil False Claims Act that the company illegally promoted four drugs Bextra; Geodon, an anti-psychotic drug; Zyvox, an antibiotic; and Lyrica, an anti-epileptic drug and caused false claims to be submitted to government health care programs for uses that were not medically accepted indications and therefore not covered by those programs." Department of Justice. Office of Public Affairs. September 2, 2009

"GSK will also pay \$2 billion to resolve its civil liabilities with the federal government under the False Claims Act, as well as the states. The civil settlement resolves claims relating to Paxil, Wellbutrin and Avandia, as well as additional drugs, and also resolves pricing fraud allegations." Department of Justice. Office of Public Affairs. July 2, 2012

¹⁹ Recent Developments in Medicare Coverage of Off-Label Cancer Therapies Copyright © 2009 by American Society of Clinical Oncology. <http://jop.ascopubs.org/content/5/1/18.full>

²⁰ 21 CFR 201.128

²¹ 21 CFR Sec. 201.128

²² id. § 201.5

²³ United States v. Caronia, 703 F.3d 149 (2d Cir. 2012) at 155 (citing 21 C.F.R. § 201.5)

²⁴ United States v. Caronia, 703 F.3d 149 (2d Cir. 2012); Amarin Pharma, Inc. v. FDA, No. 15-3588, 55 (S.D.N.Y. Aug. 7, 2015)

²⁵ Osborn: Can I Tell You the Truth? Yale Journal of Health Policy, Law, and Ethics, Vol. 10 (2010), Iss. 2, Art. 2

²⁶ 31 U.S.C. § 3729 et seq

sometimes in addition to criminal prosecutions under the FDCA for misbranding. Another implication of a conviction for misbranding involves the exclusion²⁷ from participation in any federal healthcare program of an individual or entity convicted of a criminal offense related to fraud in connection with the delivery of a healthcare item or service.²⁸ For example, the Office of Inspector General (OIG) for the Department of Health and Human Services (HHS) announced that on January 9, 2009, Administrative Law Judge Carolyn Cozad Hughes affirmed the OIG's imposition of a 15-year exclusion from all Federal health care programs against Michael Friedman, Paul Goldenheim, M.D., and Howard Udell for their roles as responsible corporate officers who failed to prevent misbranding and fraudulent distribution of OxyContin by Purdue Frederick, the manufacturer and distributor of OxyContin. The OIG previously excluded Purdue Frederick for 25 years as part of a global resolution between the United States, Purdue Frederick, and Purdue Pharma. The two Purdue companies agreed to pay \$600 million in restitution and to settle their civil and criminal liabilities and Purdue Pharma entered into a five-year Corporate Integrity Agreement with OIG.²⁹

It is relevant to consider how effective FCA sanctions may be for a company with an extensive pipeline of products to treat several conditions. For example, how significant to Pfizer is a FCA settlement of \$2.3 billion compared with 2014 reported revenues of \$49.6 billion? It represents almost five percent of the revenue for a given year. That money may be invested in research and development of new products to treat patient conditions.

II. Pharmaceutical Industry Off Label Promotion Settlements

In recent years the federal government has recovered billions from manufacturers in settlements of FCA actions.³⁰ Many of these settlements are related to the off label promotion of pharmaceutical drugs.³¹ Companies generally negotiate settlements with the government to

²⁷ ISTA Pharmaceuticals, a subsidiary of Bausch & Lomb was excluded from Medicare in \$33.5 million off label settlement for inducing doctors to prescribe Xibrom drug for unapproved uses. Xibrom is an ophthalmic, nonsteroidal, anti-inflammatory drug that was approved by FDA to treat pain and inflammation following cataract surgery. Some ISTA employees promoted Xibrom for unapproved new uses, including the use of Xibrom following Lasik and glaucoma surgeries, and for the treatment and prevention of cystoid macular edema. The evidence showed that continuing medical education programs were used to promote Xibrom for uses that were not approved by the FDA as safe and effective, and that post-operative instruction sheets for unapproved uses were paid for by some company employees and provided to physicians. Press Release, U.S. Dep't of Justice, ISTA Pharmaceuticals Inc. Pleads Guilty to Federal Felony Charges; Will Pay \$33.5 Million to Resolve Criminal Liability and False Claims Act Allegations (May 24, 2013), *available at* <http://www.justice.gov/opa/pr/2013/May/13-civ-606.html>

²⁸ 42 U.S.C. §1320a-7(b)(1)(A)(i)

²⁹ Office of Inspector General News. Administrative Law Judge Upholds HHS-OIG Exclusions Imposed Against Responsible Corporate Offices in OxyContin Case. January 23, 2009.

³⁰ Taxpayers Against Fraud <http://www.taf.org/general-resources/top-100-fca-cases> Top False Claims Act Cases by Civil Award Amount

³¹ Johnson & Johnson paid \$2.2 billion to resolve criminal and civil liability arising from allegations relating to kickbacks and off-label marketing of the drugs Risperdal, Invega and Natrecor. Pfizer paid a total of \$2.3 billion, of

resolve allegations of illegal off-label promotion to avoid the risk of even larger FCA penalties if a case is litigated as well as the high probability that a losing defendant will be excluded by the OIG from continuing to receive federal reimbursement funds. Companies that challenge the government's allegations in court clearly put the company at risk of extinction as a felony conviction carries with it automatic exclusion.³²

For example, AstraZeneca agreed on April 27, 2010, to pay \$520 million and entered into a corporate integrity agreement to settle civil off-label claims related to the marketing of Seroquel. "The United States alleges that AstraZeneca illegally marketed Seroquel for uses never approved by the FDA. Specifically, between January 2001 through December 2006, AstraZeneca promoted Seroquel to psychiatrists and other physicians for certain uses that were not approved by the FDA as safe and effective (including aggression, Alzheimer's disease, anger management, anxiety, attention deficit hyperactivity disorder, bipolar maintenance, dementia, depression, mood disorder, post-traumatic stress disorder, and sleeplessness). These unapproved uses were not medically accepted indications for which the United States and the state Medicaid programs provided coverage for Seroquel."³³

Allergan pled guilty on September 1, 2010, to misbranding and agreed to pay \$600 million to settle civil and criminal liability related to the off-label promotion of Botox.³⁴ The FDA had approved Botox to treat crossed eyes, involuntary eyelid and neck muscle contraction, excessive underarm sweating, and adult upper-limb spasticity, but Allergan allegedly had promoted it for headache, pain, spasticity, and juvenile cerebral palsy.

Novo Nordisk agreed on June 10 2011, to pay \$25 million and entered into a corporate integrity agreement to resolve claims related to the off-label promotion of NovoSeven. "The U.S. subsidiary, Novo Nordisk Inc., which is located in Princeton, N.J., promoted NovoSeven to health care professionals for off-label uses, including as a coagulatory agent for trauma patients, general surgery, cardiac surgery, liver surgery, liver transplants and intra-cerebral hemorrhage. As a result of this unlawful promotion, Novo Nordisk allegedly caused false claims to be submitted to government health care programs that were not reimbursable by those programs. Medicare and Medicaid paid for off-label prescriptions throughout the United States as a result of Novo's focused campaign to influence doctors and hospitals. The federal share of the civil settlement is \$21,425,790.59, and the state Medicaid share of the civil settlement is \$3,574,209.41".³⁵

which \$1.3 billion was a criminal fine for kickbacks and off-label marketing and \$1 billion was paid under the False Claims Act. Abbott Laboratories paid over \$1.5 billion to settle civil and criminal charges in part brought by four False Claims Act *qui tam* cases alleging the company promoted the off-label use of Depakote, an anti-seizure drug.

³² Osborn: Can I Tell You the Truth? Yale Journal of Health Policy, Law, and Ethics, Vol. 10 (2010), Iss. 2, Art. 2

³³ Press Release, United States Department of Justice, Pharmaceutical Giant AstraZeneca to Pay \$520 Million for Off-label Drug Marketing (Apr. 27, 2010), available at <http://www.justice.gov/opa/pr/2010/April/10-civ-487.html>.

³⁴ Press Release, United States Department of Justice, Allergan Agrees to Plead Guilty and Pay \$600 Million to Resolve Allegations of Off-Label Promotion of Botox® (Sept. 1, 2010), available at <http://www.justice.gov/opa/pr/2010/September/10-civ-988.html>.

³⁵ Press Release, United States Department of Justice, Danish Pharmaceutical Novo Nordisk to Pay \$25 Million to Resolve Allegations of Off-Label Promotion of Novoseven (June 10, 2011), available at <http://www.justice.gov/opa/pr/2011/June/11-civ-764.html>.

Abbott pled guilty on May 7, 2012, to misbranding, agreed to pay \$1.5 billion and entered into a corporate integrity agreement to resolve criminal and civil claims related to the off-label promotion of Depakote.³⁶ The FDA had approved Depakote only for epileptic seizures, bipolar mania, and the prevention of migraines, but Abbott Labs had promoted it for other uses, including treating schizophrenia.

GlaxoSmithKline LLC (“GSK”) pled guilty in 2012 in the District of Massachusetts to introducing two misbranded drugs into interstate commerce, and paid a \$1 billion fine and forfeiture. One misbranding charge was based on GSK’s promotion of the drug Paxil for treating depression in patients under age 18; the FDA had not approved Paxil for pediatric use. The other was based on GSK’s promotion of the drug Wellbutrin for weight loss, and to treat sexual dysfunction, substance addictions, and attention deficit hyperactivity disorder; the FDA had approved the drug only to treat major depressive disorder.

On March 5, 2013, Par Pharmaceuticals pled guilty and agreed to pay \$45 million to resolve civil and criminal allegations related to the off-label marketing and misbranding of Megace ES. “Megace® ES, a megestrol acetate drug product, was approved by the FDA to treat anorexia, cachexia, or other significant weight loss suffered by patients with AIDS (the “AIDS Indication”). The Megace® ES distributed nationwide by Par was criminally misbranded because its FDA-approved labeling lacked adequate directions for use in the treatment of non-AIDS-related geriatric wasting, a use that was intended by Par but never approved by the FDA. The FDCA requires companies such as Par to specify the intended uses of a product in an application to the FDA. Once approved, a drug may not be distributed in interstate commerce for unapproved or “off-label” uses until the company receives FDA approval for the new intended uses. In addition to the criminal fine and forfeiture, the plea agreement mandates that Par implement several compliance measures and annually provide the U.S. Attorney’s Office with a sworn certification from its chief executive officer that the company has not unlawfully marketed any of its pharmaceutical products.”³⁷

One recent example of the application of the criminal side of off label promotion was shown on *United States v. Vascular Solutions, Inc.* prosecutors alleged that the medical device company and its chief executive officer engaged in off label promotion. According to the indictment filed on November 13, 2014, “the Vari-Lase products were cleared by the FDA only for the treatment of superficial veins but Root and VSI sold them for the ablation, or removal of “perforator” veins, which connect the superficial vein system to the deep vein system. Because perforator veins come into direct contact with deep veins, treating them with lasers was a more difficult and risky procedure”³⁸. The Judge provided the instructions to the jury specifying that is not a crime for a

³⁶ Press Release, United States Department of Justice, Abbott Labs to Pay \$1.5 Billion to Resolve Criminal & Civil Investigations of Off-label Promotion of Depakote (May 7, 2012), *available at* <http://www.justice.gov/opa/pr/2012/May/12-civ-585.html>.

³⁷ Press Release, United States Department of Justice, Par Pharmaceuticals Pleads Guilty and Agrees to Pay \$45 Million to Resolve Civil and Criminal Allegations Related to Off-Label Marketing (March 5, 2013), *available at* <http://www.justice.gov/opa/pr/2013/March/13-civ-270.html>.

³⁸ Justice News. Department of Justice. Office of Public Affairs. Vascular Solutions Inc. and its CEO Charged with Selling Unapproved Medical Devices and Conspiring to Defraud the United States. November 13, 2014

company or representative to give doctors truthful and non-misleading information about the unapproved use of a device.³⁹ The jury found the defendants not guilty.

Some commenters argue that if the company is making a higher profit in consideration with the amount included in the settlement, then such payment is just another cost of doing business.⁴⁰ Many of them emphasize that the company executives should be more accountable of the misconduct and in contrast the reality is that the CEO's of the biggest pharmaceuticals companies receive millions dollars compensation even though where the company is subject to a settlement for different types of violations.

III. Individuals' Accountability for Corporate Wrongdoing

The Department of Justice recent approach has been focused on prosecuting accountability when dealing with corporate misconduct besides corporate fines and penalties. The Yates Memorandum⁴¹ dated September 9, 2015 established that civil attorneys investigating corporate wrongdoing should maintain a focus on the responsible individuals. The Department of Justice has a top priority of fighting the corporate fraud by identifying culpable individuals. The aforementioned guidance applies to investigations of corporate wrongdoing based on the following six steps:

1. In order to be eligible for any credit for cooperation, the company must identify all individuals involved in or responsible for the misconduct at issue, regardless of their position, and provide to the Department all facts relating to that misconduct.
2. Both criminal and civil attorneys should focus on individual wrongdoing from the very beginning of any investigation of corporate misconduct.
3. Early and regular communication between civil attorneys and criminal prosecutors handling corporate investigations can be crucial to effectively pursue individuals and evaluating remedies.

³⁹ Proposed Jury Instructions, *U.S.A. v. Vascular Solutions, Inc. & Howard C. Root*, Criminal No. SA:14-CR-926-RCL, filed Jan 7, 2016.

⁴⁰ "What we're learning is that money doesn't deter corporate malfeasance," said Eliot Spitzer, who, as New York's attorney general, sued GlaxoSmithKline in 2004 over similar accusations involving Paxil. "The only thing that will work in my view is C.E.O.'s and officials being forced to resign and individual culpability being enforced." Glaxo Agrees to Pay \$3 Billion in Fraud Settlement By KATIE THOMAS and MICHAEL S. SCHMIDT JULY 2, 2012 http://www.nytimes.com/2012/07/03/business/glaxosmithkline-agrees-to-pay-3-billion-in-fraud-settlement.html?_r=0

⁴¹ Memorandum from Deputy Attorney General. Individual Accountability for Corporate Wrongdoing. September 9, 2015 available at <https://www.justice.gov/dag/file/769036/download>

4. Based on the importance of holding responsible individuals to account, absent extraordinary circumstances, lawyers should not agree to a corporate resolution that includes an agreement to dismiss charges against, or provide immunity for, individual officers or employees.
5. If a decision is made by government prosecutors at the conclusion of the investigation not to bring civil claims or criminal charges against the individuals who committed the misconduct, the reasons for that determination must be memorialized and approved by the United States Attorney or Assistant Attorney General.
6. The fact that an individual may not have sufficient resources to satisfy a significant judgment should not control the decision on whether to bring an enforcement action against individuals.

According to the Deputy Attorney General Sally Quillian Yates: "One of the most effective ways to combat corporate misconduct is by seeking accountability from the individuals who perpetrated the wrongdoing. Such accountability is important for several reasons: it deters future illegal activity, it incentivizes changes in corporate behavior, it ensures that the proper parties are held responsible for their actions, and it promotes the public's confidence in our justice system".⁴² The Yates Memorandum established some reasons to investigate the conduct of the individuals such as: an effective way to determine the facts and extent of any corporate misconduct, increase the likelihood that individuals with knowledge of the corporate misconduct will cooperate with the investigation and provide information against individuals higher up the corporate hierarchy and to maximize the chances that the final resolution of an investigation uncovering the misconduct will include civil or criminal charges against not just the corporation but against culpable individuals as well.

Extensive marketing programs and monetary incentives for sales representatives also show the extent of manufacturer focus to increase sales even when that risks large penalties and settlements. The OIG will exclude responsible corporate officers from participations in the federal healthcare programs when the individuals are convicted of a criminal offense related to the delivery of an item or service under a federal or state healthcare program.⁴³ The OIG exercised his authority to exclude the responsible corporate officers who failed to prevent misbranding and fraudulent distribution of OxyContin by Purdue Frederick, the manufacturer and distributor of OxyContin. It shows an increasing trend to hold executives accountable based on their responsibility and authority to prevent or correct drug misbranding.

IV. Physician off label use of FDA regulated products

There is an inherent dichotomy between pharmaceutical manufacturers and physicians. Manufacturers cannot promote an off label use of a drug, but physicians can freely prescribe the drug for any use, whether approved or not. Physicians may be relying on a drug to treat a medical condition that the Food and Drug Administration has not evaluated and the pharmaceutical company has not initiated the process to get the approval to make that specific claim.

Although pharmaceutical company misbranding is a crime, physician off-label prescriptions are both legal and common, with perhaps more than twenty percent of

⁴² Memorandum from Deputy Attorney General. Individual Accountability for Corporate Wrongdoing. September 9, 2015 available at <https://www.justice.gov/dag/file/769036/download>

⁴³ 42 U.S.C. § 1320a-7(a)

prescriptions written for off-label uses.⁴⁴ The FDCA contains an explicit practice of medicine exception.⁴⁵ Thus, the FDA does not regulate physician off-label prescriptions. After a drug has been approved by the FDA, a doctor may lawfully prescribe it for both FDA-approved and non-FDA approved off-label uses. The FDA itself stated: "Once a drug has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances. Off-label prescriptions often, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature".⁴⁶

A doctor's off-label prescription also may involve using a drug for an approved condition but at an unapproved dosage or directed to an unapproved patient population.⁴⁷ Physicians prescribe drugs to patients based on their clinical judgment, practices accepted by the medical community as well as treatment guidelines for specific conditions. On a daily basis, physicians decide which drug therapy is the best course of treatment for these patients.

Although the FDCA broadly prohibits manufacturers from circulating "misbranded" drugs for non-approved use, the FDCA does not limit or interfere with the authority of healthcare professionals to prescribe or administer legal drugs to treat any condition or disease in any manner. The FDA has acknowledged that "once a drug or medical device has been approved or cleared by the FDA, generally, healthcare professionals can lawfully use or prescribe that product for uses or treatment indications that are not included in the product's approved labeling".⁴⁸ The FDA has recognized that the off-label uses or treatment regimens may be important therapeutic options and may even constitute a medically recognized standard of care

V. Off-label marketing and the first amendment

In recent years, there has developed a tension between the FDCA's prohibition on off-label promotion and the First Amendment's protection of free speech. This tension has been reflected in a number of cases where manufacturer companies were seeking constitutional protection based on the First Amendment of the United States Constitution for specific off label marketing and information dissemination related to drugs. The First Amendment protection will not be available for false or misleading claims about a product.

The history begins with the Washington Legal Foundation⁴⁹ cases. In the 1998 District Court decision in *Washington Legal Foundation v. Friedman*⁵⁰, the Court granted summary judgment

⁴⁴ David C. Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1023 (2006).

⁴⁵ 59 Fed.Reg. 59820, 59821 (1994)

⁴⁶ *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012)

⁴⁷ Most prescription drugs are approved with no or very limited testing in children or teens under age 18. As a result, the vast majority of drugs that are approved to treat diseases and conditions that primarily strike adults are prescribed off label when a doctor chooses to use them to treat a child or teen. "Off label" drug use. *Shopper Guide to Prescription Drugs Number 6*. <https://www.consumerreports.org/health/resources/pdf/best-buy-drugs/money-saving-guides/english/Off-Label-FINAL.pdf>

⁴⁸ FDA Draft Guidance for Industry Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices, 2011

⁴⁹ Nonprofit public interest law and policy center that defends the rights of individuals and businesses to go about their affairs without undue influence from government regulators.

⁵⁰ 13 F. Supp. 2d 51 (D.D.C.1998).

against the defendant government officials and agency, holding that the FDA was violating the First Amendment rights of plaintiff's members by unduly limiting the manner in which drug manufacturers may disseminate information relating to unapproved or "off-label" uses of FDA-approved drugs.

At the time of that decision, the FDA's policies which were found unconstitutional were included in Guidance Documents regulating the dissemination of journal articles and reference texts and manufacturer support of continuing medical education (CME) activities. However, the Guidance Documents were superseded in 1997 by the Food and Drug Administration Modernization Act. The FDAMA permits a drug manufacturer to disseminate journal articles and reference texts only under certain conditions such as follows:

1. The drug must be the subject of an approved application or otherwise lawfully marketed.
2. The disseminated information must be unabridged, not false or misleading, and not pose a significant risk to the public health.
3. The information must not be derived from clinical research by another manufacturer without that manufacturer's permission.
4. The manufacturer must submit an advance copy of the information to be disseminated to FDA along with any clinical trial information and reports of clinical experience.
5. The manufacturer must submit a supplemental new drug application for the off-label use or have certified that such an application will be submitted within the applicable statutory deadline, unless the Secretary determines that the manufacturer is exempt from this requirement because a) such supplemental application would be prohibitively expensive or b) it would be unethical to conduct the necessary studies.
6. The disseminated information must include a prominent disclosure that a) the material concerns an off-label use not approved by the FDA; b) the material is disseminated at the manufacturer's expense; c) identifies the authors of the information that have received compensation from or have financial interests in the manufacturer; d) includes the product's current approved labeling; e) includes a statement that there exist products approved for the particular intended use (if applicable); f) identifies the person providing funding for a study of the off-label use; and g) gives a bibliography of other scientific articles concerning the off-label use.
7. The manufacturer must prepare and submit semi-annually to the FDA lists of the articles and reference publications disseminated and the categories of recipients.

In the case of *Washington Legal Foundation v. Henney*⁵¹ the plaintiff objected to the aforementioned requirements as unconstitutional and inconsistent with the Court's 1998 order and injunction. The Court concluded that the FDAMA unconstitutionally restricts protected commercial speech.

The government appealed a district court decision holding that the Food and Drug Administration Modernization Act of 1997, which establishes procedures by which drug and medical device manufacturers may disseminate information about "off-label" uses for their

⁵¹ 56 F. Supp. 2d 81 (D.D.C. 1999)

products, violates the First Amendment. In February 11, 2000 the U.S. Court of Appeals for the District of Columbia Circuit⁵² dismissed the appeal and vacated the district court's injunction.

In February 2014, the FDA issued the Guidance for Industry Distributing Scientific and Medical Publication on Unapproved New Uses Recommended Practices related to the dissemination of scientific or medical journal article distributed by a manufacturer. The FDA authorized manufacturers to distribute such articles relating to unapproved uses of drugs, under certain conditions.

It specified that a scientific or medical journal should be distributed separately from the delivery of information that is promotional in nature. For example, if a sales representative delivers a reprint to a physician in his or her office, the reprint should not be attached to any promotional material the sales representative uses or delivers during the office visit. To the extent that the recipients of the scientific or medical journal article have questions, the sales representative should refer the questions to a medical/scientific officer or department, and the officer or department to which the referral is made should be independent of the sales and/or marketing departments. Similarly, while reprints may be distributed at medical or scientific conferences in settings appropriate for scientific exchange, reprints should not be distributed in promotional exhibit halls or during promotional speakers' programs.

The FDA 2014 guidance is very similar to the content included in the 2009 guidance as follows:

"the scientific journal should be distributed separately from information that is promotional in nature. For example, if a sales representative delivers a reprint to a physician in his office, the reprint should not be *physically* attached to any promotional material the sales representative uses or delivers during the office visit and should not be the subject of discussion between the sales representative and the physician during the sales visit. Similarly, while reprints may be distributed at medical or scientific conferences in settings appropriate for scientific exchange, reprints should not be distributed in promotional exhibit halls or during promotional speakers' programs."⁵³

When a manufacturer distributes journal articles that include information on off-label uses of its drug, the FDA stated, it will not use such distribution as evidence of the manufacturer's intent that the drug be used for an unapproved use, provided that the manufacturer makes certain disclosures with the articles. However, if a manufacturer engages in other conduct that unlawfully promotes an unapproved use of a medical product whether or not the manufacturer also engages in conduct in conformance with the recommendations in the guidance such other conduct may result in enforcement action. The FDA has stated that if a sales representative suggests that a drug is safe or effective for an unapproved use, the agency may use such speech as evidence that the manufacturer intended to promote that use.

In my opinion, the FDA guidance is not always practical when the dissemination of information is so fast and information is widely-available. There are many sources of clinical data on

⁵² Washington Legal Foundation, Appellee v. Jane E. Henney, Commissioner, Food and Drug Administration, and Donna E. Shalala, Secretary, U.S. Department of Health and Human Services, Appellants 202 F.3d 331 (D.C. Cir. 2000)

⁵³ 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 (2009, January)<http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm>

reprints, website and other sources. The point to distribute the scientific journal separately from information that is promotional may not be practical. The physician knows that the sales representative will deliver a promotional message to emphasize the features and benefits of his product. The information contained in a scientific journal is truthful and made independently from the judgment of the sales representative. Therefore, such communication should not be prosecuted. The requirement that when the physician has questions related to the scientific or medical journal article, the sales representative should refer the questions to a medical/scientific officer or department independent of the sales and/or marketing departments can be ambiguous. The medical department of the pharmaceutical company often includes physicians or pharmacists that are employees. Therefore, I acknowledge that they may engage in a more deeply clinical information about the drug but the off label information included in the scientific journal remains the same. The goal of exchanging objective scientific information can be accomplished when the scientific liaisons are trained under policies and procedures assuring that the promotional message is provided by sales representatives only. The truthful off label information that is generally available to the medical community can be accompanied with a statement that the FDA has not approved that drug for a new indication.

United States v Caronia⁵⁴

Alfred Caronia appealed from a judgment of conviction entered in the United States District Court for the Eastern District of New York on November 30, 2009, following a jury trial at which Caronia was found guilty of conspiracy to introduce a misbranded drug into interstate commerce, a misdemeanor violation of 21 U.S.C. §§ 331(a) and 333(a)(1). Caronia was a pharmaceutical sales representative for Orphan Medical, which was later acquired by Jazz Pharmaceutical that allegedly promoted the drug Xyrem for off-label use. In his appeal to the Second Circuit, Caronia argued that he was convicted for his speech for promoting an FDA approved drug for off label use in violation of his right of free speech under the First Amendment.

In July 2002, the FDA approved Xyrem to treat narcolepsy patients who experience cataplexy, a condition associated with weak or paralyzed muscles. In November 2005, the FDA approved Xyrem to treat narcolepsy patients with excessive daytime sleepiness ("EDS"). The FDA required a "black box" warning to accompany Xyrem stating that the drug's safety and efficacy were not established in patients less than 16 years of age, and the drug had very limited experience among elderly patients. The FDA also regulated Xyrem distribution allowing only one centralized Missouri pharmacy to distribute Xyrem nationally in order to identify patients suffering side effects from the drug.

Under the manufacturer procedures, if Caronia, as a sales consultant for Xyrem, was asked about the off-label use of Xyrem, he was not permitted to answer; instead, Orphan sales consultants would fill out medical information request forms and send them to the company, and Orphan would send information to the inquiring physician. However, the physicians employed by Orphan as promotional speakers for Xyrem were permitted to answer off-label use questions. Caronia was audio-recorded on two occasions promoting Xyrem for unapproved uses, including unapproved indications and unapproved subpopulations.

⁵⁴ United States v. Caronia, 703 F.3d 149 (2d Cir. 2012)

Caronia was charged with conspiracy to introduce a misbranded drug into interstate commerce in violation of 21 U.S.C. §§ 331(a) and introducing a misbranded drug, Xyrem, into interstate commerce, in violation of 21 U.S.C. §§ 331(a) and 333(a)(2). Before trial, Caronia moved to dismiss the aforementioned charges. In part, Caronia argued that the application of the FDCA's misbranding provisions to his off-label promotional statements unconstitutionally restricted his right to free speech under the First Amendment. The government argued that the pharmaceutical sales representative was marketing a dangerous drug for a use not approved by the FDA; that he admitted he knew the rules that the product should not be promoted for uses that had not been approved by the FDA and that his actions constituted misbranding among other arguments.

In 2008, the jury found Caronia guilty for conspiracy to introduce a misbranded drug into interstate commerce under 18 U.S.C. § 371(a) and 21 U.S.C. § 331(a). On November 30, 2009, the district court sentenced Caronia to one year of probation, 100 hours of community service, and a \$25 special assessment. On appeal of his conviction to the Second Circuit, Caronia principally argued that the misbranding provisions of the FDCA prohibit off-label promotion, and therefore, unconstitutionally restrict speech. Caronia argued that the First Amendment does not permit the government to prohibit and criminalize a pharmaceutical manufacturer's truthful and non-misleading dissemination to physicians of scientifically accurate information regarding off-label uses of an FDA-approved drug where such uses were not in themselves illegal and others are permitted to engage in such speech.

The Second Circuit vacated the judgment of conviction. The court found that while the FDCA makes it a crime to misbrand or conspire to misbrand a drug, the statute and its accompanying regulations do not expressly prohibit or criminalize off-label promotion. Rather, the FDCA and FDA regulations reference "promotion" only as evidence of a drug's intended use.⁵⁵ "Thus, under the principle of constitutional avoidance, we construe the FDCA as not criminalizing the simple promotion of a drug's off-label use because such a construction would raise First Amendment concerns. Because we conclude from the record in this case that the government prosecuted Caronia for mere off-label promotion and the district court instructed the jury that it could convict on that theory, we vacate the judgment of conviction".⁵⁶

The court found that the government never suggested that Caronia engaged in any form of misbranding other than the promotion of the off label use of an FDA-approved drug.⁵⁷ The government never suggested, for example, that Caronia conspired to place false or deficient labeling on a drug. Rather, the record makes clear that the government prosecuted Caronia only for his promotion and marketing efforts.⁵⁸ The Court of Appeals cited the Supreme Court's *Sorrell* decision: "Speech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment."⁵⁹

The court concluded: "we decline the government's invitation to construe the FDCA's misbranding provisions to criminalize the simple promotion of a drug's off-label use by

⁵⁵ 21 U.S.C. §§352(a)-(n)

⁵⁶ United States v. Caronia, 703 F.3d 149 (2d Cir. 2012) Page 26

⁵⁷ United States v. Caronia, 703 F.3d 149 (2d Cir. 2012) Page 29

⁵⁸ United States v. Caronia, 703 F.3d 149 (2d Cir. 2012) Page 30

⁵⁹ *Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653, 2659 (2011)

pharmaceutical manufacturers and their representatives because such a construction and a conviction obtained under the government's application of the FDCA would run afoul of the First Amendment".⁶⁰

First, the court noted that "off-label drug usage is not unlawful, and the FDA's drug approval process generally contemplates that approved drugs will be used in off-label ways⁶¹. In effect, even if pharmaceutical manufacturers are barred from off-label promotion, physicians can prescribe, and patients can use, drugs for off-label purposes." As off-label drug use itself is not prohibited, it does not follow that prohibiting the truthful promotion of off-label drug usage by a particular class of speakers would directly further the government's goals of preserving the efficacy and integrity of the FDA's drug approval process and reducing patient exposure to unsafe and ineffective drugs."⁶²

Second, prohibiting off-label promotion by a pharmaceutical manufacturer while simultaneously allowing off-label use "paternalistically" interferes with the ability of physicians and patients to receive potentially relevant treatment information. Indeed, such barriers to information about off-label use could inhibit, to the public's detriment, informed and intelligent treatment decisions.⁶³ Notably, while some off-label information could certainly be misleading or unhelpful, this case does not involve false or misleading promotion.⁶⁴

The position of the court is that in order to minimize off-label use, or manufacturer evasion of the approval process for such use, the government could create other limits, including ceilings or caps on off-label prescriptions. The FDA could further remind physicians and manufacturers of, and even perhaps further regulate, the legal liability surrounding off-label promotion and treatment decisions.⁶⁵ "If the First Amendment means anything, it means that regulating speech must be a last not first resort."⁶⁶

The court concluded that the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug. Jonathan Dieneshaus⁶⁷ spoke from the perspective of a former senior trial counsel in the Civil Division of the Department of Justice. Dieneshaus states that *Caronia* does change the legal landscape for sales representatives. A drug rep whose only conduct is speech and whose speech is not directly false will not be prosecuted even if the speech is off-label.⁶⁸

⁶⁰ United States v. Caronia, 703 F.3d 149 (2d Cir. 2012) Page 33

⁶¹ United States v. Caronia, 703 F.3d 149 (2d Cir. 2012) Page 43

⁶² *Sorrell*, 131 S. Ct. at 2668-69

⁶³ *Va. Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 770(1976)

⁶⁴ United States v. Caronia, 703 F.3d 149 (2d Cir. 2012) Page 46

⁶⁵ United States v. Caronia, 703 F.3d 149 (2d Cir. 2012) Page 49

⁶⁶ *Thompson*, 535 U.S. at 373

⁶⁷ U.S. v. Caronia, One Year Later: The First Amendment and Federal Oversight of Off-Label Promotion Published on Jan 16, 2014 Coleen Klasmeier of Sidley Austin LLP, Jonathan Dieneshaus of Hogan Lovells US LLP, and Geoffrey Levitt of Pfizer Inc. discuss the impact of the Second Circuit's US v. Caronia ruling and developments to watch for in 2014 in federal regulation of speech on so-called off-label uses of drugs and devices. <https://www.youtube.com/watch?v=NRe1t2Mks1o>

⁶⁸ Thomas Sullivan - Policy & Medicine Writing Staff at 05:14:00 AM in FDA, Medical Legal Fe 20, 2014 US v. Caronia, One Year Later: FDA's Position on Off-Label Promotion Remains the Same, But Changes are Looming

Amarin Complaint Against the FDA

Amarin and three physicians brought a complaint against the FDA making an express First Amendment challenge to FDA regulations that prohibited Amarin, a pharmaceutical company, from making truthful and non-misleading statements about its product to healthcare professionals. Amarin manufactured the prescription drug called Vascepa®, which is an omega-3 fatty acid. Based on a clinical trial conducted by Amarin, the FDA had approved the marketing of Vascepa® for use as an adjunct to diet to reduce triglyceride levels in adult patients with very high triglycerides defined as triglyceride levels of 500 mg/dL of blood or above. Allegedly many doctors, including Doctor Plaintiffs, prescribed Vascepa® to treat patients with persistently high triglycerides between 200-499 mg/dL of blood, which was an indication that had not approved by the FDA.

Amarin had conducted a double-blind, placebo-controlled clinical trial demonstrating that Vascepa® reduced triglyceride levels and had other favorable effects in adult patients with persistently high triglycerides. However, the FDA advised Amarin that it had not approved Vascepa® for that patient population. Amarin's complaint states that FDA had permitted dietary supplement manufacturers that sold supplements containing omega-3 fatty acid make the following claim to consumers:

"Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease."

Amarin's Complaint asked the Court "to hold that FDA's prohibitions on 'off label' promotion, as applied to the truthful and non-misleading speech Amarin wishes to make, are unconstitutional under the First Amendment, and to declare that Amarin may engage in its proposed speech about Vascepa⁶⁹®." Amarin argued that its requested relief fell squarely within Second Circuit precedent.⁷⁰ To ensure that this speech is not misleading, Amarin would also contemporaneously disclose to healthcare professionals detailed disclaimers, including that FDA has not approved Vascepa® to treat patients with persistently high triglyceride levels.

Plaintiffs sought a declaration that (1) FDA regulations promulgated under the Federal Food, Drug, and Cosmetic Act (the "FDCA") (including 21 C.F.R. § 202.1(l)(2), 21 C.F.R. § 202.1(e)(4)(i)(a), and 21 C.F.R. §§ 201.5 and 201.100), and FDA's interpretations of the provisions thereof (including 21 U.S.C. §352(a) and 21 U.S.C. §352(n)), are unconstitutional, (2) that Amarin had a First Amendment right to engage in truthful and non-misleading speech about Vascepa®, even if that speech is off-label promotion, and (3) that the Doctor Plaintiffs had a First Amendment right to receive such truthful and non-misleading information about Vascepa® from Amarin, without fear of (a) criminal prosecution of Amarin or its directors, officers, employees, or agents through application of FDA regulations promulgated under the FDCA or (b) civil liability of Amarin or its directors, officers, employees, or agents under the False Claims Act.

Alternatively, Plaintiffs sought a declaration that the FDA's regulatory regime is unconstitutionally vague in violation of the Due Process Clause of the Fifth Amendment because it did not provide Amarin with fair notice of what off-label promotion is permitted and what off label promotion is forbidden under FDA regulations. Amarin and the Doctor Plaintiffs

⁶⁹ Amarin Pharma Inc. v FDA Civil Action No. 15-cv-3588 (PAE) Page 6

⁷⁰ United States v. Caronia, 703 F.3d 149 (2d Cir. 2012)

also sought injunctive relief to ensure their ability to engage in truthful and non-misleading speech free from the risk of criminal and civil liability.

Despite being approved to treat patients with very high triglyceride levels, Vascepa® is still considered an unapproved “new drug” under FDA’s regulatory regime regarding uses not included in its FDA-approved label, including the treatment of patients with high triglyceride levels.⁷¹ To obtain FDA approval for Vascepa®’s use in these patients, Amarin had to submit a “supplemental new drug application” that included detailed reports of pre-clinical and clinical trials demonstrating safety and efficacy and proposed labeling for the new use.⁷²

Amarin argued that despite having done everything it could to design, pre-approve with FDA, and conduct a successful clinical trial that would establish the evidentiary requirements for approval, Amarin now found itself unable to engage in a full and truthful dialogue with healthcare professionals about the success of the ANCHOR trial and the effectiveness of Vascepa® in lowering triglycerides and improving other parameters relevant to cardiovascular health in patients with persistently high triglycerides, even if Amarin stated that Vascepa® has not been shown to reduce the risk of cardiovascular disease. Amarin argued that the FDA’s prohibition on Amarin from discussing the ANCHOR study and its results with doctors, actually misleads doctors and the public. They cited *Sorell v. IMS Health, Inc.* case to express the following:

"The First Amendment “directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good, ”particularly applicable when the audience consists of prescribing physicians considered to be “sophisticated and experienced consumers.”⁷³ To allow lay consumers but not sophisticated doctors to receive qualified health claims about the potential cardiovascular benefits of omega-3 fatty acids defies common sense and violates the First Amendment. This outcome not only violates Amarin’s First Amendment right to provide such information, but also violates the Doctor Plaintiffs’ First Amendment right to receive the information they need to properly evaluate and prescribe an FDA-approved product.⁷⁴

The plaintiffs emphasized that the FDA has been unclear about what is permitted and what is not permitted, post-*Caronia*. The resulting uncertainty, coupled with the very real threats of criminal prosecution or massive civil liability, had chilled drug manufacturer’s speech about off-label uses.⁷⁵

Amarin v FDA Opinion and Order dated August 7, 2015

On May 22, 2015, Amarin moved for an injunction that would prohibit the FDA from bringing a misbranding action against Amarin for its truthful and non-misleading statements to doctors regarding Vascepa, including the statements set out in the Complaint. Amarin later confirmed that, as an alternative to an injunction blocking enforcement action, effective relief could take the form of a declaration to the effect that the communications it intended were protected against a misbranding action. Amarin moved primarily under the First Amendment, but alternatively, under

⁷¹ 21 U.S.C. §321(p)

⁷² 21 U.S.C. §355(b)

⁷³ *Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653, 2671 (2011)

⁷⁴ *Amarin Pharma Inc. v FDA* Civil Action No. 15-cv-3588 (PAE) Page 38

⁷⁵ *Amarin Pharma Inc. v FDA* Civil Action No. 15-cv-3588 (PAE) Page 48

the due process clause, on the ground that the FDA's regulations as to misbranding were vague and did not "fairly notify Amarin of what off-label promotion is permitted and what is forbidden".⁷⁶

The FDA opposed granting preliminary relief under the argument that Amarin's plan to make proactive statements to doctors regarding an off-label use of Vascepa was a frontal assault on the framework for new drug approval that Congress created in 1962. "Amarin was seeking to distribute its drug Vascepa under circumstances which could establish that Amarin intends an unapproved new use for Vascepa, a use for which FDA has not determined the drug is safe and effective".⁷⁷ The FDA argued, were it to bring a misbranding claim against Amarin based on its promotional statements, this would not "prohibit speech."

The court established that Amarin clearly has standing to challenge the FDA's threat to bring a misbranding action against it if it promotes Vascepa for an off-label use.⁷⁸ In sum, because Amarin did not accept the conditions set in the Woodcock Letter, that letter did not vitiate the Complete Response Letter (CRL) threat of a misbranding action against Amarin or moot this controversy. "The FDA there acknowledged that the ANCHOR study had been carried out consistent with its specifications".⁷⁹

Amarin alleged that the FDA is wrong to assert the authority to bring a misbranding action against a manufacturer based solely on truthful and non-misleading statements promoting an off-label use. Furthermore, Amarin argues, under *Caronia*, a misbranding action based on such statements simply cannot be brought. Amarin contends, the specific statements it proposes to make about Vascepa are truthful and non-misleading, so as to be protected under *Caronia*. These statements, Amarin notes, all derive from the FDA-approved ANCHOR study or writings by (or approved by) the FDA. Amarin argues that the FDA is wrongly disputing that these statements are truthful and non-misleading.

As the Second Circuit emphasizes: "The proscribed conduct for which *Caronia* was prosecuted was precisely his speech in aid of pharmaceutical marketing." This finding, in turn, led the Second Circuit to analyze, more broadly, the constitutionality of a misbranding prosecution based solely on truthful promotional speech. The issue, the Second Circuit stated, was whether, consistent with the First Amendment, a misbranding prosecution can be based on such speech "the simple promotion of a drug's off-label use".⁸⁰

On the contrary, the Second Circuit, at the close of its *Caronia* analysis, presented its holding as a definitive one of statutory construction:

"We decline to adopt the government's construction of the FDCA's misbranding provisions to prohibit manufacturer promotion alone as it would unconstitutionally restrict free speech. We construe the misbranding provisions of the FDCA as not prohibiting and criminalizing the truthful off-label promotion of FDA-approved prescription drugs. Our conclusion is limited to FDA-approved drugs for which off-label use is not prohibited, and we do not hold, of course, that the FDA cannot regulate the marketing of prescription drugs. We conclude simply that the

⁷⁶ Amarin Pharma Inc. v. Food and Drug Administration Opinion and Order 15 Civ. 3588 (PAE) Page 31

⁷⁷ Amarin Pharma Inc. v. Food and Drug Administration Opinion and Order 15 Civ. 3588 (PAE) Page 35

⁷⁸ Amarin Pharma Inc. v. Food and Drug Administration Opinion and Order 15 Civ. 3588 (PAE) Page 40

⁷⁹ Amarin Pharma Inc. v. Food and Drug Administration Opinion and Order 15 Civ. 3588 (PAE) Page 24

⁸⁰ Amarin Pharma Inc. v. Food and Drug Administration Opinion and Order 15 Civ. 3588 (PAE) Page 46

government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug”.⁸¹

The Court in reviewing Caronia assert that the holding was that the FDCA’s misbranding provisions cannot constitutionally criminalize, and therefore do not reach, the act of truthful and non-misleading speech promoting off-label use. The Circuit did not limit that holding to a subset of truthful promotional speech, such as statements responding to doctors’ queries or statements by non-sales personnel. Caronia instead construed the misbranding provisions not to reach any “truthful off label promotion of FDA-approved prescription drugs”.⁸²

The Court held that Amarin’s proposed communications, as modified, are presently truthful and non-misleading. They also recognized that a statement that is fair and balanced today may become incomplete or otherwise misleading in the future as new studies are done and new data is acquired. Therefore, the Court’s approval was based on the communications evaluated at that moment.

The Court’s approval of proposed communication as modified was based on the evaluated record. Therefore, Amarin is responsible to assure that its communications to doctors regarding off-label use of Vascepa remain truthful and non-misleading. The court’s point of view of the case was that Amarin has established irreparable harm. Without relief, its First Amendment rights will be chilled by the threat of a misbranding action. Finally, they considered that there is no basis to fear that promoting Vascepa for this off-label purpose would endanger the public health because it is a fish oil product and it is already widely prescribed to treat patients with persistently high triglycerides.

Proposed Stipulation and Order of Settlement

On March 8, 2016 Amarin Pharma, Inc. and the FDA filed a Proposed Stipulation and Order of Settlement where the parties agreed that Amarin may engage in truthful and non-misleading speech promoting the off label use of Vascepa and such speech may not be basis of a prosecution for misbranding. Amarin has the responsibility of assuring that the communications to doctors regarding the off label use of the drug remain truthful and not misleading.

It is important to emphasize that the proposed settlement included a process to evaluate off label communications. Amarin may submit a preclearance procedure to the FDA up to two proposed communications per calendar year about Vascepa off label use before communicating them to doctors in addition to the procedures generally available to submitting information to FDA for comment. If FDA has concerns about the proposed communication, the agency will contact Amarin with its specific objection within 60 calendar days. Then, Amarin will have 45 days to provide a response. If the dispute remains either party may request that the Court resolve the matter. The aforementioned procedure will cease on December 31, 2020.

Analysis

“Contrary to the FDA’s concern, Caronia leaves room for prosecuting off-label marketing as misbranding. Two limits to Caronia’s holding are worth highlighting. First, the First Amendment does not protect false or misleading commercial speech. Caronia’s construction of the

⁸¹ Amarin Pharma Inc. v. Food and Drug Administration Opinion and Order 15 Civ. 3588 (PAE) Page 48

⁸² 703 F.3d at 168–69.

misbranding provisions so to exclude truthful promotion speech affords no protection to a manufacturer that uses false or misleading communications to promote an off label use. Second, the First Amendment protects expression, not conduct. A manufacturer that engages in non-communicative activities to promote off-label use cannot use the First Amendment as a shield. Caronia holds protected, and outside the reach of the FDCA's misbranding provisions, off-label promotion only where it wholly consists of truthful and non-misleading speech."⁸³

The aforementioned Amarin settlement appears to attempt to balance the regulatory enforcement of the Food and Drug Administration while also protecting the constitutional right of the pharmaceutical company to communicate truthful and non-misleading scientific based information to physicians. The settlement established a procedure allowing the manufacturer to submit the proposed off label use of a FDA approved drug with the scientific evidence in order to obtain an approval of such communication before sharing it with the physicians. However, it is limited to Amarin and its representatives. It is important to consider that Amarin already submitted clinical trials information for the FDA consideration and that the new indication even though it was not approved was related or similar to the one already granted. The proposed settlement described for this particular case differs from an approved FDA drug seeking a completely unrelated new indication, for example, to treat another disease.

In my opinion, the process included in the Amarin settlement can and should be applied to other pharmaceutical companies as well. The FDA should establish drug categories or classes depending on the safety concerns or potential risk to patients. Based on those categories, the FDA can determine what type of supportive scientific evidence the manufacturer should provide in order to evaluate if the off label statement is truthful and non-misleading. This process can be available for drugs and medical devices already approved by FDA and for which scientific data information regarding safety and efficacy can be obtained independently of the manufacturer funded clinical trials. If the scientific data available is solely funded by the manufacturer, there can be a disclosure.

The process can include that if the parties do not reach an agreement regarding the statement that can be communicated to the physicians, then the agency can have a mediation session to try to solve the dispute. If the issue continues beyond mediation, then the manufacturer could seek prompt court review. The mediation process reduces time and cost. Moreover, when talking about truthful and non-misleading information, the FDA is in better position to determine which information complies and what materials or visual aids can be used.

By following that rule or guideline, the FDA can assure that the information is truthful and non-misleading and the pharmaceutical company can avoid prosecution for misbranding. Such proposed communications may include a statement that the information is based on scientific data or research but making reference to the FDA indication that the drug actually has or that the drug has not been approved for the specific course of treatment. The FDA is the agency with the technical knowledge to evaluate safety and efficacy and the physician is the one with the clinical experience and medicine studies to determine which drug is better to treat his or her patient condition by being informed of the scientific data available.

⁸³ Amarin Pharma Inc. v. Food and Drug Administration Opinion and Order 15 Civ. 3588 (PAE) Page 52

VI. Conclusion

Responsible promotional efforts by pharmaceutical companies can give health care professionals valuable information about the latest drug treatments. But when drug promotion is misleading or unbalanced, the Food and Drug Administration (FDA) should be able to take the necessary steps to stop the promotion.⁸⁴

The FDA restricts the First Amendment protection when a pharmaceutical representative is discussing true information supported by scientific evidence with a physician. The access to information through the Internet and other sources is very easy today and more often the patients are searching for information related to symptoms, condition and drugs in webpages. The government can establish a procedure to review the scientific data available and decide which communication can be discussed with the physicians. The manufacturer company has valuable information related to its products that will be useful for the physicians to be informed about. Such information exchange, the clinical practice guidelines and the accepted treatments by the medical community can contribute to better decisions related to which drug can benefit a specific patient.

The pharmaceutical industry is already highly regulated beginning with the process to introduce a new drug in the market, what type of information it can distribute and how the promotional activities can be conducted. There are many diet pills, shakes and devices that people buy – based on information provided by ordinary people rather than by a scientist or marketing professional trained by a pharmaceutical company -- that can be more harmful for a patient than the same patient using a FDA-approved drug for an off-label use. The manufacturer of a drug is the one with the majority of information about a specific drug and should be entitled to speak freely about how the drug works.

"The FDA has an obligation to develop and promulgate comprehensive guidance on promotional activities, medical education, and physician consulting engagements".⁸⁵ There is a need to have clear and specific instances wherein the pharmaceutical companies may share valuable scientific information without facing potential liability. In order to be protected under the First Amendment the speech must be truthful and non-misleading. The FDA can make that assessment. The FDA can establish a process to review off-label scientific information. The pharmaceutical companies could be permitted to submit to the FDA scientific articles on off-label uses. The FDA has the expertise to review them and evaluate how reliable the scientific information is. Then, the manufacturers could be permitted to distribute approved scientific articles with immunity from off-label prosecution, and perhaps even some marketing based on previously approved proposed communications.

⁸⁴ Bad Ad Program: FDA Aims to Keep Drug Promotion Truthful. (April 29, 2015)<http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm211791.htm>

⁸⁵ Osborn: Can I Tell You the Truth? Yale Journal of Health Policy, Law, and Ethics, Vol. 10 (2010), Iss. 2, Art. 2

The companies will always need to have a robust compliance program in place to monitor how the information is delivered. The correction plan implemented to address any issue should be taken into consideration. How proactive is the manufacturer in solving the alleged wrongdoing and preventing it from happening again? Is the company involved in a pattern or are the activities isolated? The Agency should consider offering a mediation process as a step available prior to Department of Justice prosecution or before entering a Corporate Integrity Agreement. What happens when the company has an effective compliance program that the majority of employees follow and yet still the possibility that some employees may be willing to overlook the company's compliance program in order to seek and obtain compensation as whistleblowers?

We will need to see in the next years whether other Circuits of the Court of Appeals will follow the reasoning stated in *United States v. Caronia* or a precedent established by the United States Supreme Court. Such developments may affect off label enforcement and the FDA's regulatory process.