On August 7, 2015, the US District Court in *Amarin v FDA* handed down a ruling that the US Food and Drug Administration (FDA) lacked the authority to prohibit nonmisleading forms of off-label speech.\(^1\) When a drug is approved by the FDA for a specific indication, licensed clinicians are nevertheless free to prescribe it for any clinical use they see fit. In fact, off-label drug use (ie, prescribing medications for a different disease or medical condition, different route of administration, and/or different dosage than that approved by the FDA) is relatively common, with a 2006 study estimating that 21% of commonly used drugs are prescribed off-label.\(^2\) Despite regular off-label use of prescription drugs (including high rates in certain patient populations and conditions such as pediatrics, cancer, and psychotic disorders), manufacturers are only allowed to engage in product promotion for the indication approved on the label.\(^3\) When manufacturers engage in promotion for any indication, dosage, or administration outside the FDA approval, they engage in illegal off-label promotion.\(^4\) However, the lines between illegal and permitted off-label promotion are now being blurred in the wake of the *Amarin* decision, which is likely to have a lasting impact on future drug promotion practices, regulatory and enforcement activities, and the role of the physician in patient care.

### Eroding FDA Off-label Oversight

Although the Food, Drug, and Cosmetic Act (FDCA) does not specifically delineate FDA powers to prohibit off-label promotion, the FDA has maintained that by marketing off-label, a manufacturer violates the FDCA by introducing a “misbranded” drug into interstate commerce. Evidence of intent to promote off-label use can be promotional statements (speech) or actions/conduct by manufacturers or sales representatives.\(^5\) Importantly, the FDA views its regulatory oversight over off-label promotion as important in ensuring the integrity of its regulatory approval processes.

However, the FDA's interpretation of its regulatory authority has been challenged. In the late 1990s, the Washington Legal Foundation, a non-profit conservative legal organization, pursued litigation against the FDA, challenging guidance it had issued on the dissemination of off-label use information in scientific literature and industry-sponsored continuing medical education.\(^5,6\) Guidance came at a time when indirect forms of promotion, such as continuing medical education that included promotion of off-label uses, was being used to encourage physicians to prescribe for off-label use.\(^4,6\) The first decision in Washington Legal Foundation litigation resulted in a district court finding that the FDA guidance documents violated commercial free speech protections, which required the FDA to rethink its legal strategy on the topic.\(^6\)

Following this setback and another district court decision that struck down the FDA requirements for off-label information dissemination and approval enacted under the Food and Drug Administration Modernization Act of 1997 (FDAMA), the FDA responded by reframing its regulatory interpretation of off-label regulations. The FDA argued that off-label regulations under the FDAMA constituted “safe harbors” (ie, establishing a set of conditions that protect a party from regulatory action/prosecution) and hence did not specifically prohibit commercial speech.\(^5,7\) This change allowed the FDA to moot the legal argument of constitutionality regarding commercial off-label speech, leading to an appellate court dismissing and vacating prior rulings. The reframing resulted in regulatory ambiguity but also allowed the FDA to retain some regulatory and enforcement authority.\(^5\)
What followed was a decade of FDA off-label draft guidance as well as both increased illegal off-label promotion activity and record-breaking off-label health care fraud and abuse prosecutions by the FDA and US Department of Justice (DOJ). A few notable examples include the 2005 $1.415 billion DOJ criminal and civil settlement with Eli Lilly and Company for its off-label promotion of Zyprexa and the 2009 $2.3 billion settlement against Pfizer Inc for several products including off-label promotion of Bextra.

### Off-Label Regulation: Questions of Constitutionality

In 2012, in *US v Caronia*, the debate regarding the constitutionality of off-label promotion reemerged with a new case in a federal district court challenging the FDA’s off-label regulatory interpretations. Alfred Caronia, a drug salesperson for Orphan Medical, Inc, was caught during a criminal investigation promoting the drug Xyrem (sodium oxybate) for off-label uses beyond its indication for cataplexy treatment in patients with narcolepsy (it also has several contraindications, is a controlled substance, and carries a black box warning). A federal jury convicted Caronia, but on appeal, the federal circuit court vacated his conviction, holding that the FDA’s construction of the FDCA’s misbranding provisions unconstitutionally restricted his lawful free speech under the First Amendment. In response, as has become typical, the FDA declined to appeal the ruling, instead updating its draft guidance on journal article dissemination, issuing a statement that it would not change its enforcement activities, and effectively adopting a narrow “fact-bound” interpretation of the ruling. Based on Caronia, Amarin Pharma, Inc sought protection from FDA off-label prosecution, a move that further challenges the FDA’s authority to regulate off-label marketing by manufacturers. The case involved a hypertriglyceridemia drug Vascepa (icosapent ethyl), which the FDA earlier approved for treating patients with severe hypertriglyceridemia. It is also chemically similar to dietary supplements (icosapentaenoic acid and docosahexaenoic acid omega-3 fatty acids) already sold directly to consumers. At question in the case was Amarin’s right to promote a second indication for treating patients with persistently high triglyceride levels and the much broader claim that the drug lowered the risk of coronary artery disease. Complicating the case was a special protocol assessment agreement between the company and the FDA, which Amarin complied with, including completing a clinical trial (the ANCHOR Study [Evaluation of the Effect of Two Doses of AMR101 (Ethyl Icosapentate) on Fasting Serum Triglyceride Levels in Patients With Persistent High Triglyceride Levels (> 200 mg/dL and < 500 mg/dL) Despite Statin Therapy]) that supported a supplemental New Drug Application approval for the second indication. However, the FDA rescinded the special protocol assessment agreement in response to efficacy concerns raised by its public advisory committee examining the drug.

After unsatisfactorily pursuing administrative appeals through the FDA processes, Amarin filed a civil complaint challenging the FDA’s decision and threat to prosecute the company for off-label speech on the grounds that it unconstitutionally prohibited its truthful and nonmisleading speech. Specifically, it asked the court to protect it from FDA prosecution and rule that it could engage in certain physician-directed communication, including use of off-label statements, dissemination of publication reprints, and distribution of a written summary of the ANCHOR Study results supporting the second unapproved indication. Amarin also agreed to make contemporaneous disclosures to assure that its off-label statements were not interpreted as misleading.

The FDA responded to Amarin’s challenge by stating that (1) it viewed some of Amarin’s proposed communication as unproblematic, (2) the FDA would not object to Amarin’s off-label communications provided certain changes and additional disclosures as required by the FDA were made, and (3) if its conditions were accepted, there would be no basis for enforcement action and hence the complaint was moot. However, the FDA strongly objected to the proposed marketing statement that “EPA [icosapentaenoic acid] and DHA [docosahexaenoic acid] omega-3 fatty acids may reduce the risk of coronary heart disease,” which Amarin argued should be permitted because such claims were
The court, heavily relying on the Caronia decision (and a previous US Supreme Court decision inIMS v Sorrell) held that Amarin’s off-label speech was indeed truthful and nonmisleading and therefore should be permissible. The decision effectively foreclosed the FDA’s ability to bring a misbranding action against at least Amarin, and if accepted by other courts, the decision could extend protections to any pharmaceutical manufacturer that engages in off-label communications solely based on truthful promotional speech.11

Post-Amarin v FDA: What Comes Next?

Although successful in evading early challenges and maintaining some of its regulatory oversight, the Caronia and Amarin cases have exposed fundamental weaknesses in the FDA’s interpretation of its regulatory authority regarding off-label promotion. The decisions also rely that courts are adopting a position of constitutional avoidance, which favors the protection of constitutional principles of commercial speech even when it may conflict with patient safety and public health concerns.10 Critically, the FDA’s decision not to pursue appeal in Caronia or contest the truthfulness of his off-label speech opened the door to an even broader ruling/interpretation in Amarin, which has resulted in a rapid erosion of the FDA’s regulatory off-label promotion oversight powers under the two decisions.

The FDA’s strategy to forego appeal in Amarin is also consistent with the agency’s prior legal strategies that have focused on avoiding further damage by focusing on retention of diminishing regulatory enforcement powers in the face of increased legal scrutiny and adverse court decisions on the subject of commercial free speech restrictions. This strategy is also reflected in the trepidation of the FDA in appealing the case or petitioning it to the Supreme Court of the United States, a recognition by the agency of the court’s presumptive commercial speech jurisprudence favoring its protection over regulation.10,12,13 Specifically, in an August 2015 letter filed with the court, Amarin’s counsel asked for a stay in the proceedings, indicating that both parties are working toward a negotiated settlement and that an appeal by the FDA is unlikely.

Most importantly, Amarin also raises fundamental questions about who will decide what constitutes “truthful” and “nonmisleading” health information regarding prescription drugs, biologics, medical devices, and other medical products and services. The decision effectively shifts the decision-making process of what is considered truthful off-label promotion to industry rather than the FDA by giving deference to manufacturers in making this initial determination.11 At the heart of this rationale was the court’s logic that it is beneficial for physicians to have “more, not less, information,” even though concerns clearly exist regarding the source credibility, whether it is evidence based, the quality of evidence used in such information, and the inherent conflict of interest on the part of manufacturers and the drugs they promote.1

Relying on manufacturers to self-regulate truthful and nonmisleading off-label promotion activities is concerning given previous billion-dollar DOJ prosecutions for illegal off-label promotion activities and the simple fact that substantial profits can be realized from increased sales emanating from off-label drug uses that can be influenced by physician-targeted promotion.14,15 Further, other studies have found that physicians are only able to identify the FDA-approved indication about half the time and that off-label use of drugs is often associated with adverse drug events (especially when not supported by strong scientific evidence.)16,17 This tenuous situation could also provide an opportunity for other less reliable sources (eg, third-party marketers, contracted marketing firms, independent sales representatives, social media marketers) to take advantage of this regulatory opening in order to avoid prosecution under the FDCA. Further, the court’s decision to allow health claims made in dietary supplement products to extend to off-label promotion of a prescription drug may set a dangerous precedent and open the floodgates to a host of unsubstantiated forms of marketing. Collectively, these factors introduce important concerns regarding patient safety, quality of health information, and potential waste of health care resources.

The Amarin decision could also negatively impact the deterrent effect of fraud and abuse
penalties issued against illegal industry-based off-label promotional activities that have resulted in some of the largest US civil and criminal fines in history. Specifically, federal fraud and abuse laws and regulations, including the False Claims Act and the Anti-Kickback Statute, rely on whistle-blowers (who share in fraud and abuse claims in qui tam lawsuits) and regulators to actively pursue a case based on its merits and the potential for successful recovery.

Amarin may now further disincentivize illegal off-label promotion reporting and prosecution given that the decision now shifts the burden to the FDA and DOJ of proving that a specific off-label promotion is in fact not truthful and/or misleading. In response, whistle-blowers and regulators may need to be more judicious in the cases they report, investigate, and ultimately decide to prosecute.

Hence, in the post-Amarin landscape, important changes to the FDA's off-label regulatory scheme now seem an absolute necessity in order to modernize the agency's approach regarding off-label promotion. Future reforms should embark beyond a simple refresh of the FDA's current confusing and disjointed set of regulatory guidance documents following expiration of the FDAMA (something the agency has already promised to address) and instead boldly work toward establishing a clear and codified "safe harbor" process (through new legislation that also will harmonize the existing FDA patchwork of off-label guidance) to prereview, amend, and qualify off-label communication to ensure that it is nonmisleading. By developing such a system, manufacturers would be incentivized to both presubmit and collaboratively work with the agency to formulate off-label communication that is evidence based, is of benefit to clinicians and their patients, and could also mitigate adversarial legal proceedings between industry and the FDA.

Specifically, an off-label safe harbor regulatory regime could be modeled after similar processes under the federal Anti-Kickback Statute that describes payments and business practices that are determined by the US Department of Health and Human Services Office of Inspector General as not in violation of the statute. This step would introduce a more efficient and collaborative pathway for FDA-industry engagement and off-label promotion guidance and also potentially allow for more targeted prosecution of clearly harmful off-label marketing by differentiating good from bad off-label promotion. Importantly, an off-label safe harbor regulatory regime may also be viewed by the courts as legally compatible with commercial free speech protections, given that it would not specifically prohibit speech for certain conduct and merely provides a set of requirements that, if met, would preclude future enforcement action. Establishing a clear process for this determination would arguably be of greater benefit for manufacturers than relying on the framework for truthful and nonmisleading off-label speech outlined by the court, not the FDA, in the Amarin decision.

Additionally, off-label use and promotion for drugs that treat patients with orphan or rare diseases, cancer, and antipsychotic disorders should be particularly prioritized, protected, and monitored through robust postmarket surveillance given widespread off-label use in these patient populations and the need for better data on safety and efficacy. The Amarin decision could actually act to facilitate needed dissemination of good evidence-based off-label information to educate clinicians about the treatment options for vulnerable populations who often have no treatment that has been approved for their condition. The need for improved postmarket surveillance and data collection on off-label drug use could start with support from regulators, physician groups, and payers for disclosure of treatment indications and outcomes in electronic health records as has already been explored.

This data could be potentially deidentified or aggregated in order to limit its use strictly for research, surveillance, and drug and patient safety in order to avoid concerns regarding medical liability or reimbursement.

Finally, in addition to regulatory responses to Amarin, health care professionals should be well versed to understand the needs of their patients for all pharmaceutical treatments, including having knowledge of approved indications for drugs they prescribe and evidence-based off-label uses. With the Amarin decision, much more latitude on the extent and/or quality of off-label promotion is likely to occur, but the implications for physicians are not yet known. Physicians and other prescribers...
should respond proactively as needed learned intermediaries by carefully scrutinizing industry off-label promotional claims and their source credibility, especially promotion that has not been vetted by the FDA. Further, off-label promotion of drugs that have limited data and/or high sensitivity should be carefully considered by health care professionals before being prescribed. In cases in which a drug has a high risk profile, disclosure of the fact that the drug is being used off-label and its potential risks during the informed consent process should also be encouraged in order to ensure that patients are aware of attendant risks and benefits.

Conclusion

Although the Amarin decision is limited to a federal trial court ruling, thus having questionable precedential authority, it nevertheless marks a critical juncture in a growing body of legal cases that are eroding the FDA’s regulatory oversight powers, necessitating rethinking off-label promotion regulation. Further, given the unlikelihood of an FDA appeal to the Amarin case, regulators, physicians, policymakers/lawmakers, and consumer advocacy groups should recognize that regulatory liberalization of off-label promotion will likely lead to a new wave of drug promotion that may be of questionable quality, truthfulness, and reliability. Stakeholders should address problematic off-label promotion now, while advocating for better data and tools for filtering, identifying, and promoting truthful information about off-label uses currently permitted and even encouraged after the Amarin decision. Industry stakeholders should also view this as an opportunity to collaboratively work with the FDA to promote development of a regulatory safe harbor process that can provide a set of clear requirements on what constitutes truthful off-label communication in order to ensure evidence-based dissemination without the fear of enforcement. Off-label promotion reform efforts should also run in tandem with broader policy changes aimed at incentivizing manufacturers to seek FDA approval for new indications so that the safety and efficacy of prescription drug use can be optimized. Additionally, despite the modernization of the physician’s role, Amarin now places heightened importance on the traditional responsibility of the physician as the learned intermediary when making decisions about drug prescribing. With the FDA’s off-label regulatory authority in decline, new and innovative solutions to address both the potential harms and utility of off-label use need to be explored in order to ensure truthful future off-label communication.

ACKNOWLEDGMENTS

Dr Mackey would like to thank FDANews for their invitation and his participation in the webinar debate titled “The Debate on Off-Label Promotion” that helped formulate certain opinions expressed in this article.

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