North Carolina Central University Science & Intellectual Property Law Review

Volume 9 | Issue 1 Article 3

4-1-2016

Post Amarin: Drug Promotion Superhighway or Speed Trap

Beth E. Wolfe

"POST AMARIN: DRUG PROMOTION SUPERHIGHWAY OR SPEED TRAP"

BETH E. WOLFE*

INTRODUCTION

Consider a child diagnosed with a rare and life-threatening disease. Now, consider a pharmaceutical manufacturer that has tested a drug and has evidence that it can cure that disease, but, while the Food Drug Administration ("FDA") has approved that drug for other uses, the FDA has not approved the drug for this new use. Would you want that child's physician to know about this? Would you care how they learned about it? Are you willing to leave it up to a busy physician to spend countless hours researching in hopes of finding some treatment that will work? Is it reasonable to expect this? Currently pharmaceutical manufacturers are restricted in their ability to promote uses of drugs that have not been approved by the FDA.[1] Physicians are left to their own research to find possible drug treatments for some of their most challenging patient illnesses.[2] Recent challenges in the court may be about to change this.

Pharmaceutical manufacturers have been subjected to costly lawsuits for the truthful promotion of off-label uses of drugs that could save lives.[3] The government has claimed billions of dollars from pharmaceutical companies in settlement of claims for alleged illegal promotion of uses of pharmaceuticals not approved by the

---

*Ms. Wolfe is a J.D. Candidate at North Carolina Central University School of Law. She received her B.S. from the University of Michigan – Dearborn, and her M.B.A. from the Open University Business School in the United Kingdom.

1.Amarin Pharma, Inc. v. U.S. FDA, 119 F. Supp. 3d 196, 203 (S.D.N.Y. 2015).

2.*Id*. at 200.

3.C. Lee Ventola, MS, *Off-Label Drug Information: Regulation, Distribution, Evaluation, and Related Controversies*, 34(8) Pharmacy & Therapeutics 428-440, (2009), available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2799128/.

FDA.[4] This has been achieved by a provision based on criminal misbranding under the Food, Drug, Cosmetic Act (FDCA).[5] Any drug that has been put into market and has been misbranded subjects the manufacturer or their representative to penalties under the FDCA including fines and imprisonment.[6]

Drug companies are now fighting back. In August 2015, the Southern District of New York granted Amarin Pharma a preliminary injunction preventing the FDA from prosecuting them for the promotion of drug usages that were not approved by the FDA.[7] Amarin wanted to promote their drug Vascepa, approved for one patient population, for use by a different patient population for whom the drug was not yet approved by the FDA.[8] Amarin had already completed testing that proved the effectiveness of this additional use, and the FDA agreed that the testing did show the drug's effectiveness for this new population.[9] Amarin argued that preventing promotion of truthful uses of their drugs is a violation of their free speech rights.[10] The United States District Court for the Southern District of New York agreed and granted Amarin's application for preliminary relief.[11] This case is a victory for free speech and could expand the availability of truthful and valuable uses of approved drugs to physicians who might otherwise not have access. It could enable crucial information to reach more physicians, so that they can use drugs in patients where the drug use for that patient's illness might otherwise be unknown. The question is – does this open the door for a flood of pharmaceutical manufacturers promoting all tested uses of their product, or is it a trap for the unwary, allowing promotion of the uses, but opening up the potential for suits under the FDCA?

This paper will look at the cases leading up to this decision, the arguments that have won and lost, and the implications for the future. It will examine if this is a victory for free speech or if it is a danger

---

4.*Amarin Pharma,* 119 F. Supp. 3d at 204.
5.*See* 21 U.S.C.S. § 331 (LEXIS 2011) (amended 2015).
6. *Id*.
7.*Amarin Pharma*, 119 F. Supp. 3d at 237.
8.*Id.* at 198.
9. *Id*.
10.*Id*.
11.*Id*. at 237.

by usurping the authority of the FDA and allowing promotion directly to physicians. It will also forecast the risks and rewards that can be expected going forward. Will this put lifesaving cures into the hands of physicians to treat those with little hope and extend, improve, or save lives? Or will it open the floodgates for the promotion of unapproved drugs, and fill the courts with lawsuits for years to come, examining the fine line between truthful and hopeful claims?

This article first reviews the 2015 *Amarin Pharma, Inc. v. United States FDA*[12] case and the events leading up to the challenge in court. It then provides the background and history on drug approval, labeling, and off label promotion, and the cases that have been settled based on FDA prosecution for promotion of off label uses of drugs. Next, it reviews the rationale behind the approval of the injunction sought by Amarin based on the *United States v. Caronia*[13] case from 2012. This case note then explores the benefits and arguments against expanding allowable promotion of off label uses of drugs. Finally, it argues that while this is a victory for first amendment protection of free speech, drug makers should be wary of the risks of continued prosecution as the holding may be found to be fact specific to *Amarin*.

THE CASE

On May 7, 2015, Amarin Pharma, Inc. brought suit against the United States Food and Drug Administration (FDA) seeking an injunction against a threatened misbranding action under the Food, Drug, and Cosmetic Act (FDCA) for its promotion of a triglyceride lowering drug, Vascepa, for a use that was not approved by the FDA.[14]

Vascepa is a drug developed to improve cardiovascular health.[15] In 2011, Amarin sought FDA approval for two uses of Vascepa.[16] The first use was for treating adult patients with very high

12.*Id*. at 196.
13.United States v. Caronia, 703 F.3d 149 (2d Cir. 2012).
14.*Amarin Pharma*, 119 F. Supp. 3d at 198.
15.*Id*. at 209.
16.*Id*.

triglyceride levels above 500 mg/DL of blood (also called "severe hypertriglyceridemia").[17] The second use was for treating patients with persistently high triglyceride levels between 200 and 499 mg/dL of blood and who were already on statin therapy.[18] The first use received FDA approval on July 26, 2012.[19] The FDA did not approve the second use, and it is this use that was at issue in the case. The FDA denied Amarin's application for this use because, although their studies proved that Vascepa was effective in reducing triglyceride levels, there were studies that questioned whether this subsequently reduced the risk of cardiovascular events.[20]

Vascepa has been shown to be effective in reducing triglyceride levels.[21] FDA-approved studies have been done confirming this, and the FDA has agreed with this in correspondence with Amarin.[22] Vascepa is also safe and can be safely used by people with severe hypertriglyceridemia.[23] Amarin gained agreement with the FDA to conduct clinical trials testing whether Vascepa was effective for those with persistently high triglycerides on July 6, 2009 ("the unapproved use").[24] Additionally, this agreement for testing included approval for testing other factors relevant to cardiovascular health.[25] This study was called the ANCHOR Study.[26] The agreement was an FDA "special protocol assessment" (SPA agreement) which provides that if the study is done and the benchmarks set in the agreement are met, that the FDA would approve the drug.[27] At that time, the FDA required, and Amarin agreed, that Amarin would later conduct a study on whether Vascepa could prevent major cardiovascular events in high-risk patients including those with persistently high triglycerides.[28] This study was called the REDUCE-IT Study, and

---

17.*Id*.
18.*Id*.
19.*Id*.
20.*Id*.
21.*Id*. at 213.
22.*Id*. at 209.
23.*Id*.
24.*Id*. at 210.
25.*Id*.
26.*Id*.
27.*Id*.
28.*Id*.

the agreement was the REDUCE-IT SPA Agreement.[29] The FDA intended this later study to be underway to provide input before they would approve the use of Vascepa for this patient population.[30]

The ANCHOR study achieved its benchmark requirements and showed that Vascepa significantly reduced triglyceride levels in patient populations with persistently high triglycerides.[31] However, after Amarin applied for approval for Vascepa for this use, the FDA determined, through a public advisory committee convened in October 2013, that while Vascepa reduced triglyceride levels in this patient population, this had no impact on reducing risks of cardiovascular events.[32] As a result, despite Amarin meeting the benchmark terms in the ANCHOR study, the FDA rescinded the ANCHOR SPA agreement and would not approve Vascepa for usage in this population unless this correlation could be proven.[33] The FDA claimed that other drugs that successfully reduced triglyceride levels had failed to yield a reduction in cardiovascular events.[34] They claimed that reduction in cardiovascular events was a premise of the ANCHOR study, and, therefore, it was appropriate to rescind that SPA agreement.[35] They further stated that if Amarin was able to show a reduction in cardiovascular events from the REDUCE-IT study, then these results could be used to satisfy the approval requirements.[36] "Amarin appealed the rescission of the ANCHOR-SPA agreement through three successive levels of the FDA review."[37]

In addition to not approving Amarin for use for those with persistently high triglyceride levels, the FDA told Amarin that they would consider Vascepa to be misbranded under the FDCA 21 U.S.C.A. § 352 (West 2013),[38] if the FDA marketed it for this use

---

29.*Id*.
30.*Id*.
31.*Id*.
32.*Id.* at 211.
33.*Id*. at 212.
34.*Id*.
35.*Id*.
36.*Id*.
37.*Id*. at 211.
38.*See* 21 U.S.C.S. § 352 (2007) (defines ways in which drugs will be deemed to be misbranded including false or misleading labels and packaging).

prior to any approval of this use.[39] This was a clear threat of criminal litigation under FDCA § 331 (prohibited acts).

On May 7, 2015 Amarin brought a first amendment challenge to the Southern District of New York claiming the FDA was prohibiting them from promoting truthful and non-misleading statements, citing the results from the ANCHOR study.[40] Amarin claimed that the FDA restrictions on promotion significantly reduced their ability to provide truthful information to physicians so that physicians could determine whether to prescribe Amarin to patients with persistently high triglycerides. [41] Amarin claimed that these prohibitions were a violation of their first amendment rights to engage in truthful and non-misleading speech.[42] Further, they claimed that they should be able to provide information about these trials and results and uses without fear of criminal litigation.[43] Amarin's relied on the 2012 holding in *United States v. Caronia*,[44] and argued that drug manufacturers should be allowed to provide information that consists of solely truthful and non-misleading speech.[45]

While the FDA did attempt to make concessions allowing for some dissemination of information without the risk of criminal prosecution, they objected to the preliminary injunction.[46] They offered that providing the results of the ANCHOR study would not put Amarin under threat of prosecution,[47] but making statements about the off label use of Vascepa was a violation that directly struck

---

39.*Amarin Pharma*, 119 F. Supp. 3d at 212.
40.*Id.*
41.*See generally "Off Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices – Information Sheet*, US Food and Drug Administration Regulatory Information, (Jan. 25, 2006), http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm (The FDA does not regulate physicians in the prescribing of drugs, so they are able to prescribe drugs for usage that are not FDA approved.).
42.*Amarin Pharma*, 119 F. Supp. 3d at 212.
43.*Id.* at 213.
44.*See* United States v. Caronia, 703 F.3d 149, 169 (2d Cir. 2012) (holding 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.").
45.*Amarin Pharma*, 119 F. Supp. 3d at 198.
46.*Id*. at 216.
47.*Id.*

at the heart of the principles of the drug approval framework established by Congress in 1962.[48] Further, the FDA claimed that bringing a misbranding claim on promotional statements would not "prohibit speech" and was intended to protect the promotion of the use of a drug that was not deemed safe and effective by the FDA.[49] The FDA argued that while their enforcement was to be based on speech alone, there are other crimes where criminal liability can attach where speech is the only act.[50] These acts include jury tampering, blackmail, and insider trading.[51]

These arguments to obtain a preliminary injunction against any enforcement actions by the FDA against Amarin were heard on July 7, 2015.[52] In the hearing, the court considered the likelihood of success of the case on its merits and granted the preliminary injunction.[53] The court held that a misbranding prosecution cannot be based on free speech and that Amarin may engage in truthful and non-misleading speech, and that based on the facts provided, the information they wish to promote about Vascepa is truthful and non-misleading.[54]

BACKGROUND

The Federal Food, Drug, and Cosmetic Act ("FDCA") is a set of laws passed by Congress in 1938 to oversee the safety of food, drugs, and cosmetics.[55] Congress gives authority to the FDA to oversee and enforce this act.[56]

The FDA's early jurisdiction focused on accurate labeling of drugs and did not include safety or effectiveness.[57] However, after some significant public health disasters occurred, the FDA's role expanded

---

48.*Id.* at 218.
49.*Id.*
50.*Id*. at 224.
51.*Id*.
52.*Id*. at 219.
53.*Id*. at 237.
54.*Id*.
55.Ventola, *supra* note 3, at 428.
56.*See* 21 USCS §§ 301 et seq.
57.Jerry Avorn,, *Two Centuries of Assessing Drug Risks*, 367 New Eng. J. Med. 193, 195 (2012).

to protect the public from unsafe drugs.[58] In 1937, more than 100 children had been poisoned by a sulfanilamide preparation that used a substance known to be lethal.[59] This resulted in a public that demanded that the FDA ensure that drugs were safe for the public.[60] Then, in 1962, more than 10,000 children worldwide were born with birth defects as a result of their pregnant mother's use of Thalidomide.[61] Public outcry led to further legislation, giving the FDA the rights to ensure drug effectiveness as well as drug safety.[62]

Obtaining FDA approval is a long, costly and complex process and it can take decades before a drug can be used in the market and prescribed by physicians.[63] The labeling, marketing, and promotion of the drug in the market is limited to the FDA approved uses.[64] If new uses are found but not FDA approved, the use is referred to as 'off label' use.[65] While promotion of off label uses is limited by the FDCA, off label prescribing by physicians is not.[66] A physician may use their medical judgment to prescribe drugs for uses not approved by the FDA, but pharmaceutical companies cannot label or promote the drugs for those uses.[67]

Off label uses can be shared with physicians in limited ways. Scientific studies may be published by manufacturers in peer reviewed scientific journals or through presentation of journal articles, or through trainings and workshops through independent sources not funded and not sponsored or presented by the

---

58.*Id*.
59.*Id*.
60.*Id*.
61.*Id*. at 196.
62.*Id*.
63.Fed. Drug Admin., *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective* (Nov. 6, 2014),
http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm.
64.Ventola, *supra* note 3, at 432.
65.*Amarin Pharma*, 119 F. Supp. 3d at 200.
66.John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 Yale J. Health Pol'y L. & Ethics 299, 303 (2010), Available
at:http://digitalcommons.law.yale.edu/yjhple/vol10/iss2/2.
67.*Amarin Pharma*, 119 F. Supp. 3d at 200.

manufacturer.[68] To limit the promotion of off label uses, the FDA prohibits the introduction of new drugs into interstate commerce if their use has not been approved and the FDCA prohibits the misbranding of drugs.[69] A drug is misbranded if its labeling is "false or misleading."[70] While the FDCA defines labels as any material accompanying the drug,[71] the FDA's regulations are more broadly defined as anything a representative of the company or the product might present with the drug, or about the drug, even if it does not accompany the drug itself.[72] The FDA requires that pharmaceutical companies limit statements relating to the promotion of their drugs to the use for which the drug was approved.[73] Therefore, off label use would never be allowed for new drugs, and promotion of off label uses for existing approved drugs are limited through the FDCA limitations on misbranding and information dissemination of unapproved uses.

The FDA has litigated many cases against pharmaceutical manufacturers such as Allergan, GlaxoSmithKline, and Abbott that have violated the misbranding prohibition found in the FDCA.[74] These cases have resulted in billions of dollars in criminal and civil settlements.[75]

A complaint was filed in 2007 against Allergan for off-label marketing of pharmaceuticals.[76] Two other complaints followed in 2008 and 2009, and in 2010, Allergan pled guilty and paid $600 million in fines, including $375 million in criminal fines, and $225 million in civil fines for the unlawful promotion of Botox® Therapeutic, for uses not approved as safe and effective by the FDA.[77] Amongst such unapproved conditions are headache, pain,

---

68.Ventola, *supra* note 3, at 429.
69.21 U.S.C.A. § 331 (West 2013).
70.21 U.S.C.A. § 352 (West 2013).
71.21 U.S.C.A. § 321 (West 2009).
72.Food and Drugs, 21 C.F.R. § 202.1 (2009).
73.21 U.S.C.A. § 331 (West 2015).
74.*Amarin Pharma*, 119 F. Supp. 3d at 204.
75.*Id*.
76.Complaint, *U.S. v. Allergan, Inc*., No. 1-07-CV-1288 (D. Ga. Jun. 5, 2007).
77.Dep't of Justice, *Allergan Agrees to Plead Guilty and Pay $600 Million to Resolve Allegations of Off-Label Promotion of Botox® (Sept. 1, 2010),*

spasticity and juvenile cerebral palsy.[78] Allergan was particularly egregious in its promotion for pain and headaches as they increased the number of staff-held workshops held for physicians and practices focused on diagnosing and billing for Allergan for these uses.[79]

In 2011, a complaint was filed against GlaxoSmithKline for, amongst other things, promoting products which the "FDA had not deemed safe and effective."[80] In 2012, GlaxoSmithKline pled guilty and paid $3 billion to settle cases associated with promoting misbranded drugs including Paxil and Wellbutrin.[81] In this case, although the FDA never approved Paxil for pediatric use, GSK was promoting Paxil depression in patients under age 18.[82] GSK also was routinely promoting Wellbutrin for a wide variety of lucrative off label uses including weight-loss, sexual dysfunction, and ADHD and substance addictions.[83] For these two drugs, GSK paid criminal fines of $757,387,200.[84]

Similarly, criminal charges were filed against Abbott Laboratories in 2012 for misbranding of Depakote.[85] Abbot settled for $1.5 million in 2012 for promoting uses of Depakote that were not deemed safe and effective by the FDA.[86] Specifically they were

---

http://www.justice.gov/opa/pr/allergan-agrees-plead-guilty-and-pay-600-million-resolve-allegations-label-promotion-botox.

78.*Id*.

79.*Id.*

80.Complaint, *U.S. v. GlaxoSmithKline, PLC.,* C.A. No. 11-10398-RWZ (D. Mass. Oct. 26, 2011).

81.Dep't of Justice, *GlaxoSmithKline to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data, (Jul. 2, 2010),* http://www.justice.gov/opa/pr/glaxosmithkline-plead-guilty-and-pay-3-billion-resolve-fraud-allegations-and-failure-report.

82.*Id*.

83.*Id*.

84.*Id*.

85.Complaint, *U.S. v. Abbott Laboratories*, No. 1:12:CR26 (W.D. Va., May 7, 2012).

86.Dep't of Justice, *Abbott Labs to Pay $1.5 Billion to Resolve Criminal & Civil Investigations of Off-label Promotion of Depakote*, (May 6, 2012), http://www.justice.gov/opa/pr/abbott-labs-pay-15-billion-resolve-criminal-civil-investigations-label-promotion-depakote.

promoting Depakote for the treatment of agitation in dementia patients and for schizophrenia.[87]

In addition to financial settlements for civil and criminal penalties, criminal charges have been brought against sales representatives for promotion of off label uses. First amendment defenses against the FDA where criminal sentences have been levied are not always upheld based on a free speech argument. In *United States v. Caputo,* a federal appeals court in Chicago rejected a First Amendment claim of a defendant sentenced to ten years in prison for marketing a medical device to hospitals.[88] This medical device was similar to an approved device, but did not operate the same.[89] The FDA had only approved the companion product that worked differently, and did not approve the new device for any use at all.[90] The court held that this was not an off-label promotion, and thus was not a free speech issue that might receive constitutional protection under the first amendment.[91] They held that this was simply an unlawful sale and upheld the criminal charges.[92]

More recently, however, there has been a case where the defendant has been convicted of criminal charges for unlawful promotion of drugs, and the courts held that preventing his promotion of the drugs violated the defendant's free speech rights.[93] In this case, *United States v. Caronia* in 2012, Caronia, a pharmaceutical sales representative, appealed a criminal conviction for promoting off-label uses of Xyrem, a prescription drug manufactured by Orphan Medical, Inc.[94] Caronia was subjected to a $25 fine and 100 hours of community service.[95] The Second Circuit ruled that the FDA's enforcement of FDCA violated Caronia's First Amendment rights, stating: "We conclude simply that the government cannot prosecute pharmaceutical manufacturers and their representatives under the

87.*Id*.
88.
89.*Id.* at 937.
90.*Id.*
91.*Id*.
92.*Id.* at 940.
93.United States v. Caronia, 703 F.3d 149, 152 (2d Cir. 2012).
94.*Id.*
95.*Id*. at 160.

FDCA for speech promoting the lawful, off-label use of an FDA-approved drug."[96] The Second Circuit found the regulation is more extensive than is necessary to serve the government's interest.[97] The government did not appeal this ruling, and set in play a holding that established the foundation from which Amarin was decided.

AMARIN LEVERAGED THE CARONIA HOLDING

Amarin's request for a preliminary injunction was based squarely on the holding in Caronia. Amarin argued that promotion of off label uses of Vascepa was truthful speech, and the court in Caronia established that this was protected speech under the first amendment.[98] The government argued that the holding in Caronia applied only to the facts and circumstances of that case and was not a general ruling.[99] However, in Caronia, the court closely analyzed and then determined that Caronia was prosecuted for his "speech" and the simple promotion of a drug's off-label use.[100] The court concluded he was, and vacated the conviction.[101] By doing the free speech analysis, the court in Caronia was taking a categorical view of the case, rather than resting their holding based on any specific facts. The Caronia court held that the misbranding provisions in the FDCA could not reach into limiting truthful speech, which is protected by the first amendment.[102] Given this background, the government's contention in Amarin that the Caronia holding was fact-based was not supported by the court.[103]

This holding, whether narrowly fact-based or broadly applicable, does not apply to all speech about uses of drugs. The claims must be truthful and not misleading. In *Caputo*, the uses that were promoted had not been substantiated by evidence or a study, but in *Amarin*, there was a valid study and the uses promoted were true. In *Amarin*,

---

96.*Id.* at 169.
97.*Id.* at 167.
98.*Amarin Pharma*, 119 F. Supp. 3d at 219.
99.*Id.* at 224.
100.*Caronia*, 703 F.3d at 162.
101.*Id*. at 169.
102.*Id*. at 168.
103.*Amarin Pharma*, 119 F. Supp. 3d at 224.

the ANCHOR-SPA studies were completed and were valid and FDA approved studies. Any claims they intended to use to promote Vascepa were based on valid studies and would be truthful, thus protected by the first amendment.

IMPLICATIONS OF ALLOWING OFF LABEL PROMOTION

Benefits

There are many advantages gained by allowing broader promotion of truthful, off label uses of drugs. Even today, data studying 725 million prescriptions showed that 20% of these prescriptions were for off label uses.[104] Seventy percent of those 20%, or over 100 million prescriptions, were based on no or weak science.[105] Still, physicians are choosing to prescribe based on information available to them, even without this foundation.

Broader promotion allows data to be available to a wider range of physicians that might otherwise not have been able to do the research themselves. Physicians cannot keep current on all new research available, even if they are published in journals. There are many manufacturers and journals and a physician cannot reasonably be expected to know all possible uses of every medication. Important studies that may apply to their patients may easily be missed.[106]

Another argument for allowing off label promotion is to encourage and support innovation in physician's clinical practices. Without off-label promotion, manufacturers have little incentive to do research to support patients with "orphan diseases" (those that afflict fewer than 200,000 Americans such as ALS or cystic fibrosis).[107] The market is small, and without the ability to promote the uses in orphan diseases, these drugs may not be known by physicians to be used in their practice to support patients with no other alternatives.

104.David C. Radley, Susan N. Finkelstein & Randall S. Stafford, *Off-label Prescribing Among Office-Based Physicians*, 166 Arch Intern Med 1021 (2006), available at http://archinte.jamanetwork.com.
105.*Id*.
106.Ventola, *supra* note 3, at 432.
107.*Id*.

More commonly, the argument for the promotion of off label uses prior to FDA approval is to provide early notification to physicians about uses that have been studied and proven. Even with new and more efficient processes to fast-track drug approval, the process could take years, making effective treatments unavailable to patients who need them.[108] The impact of this could be tragic. Patients that could benefit from uses, validated by studies outside the FDA approval process, may die or decline significantly before the uses of the drugs are known. In patients who have died, or where there is no reversal of disease progression possible, it would be tragic not to make these drug usages known to their physicians as early as possible to slow or prevent decline, manage symptoms, or prevent or delay death.

Risks

Despite these advantages, the unfettered promotion of even truthful information raises concerns.

Promotion of drug uses through peer-reviewed articles may introduce unintended consequences that expose the profession to risks and vulnerabilities, and thus introduce safety risks to the public. These concerns include the risks of selective publication of only positive studies, the suppression of important safety data, ghost written articles, and increased focus on publishing for the purposes of promoting reprints for marketing.[109]

Other concerns are that while off label promotion will ensure broader availability of the alternative uses and data to physicians, it does not follow that physicians will do their own due diligence to seek out additional information or do further research. In these cases, physicians may rely solely on the information provided by the pharmaceutical manufacturer where the FDA has not compelled more rigorous research and proof of effectiveness. This may result in false confidence by physicians who may prescribe drugs that have limited effectiveness or pose other risks to the patient.

108.United States v. Caronia, 703 F.3d 149, 162 (2d Cir. 2012).
109.Ventola, *supra* note 3, at 435.

There are also questions about whether the FDA has enough resources to ensure that this widespread promotion is based on truthful content. The government does not have an unlimited amount of resources, and by not placing clearly defined limits on promotion, such as containing broad promotion to FDA approved uses of drugs, the public health may be at risk.[110]

Another concern is whether the ability to widely promote off-label uses of drugs provides a motivation for drug manufacturers to avoid doing extensive clinical trials required by the FDA prior to promoting to physicians. There is concern that drug manufacturers may initially conduct trials for a narrower, less complex use of a drug, as a way to get the drug into market, and then promote the off-label uses without the extensive testing normally required.[111] This situation occurred with Fenfluramine when it was used in combination with Phentermine (fen-phen) for weight loss and resulted in thousands of people with heart valve damage.[112] Fenfluramine was approved as an appetite suppressant, and there were not extensive clinical trials for the fen-phen combination that would have identified this risk and prevented this long term heart damage.[113]

Recent studies have shown that the risks are very real. In a study published on November 2, 2015, in the journal JAMA Internal Medicine, researchers at McGill University in Toronto found that patients were fifty-four percent more likely to experience adverse events if they were prescribed a drug for off label use. [114] This is particularly concerning given the prevalence of off label prescriptions written.

IS IT A TRAP?

The pharmaceutical companies certainly find that the ruling in *Amarin* may benefit their ability to communicate the off-label,

---

110.*Id.* at 438.
111.*Id.* at 431.
112.*Id.* at 428–440.
113.*Id*.
114.Karen Pallarito*, Beware Safety Risks Posed by 'Off-Label' Drug Use,* HEALTHDAY, (Nov. 2, 2015), http://consumer.healthday.com/general-health-information-16/prescription-drug-news-551/beware-safety-risks-posed-by-off-label-drug-use-704854.html.

unapproved truthful uses of drugs more broadly to the public and physicians. With the ruling in *Amarin*, it appears that this speech is protected by the first amendment and the risk of prosecution and large fines is at least minimized.

Shortly after the *Amarin* ruling, other pharmaceutical manufacturers began to seek relief from the threat of criminal prosecution similar to *Amarin*. Pacira Pharmaceutical filed a complaint on September 8, 2015 in the same court regarding EXPAREL, Pacira's local anesthetic product, asking the court to declare that the FDA may not limit Pacira's communication as it is free speech, and to declare an FDA warning letter arbitrary and capricious.[115] The parties settled and the letter was withdrawn on December 14, 2015.[116]

Nonetheless, it is unclear how broad this ruling is. While certainly a win for first amendment protected free speech, the ruling is one that protects truthful speech. In the *Amarin* ruling, the court looked closely at the wording Amarin wished to use.[117] The holding concluded that Amarin may promote truthful speech, but concluded this based on the evaluation of the information provided to the court.[118] If pharmaceutical companies determine independently that their research can be conclusively viewed as truthful, are they then subject to similar judicial review? Until this case concludes, or additional cases go forward, we will not know whether this ruling is fact specific to the *Amarin* case. Companies that act based on this ruling without further judicial holdings are at risk for negative evaluations of their claims and losses in the courtroom. Until the full precedential value of this holding is determined, drug makers should be wary of believing that this holding opens up broad off label promotion opportunities.

115.Complaint of Plaintiff*, Pacira Pharmaceuticals, Inc. et al v. United States Food & Drug Administration et al,* 15-cv-07055 (2015)(LAK).

116.Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA, to David Stack, CEO and Chairman, Pacira Pharmaceuticals (Dec. 14, 2015), available at http://media.corporate-ir.net/media_files/IROL/22/220759/The_Warning_Letter_Withdrawal_Letter.pdf.

117.*Amarin Pharma*, 119 F. Supp. 3d at 229.

118.*Id*. at 237.

WHERE SHOULD THIS GO?

The need for off label usage of drugs is inarguable. Some studies have found that the frequency of off label prescribing of drugs is as much as 38.9% of all prescriptions.[119] This varies by the type of medication, but there is no question that physicians find off label prescribing necessary. Drug makers should be able to promote off label uses of drugs, but it must be done in a safe framework that is less onerous than the full path of FDA approval.

Off label promotion of drugs should be limited to those uses where there is clear evidence to support the claims. While the FDA has made progress in providing faster drug approval paths,[120] there still must be a way to provide information to physicians for uses that have been found to be useful, particularly for orphan diseases, which may not normally have a broad enough impact on the population to invest in even the faster approval processes. The FDA needs guidelines on what evidence pharmaceutical companies must provide when they promote off label uses and not limit the evidence to only FDA approved studies.

Physicians must also have training or requirements through their licensing or medical societies to ensure they are doing proper diligence in investigating the uses of off label uses of drugs before prescribing, and are informing their patients of the off label uses and risks. While malpractice risks provide some incentive to physicians to do further research before prescribing, desperation to help a patient or unmanageable workloads may mean that the physician today isn't doing enough research to better understand the uses and risks before prescribing.

Patients have a right to know about the medications that are available in the market that have evidence indicating that the medication could help them. With this right to knowledge comes the

---

119.John L. Turner, W. David Bradford, and Jonathan W. Williams, *"Off-Label Use of Pharmaceuticals: Trends and Drivers"* (July 23, 2015). Society for Economic Measurement Annual Conference. Paper 90. Available at http://repository.cmu.edu/sem_conf/2015/full_schedule/90.

120.Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review, (2015), http://www.fda.gov/forpatients/approvals/fast/ucm20041766.htm.

responsibility of the patients to ask about the supporting evidence of the drug use for their illness and learn of the risks.

Off label marketing of drugs serves an important role in treating illnesses where there is no medication approved to help the patient. It should be allowed with a combination of regulation, information availability, and physician and patient education.

THE PATH FORWARD

The parties in the *Amarin* case were issued an order on August 10, 2015 to jointly submit the next steps to the court by August 28, 2015.[121] In response to that order, the parties asked the court for a stay until October 30, 2015, which was extended until December 17, 2015 while they considered a settlement.[122] This stay was later extended until February 17, 2016.[123] A proposed stipulation and order of settlement was filed with the FDA on March 8, 2016.[124] If approved this will close Amarin's challenge to the FDA.

While this settlement may be approved soon, the question remains whether the approval of the injunction has precedential value. On this subject, they then will have settled with Amarin, and with Pacira. It seems that they will attempt to settle where they are challenged in an effort to delay firmer grounding in the expansion of off label promotions.

121.Amarin Pharma, Inc. v. U.S. FDA, 119 F. Supp. 3d 196 (2015) (No. 15 Civ. 3588), http://www.lifescienceslegalupdate.com/wpcontent/uploads/sites/500/2015/08/15cv03588Doc74.pdf.

122.Letter filed by Floyd Abrams, Attorney to Hon. Paul A. Engelmayer, United States District Court Judge (10/30/2015), http://www.lifescienceslegalupdate.com/wp-content/uploads/sites/500/2015/08/15cv03588_Doc78.pdf.

123.Letter filed by Peter Gottesfeld, Amarin Pharma, Inc., Eric Rishe, Ralph Yung, Jonathan Herbst to Hon. Paul A. Engelmayer, United States District Court Judge (12/17/2015).

124.[Proposed] Stipulation and Order of Settlement, *Amarin Pharma, Inc. v. U.S. FDA*, 119 F. Supp. 3d 196 (2015)(No. 15 Civ. 3588), http://www.fdalawblog.net/AMRN%20Off-Label%20Proposed%20Settlement.pdf