Free speech* for pharmaceutical and device companies (*as long as it is truthful and non-misleading)

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Abstract/Executive Summary
Historically, the US Food and Drug Administration (FDA) had sweeping powers to enforce restrictions on the marketing and promotion of medical products for off label purposes. However, several recent cases in the federal court system have weakened this authority by supporting the free speech rights of pharmaceutical companies to market off-label, provided that their statements are truthful and non-misleading. The regulatory landscape surrounding off label marketing is now in flux, and the further evolution – and eventual result – of such free speech rights for pharmaceutical and medical device companies remains unclear from legal, regulatory, and business perspectives. Here, we provide an update on off-label marketing and promotion and present the opportunities and risks going forward for pharmaceutical, device, and diagnostic companies considering an expansion of off-label marketing following these recent rulings.

Background
The regulation of the promotion of medicinal drugs, devices, and diagnostics by the FDA has continually evolved since the passage of the Federal Food, Drug, and Cosmetic Act (FDCA) in 1938.[1] The original FDCA dictated that drugs could not be marketed without premarket approval for safety as a remedy for past problems with drugs with substantial toxicity. The law required the demonstration of drug safety, but it did nothing to prevent false and misleading advertising until the passage of the Drug Amendments of 1962, which requires manufacturers to demonstrate that their drugs are both safe and effective for their intended uses. Specifically, the Food and Drug Administration (FDA) was charged with approving new drug applications after evaluating a series of trials. This FDA oversight also included the approval of the indication labeling, and the FDA considers any drug manufacturer who markets or promotes an approved drug for unapproved uses in violation of the amended FDCA, although no provision of the FDCA explicitly forbids the marketing or promotion of drugs for off-label uses. The FDA has aggressively pursued the prosecution of parties engaging in off-label marketing and promotion in an effort to encourage manufacturers to submit to the drug review and approval process. Notably, in addition to potential FDA enforcement for misbranding under the FDCA, drug manufacturers may also be subject to civil penalties through the False Claims Act for claims submitted to government-sponsored reimbursement programs for non-FDA-approved uses, and these claims are often made concurrently.

Although the FDCA grants the FDA power over the pharmaceutical industry, the FDA does not have the power to regulate physicians, who are free to prescribe FDA-approved drugs for indications beyond those described on the label (in terms of disease state, target population, treatment regimen, etc.) if they deem the use appropriate for their patients.[2] An increasing array of drugs are prescribed off-label, and it is widely accepted – including by the FDA – that many of these off-label uses can be beneficial to patients. Even payer organizations have indicated a willingness to reimburse for certain off-label applications of drugs, particularly in the spheres of oncology and pediatrics, where disease severity or lack of a specific indication could otherwise restrict appropriate medications.[3,4,5,6] This universal acceptance of off-label drug use by the FDA, physicians, and payers has created a paradox with respect to the FDA's insistence on restricting marketing and promotion solely to approved label indications, leading to recent and active

litigation in the federal court system that has far reaching implications for the pharmaceutical, medical device, and diagnostics industries.

The latest challenges to FDA regulation of label-based marketing and promotion have been presented in the context of the First Amendment right to free speech. The FDA has long restricted communications regarding off-label indications, dictating specific responses from pharmaceutical companies to private and public queries and limiting the distribution of studies addressing off-label applications. As part of its guidance, the FDA has indicated that a private, unsolicited request for off-label information can be answered provided that the information is truthful, non-misleading, accurate, and balanced, but public queries cannot contain off-label information, even if it is truthful and non-misleading.[7] Historically, while these FDA policies on the regulation of "truthful and non-misleading" statements faced First Amendment challenges, modifications and refinements of FDA regulatory guidance have sufficed to quell the arguments, preventing more sweeping rulings by the federal judiciary. However, two recent cases in the Second Circuit have finally addressed the relationship between the FDA's enforcement of the FDCA's misbranding provisions and the protection of commercial free speech.

Recent Developments

United States vs. Caronia (2012) centered on the marketing and promotion of Xyrem, an FDA-approved medication for narcolepsy, by Orphan Medical Inc.[8] Caronia, a sales representative, was charged and convicted of conspiracy to misbrand for promoting Xyrem for off-label uses, although the truthfulness of his promotional statements was undisputed at his trial. The conviction was overturned on the grounds that off-label speech is constitutionally protected, commercial free speech, as long as it addresses a lawful activity (i.e. physicians are not prohibited from off-label use) and the speech was not misleading or untruthful.[9] Additionally, the government's interests could be served by restrictions short of a complete/criminal ban (i.e. off-label disclaimers and limits on off-label prescriptions) that could impose upon free speech. The broader effects of this decision were unclear until recently. Notably, the FDA interpreted the *Caronia* decision as a case-specific decision, but the decision has also been viewed as an important precedent by the pharmaceutical industry, leading to the recent decision in *Amarin vs. FDA* (2015) and likely additional litigation.

The *Amarin* case goes beyond the speech of an individual sales representative and addresses the free speech of the entire corporation with respect to the off-label marketing of Vascepa, an omega-3 fatty acid that is FDA approved for the treatment of adults with severe hypertriglyceridemia.[10,11] Following the approval of the initial indication for Vascepa, Amarin Pharmaceuticals entered into a Special Protocol Assessment (SPA) agreement with the FDA to pursue an indication in statin-treated patients with persistently high triglycerides. Such agreements typically indicate that the FDA will support approval if the proposed studies are properly conducted and meet agreed-upon objectives, and these agreements can only be altered by written agreement or when a substantial scientific issue essential to determining the safety or effectiveness of the drug is uncovered after trial initiation. After this study fulfilled the requirements of the SPA agreement, Amarin expected approval for the new indication, but due to the release of new studies downplaying the role of reducing triglycerides in reducing overall cardiovascular risks, the FDA rejected the indication with a complete response letter (CRL) and a warning that marketing for the proposed indication could constitute misbranding under the FDCA. Notably, the FDA did not dispute that Vascepa is effective in reducing triglyceride levels and has allowed chemically similar dietary supplements to be marketed.

In response to the FDA CRL, Amarin filed for a preliminary injunction to allow for providing truthful, non-misleading statements and disclosures regarding Vascepa and off-label uses to qualified healthcare professionals. Broadly, Amarin sought to provide results of their latest study, statements regarding research into omega-3 fatty acids and reductions in cardiovascular risk, and copies of scientific literature relevant to omega-3 fatty acids and cardiovascular disease. This truthful information would be

supplemented with a series of disclosures concerning Vascepa indications and reimbursement that would ensure that the information provided was not misleading. Although the FDA pursued its previous strategy of attempting to quell the argument with further guidance, it maintained its reading of the *Caronia* decision as case-specific and reserved enforcement rights under the misbranding provisions of the FDCA. The failure to resolve these issues by agreement resulted in a ruling on the preliminary injunction by the Second Circuit that validates the proposed statements and disclosures by Amarin regarding Vascepa, upholding the precedent of *Caronia* and introducing significant uncertainty into future FDA policies regarding off-label marketing and promotion.

The next steps for all parties remain unclear. Although the *Amarin* ruling is a preliminary injunction, Amarin is already promoting off-label uses of Vascepa, and other companies seem likely to pursue off-label marketing under the banner of free speech.[12] Following the truthful and non-misleading free speech precedent of *Caronia* and *Amarin*, Pacira Pharmaceuticals has filed a lawsuit against the FDA to defend its rights to promote Exparel.[13] In September 2014, Pacira received a warning letter from the FDA regarding promotion for indications beyond those used to garner FDA approval and inadequate directions for use in other indications. The warning letter was resolved in early 2015, but Pacira seems intent on pursuing more expansive Exparel marketing in the post-*Caronia*/post-*Amarin* landscape. Notably, multiple companies and groups have filed amicus briefs to support Pacira's claims, and it is unclear whether Pacira or any other company will seek damages from the FDA for past restrictions of free speech established by *Caronia* or *Amarin*.

Like the pharmaceutical companies, the FDA also has several options to pursue in order to maintain its current enforcement power for label indications. The *Amarin* ruling was only for a preliminary injunction, and the FDA had the right to file an appeal within 60 days. However, this time period has elapsed with no appeal from the FDA. However, *Caronia* and *Amarin* apply only within the Second Circuit, at present, and the FDA could pursue an antagonistic ruling in a different circuit, which would likely lead to a Supreme Court appeal to establish homogenous national policy. The FDA could also expedite its review and presentation of new guidance regarding off-label marketing and promotion. The development of such guidance has been touted by the FDA on multiple occasions – including during the *Amarin* trial – but FDA officials have been unwilling to provide a timeline. Thus far, the FDA has not attempted to retain its enforcement power through the legal system. Instead, in response to the new Pacira litigation, the FDA recently took the unprecedented action of retracting the previously issued warning letter[14]. It is unclear whether this is a temporary concession while the FDA implements a new strategy for label enforcement or whether the FDA's enforcement power has been permanently diminished.

Overall, the off-label promotion and marketing landscape remains muddled and unclear, leaving many in the healthcare industry unsure of what steps to take. Below, we address the potential future scenarios and implications for the pharmaceutical, device, and diagnostic industries.

Opportunities

The willingness of Amarin and Pacira to jump into the free speech fray demonstrates one obvious reaction to the *Caronia*/*Amarin* rulings. Many view the rulings as comeuppance for years of rulings by the FDA and will seek to immediately pursue approaches to off-label marketing and expansive interpretations of on-label marketing. The immediate upside to this approach could be increased sales and new markets for existing products. For example, Pacira's Exparel was approved using trials in hemorrhoidectomy and bunionectomy, but company financial reports suggest one of the largest (and growing) markets for Exparel is orthopedics, an indication that is not specifically listed on the label.[15,16] The rulings may also allow companies to seek damages from the government for past FDA rulings that violated their free speech rights and limited their marketing. However, with no precedent, the required litigation may substantially delay payments, if any.

Additionally, existing products could potentially be expanded to new indications simply based on medication class. Amarin's disputed Vascepa statements concern the application of other omega-3 fatty acids products to cardiovascular disease, and the logical extension is that Vascepa, as an omega-3 fatty acid, would also be useful in this setting. A similar argument could be made for any mechanistically similar medication. If drugs A, B, and C inhibit the same enzyme but are approved for different indications, why shouldn't drug A be useful in all the indications? This hypothetical example is likely extreme, but the *Caronia/Amarin* rulings may open up the potential for *de facto* approval for indications by medication class. A corollary to this idea is the approval of new drugs or new indications based solely on the approval of existing drugs in the class, which has the potential to spare companies the costs of extensive clinical trial programs.

The design of first-in-class new drug trials will also be affected by the rulings. Companies may be able to forgo multiple trials by seeking a single indication and pursuing off-label marketing and promotions. Theoretically, companies could also coordinate trials of mechanistically similar medications in different indications to jointly profit in multiple spaces by conducting a reduced number of trials.

The rulings also apply to the marketing and promotion of new devices and diagnostics, with several specific highlights. For example, historically, companies have been restricted from providing guidance and information on analyte specific reagents (ASRs) for diagnostic assays. If the truthful and non-misleading standard is applied to this setting, companies and their sales representatives will likely be able to provide additional information to their customers in the future. This additional information could lead to competitive advantages for certain manufactures based on cost effectiveness or other parameters.

Extended use of off-label marketing may also influence provider organization policies. For example, although individual physicians already use medications for off-label applications, more open off-label marketing could provide more support and incentive for institutions to include multi-application medications on their formulary instead of adopting multiple, label-restricted medications. The reduction in drugs on formulary, in combination with the ability to obtain volume discounts on a drug with multiple uses, could result in significant savings. However, it is unclear how much liability would be incurred by institutional acceptance/incentivizing of off-label use.

Risks

Pursuing these opportunities is also accompanied by several risks, both short and long term. However, before addressing the long-term effects, it is notable that adopting a strategy in response to *Caronia* and *Amarin* may be premature in the absence of rulings in multiple jurisdictions and/or a response (appeal or modified guidance) from the FDA. The current landscape may only be temporary, and making multiple strategy changes and course corrections could prove expensive.

If the current environment holds, there are still multiple risks for manufacturers in the long term, the foremost of which is litigation. If companies use the *Caronia/Amarin* standard to pursue off-label indications, they may be subject to an increased litigation. Even in the current system, with indication approval supported by extensive evidence in clinical trials, manufacturers are subjected to lawsuits, often with devastating consequences. Decisions to use medications are now made by prescribing physicians, but if companies are actively promoting off-label use, are they now liable to pay potential damages resulting from such use? Furthermore, in a setting with little or no clinical trial data to support a medication's safety and efficacy in an off-label indication, a company may be left with little defense in a trial.

The threat of litigation may also limit the market for off-label use. Off-label use may subject both physicians and payers to additional litigation for prescribing and reimbursement. Payers in particular may

be unwilling to take on the increased risk with little financial reward in the absence of cost-effectiveness studies. If the physicians and payers don't support off-label use with prescriptions and reimbursement, the upside of off-label marketing and promotion for healthcare companies may be limited.

Deciding on the path forward: Weighing benefits and risks

Deciding the proper approach in the post-*Caronia/Amarin* world will require a difficult balancing of risk versus reward. For many medications, active off-label marketing and promotion will not be worth the additional risk exposure for the manufacturer because the medication is already used extensively off-label. A number of psychiatric medications are indicated for one disorder, but they are prescribed for multiple disorders. Seroquel/quetiapine is a prime example of an antipsychotic medication that is used beyond the label indication to treat anxiety disorders, dementia, depression, and other conditions, and it is estimated that close to 80% of Seroquel prescriptions are for off-labels purposes.[17] With such a large degree of off-label prescribing in the absence of specific marketing and promotion, it makes little sense for the manufacturer to assume greater risk exposure by pursuing an off-label marketing and promotion strategy.

Oncology medications present a more mixed case. Off-label use of oncology medications is well established and accepted by the medical, reimbursement, and regulatory establishments, in part due to the stakes involved in treatment. At first, it seems that manufacturers have little to gain from promoting off-label use in the oncology setting, if these medications are already finding extended use. However, due to the serious nature of the disease and iterative nature of treatment, there may be less risk exposure for promoting off-label use of oncology medications in this setting, especially in patients with already advanced disease.

When considering potential benefits and risks, it is much more difficult to address off-label marketing and promotion in the context of non-lethal / less severe disease states. Although not approved in the US upon its initial release, the history of thalidomide (introduced in 1957) provides an example.[18] Thalidomide was originally prescribed as a sedative, but it quickly became an over-the-counter agent in Europe for the treatment of nausea, morning sickness, and a variety of other maladies. However, clinical trials did not explore the effects of thalidomide during pregnancy. We now know that thalidomide is a teratogen that caused a large number of birth defects and deaths, which led to it being pulled off the market in the 1960s. Subsequently, thalidomide (and its drug class) has found a second life as a cancer chemotherapy and continues to be used successfully in this capacity today. Its label lists multiple myeloma and erythema nodosum leprosum, but it also continues to be used in investigational research or off-label for a variety of maladies despite its history. Therefore, thalidomide presents a hypothetical consideration for the benefits and risks of off-label use. In the absence of knowledge of its teratogenic effects and only considering its immunomodulatory applications, it might be appealing to promote thalidomide for off-label uses, and in fact, there may be appropriate applications that are not included on the label, particularly in dermatology. However, such off-label use, without FDA-required studies, could potentially lead to disastrous consequences for both patients and manufacturers.

In the case of Amarin and Vascepa, the stakes appear to be much lower. Chemically similar omega-3 fatty acids are readily available as supplements and are unlikely to cause dire problems for patients, so the benefits of exploring off-label marketing and promotion of Vascepa likely outweigh the liability risks incurred. However, for each new medication, diagnostic or device, manufacturers will have to make a unique assessment based on different levels of information.

Quantitating the degree of risk involved in off-label promotion remains difficult. The amount of fines and penalties from the FDA for off-label use have increased dramatically since 2004, illustrating the potential cost for manufacturers if the precedents from *Caronia* and/or *Amarin* are overturned in the future. However, the level of financial liability incurred by manufacturers from non-government sources remains

less clear. On the surface, restricting use of a product to the FDA-approved label could insulate manufacturers from lawsuits by demonstrating that the proper legal procedures were followed, but on-label usage has provided little to no protection in past lawsuits over Actos and Vioxx, among others. If the lack of a label indication does not significantly affect the number or size of lawsuits, there may be more incentive to pursue free speech-based, off-label marketing.

Apart from financial damages due to litigation, manufacturers may also face negative publicity due to the perception that off-label marketing is circumventing established safety guidelines. Thus far, the *Caronia* and *Amarin* rulings have not produced large amounts of negative publicity, but both popular and scholarly media have commented on the rulings. Large-scale application of free speech-based marketing may lead to increased public commentary, which may or may not be favorable.

Finally, the *Amarin* opinion makes clear that free speech-based, off-label marketing and promotion must be constantly evolving. Truthful and non-misleading is not necessarily a permanent state, and companies must be diligent in their monitoring to ensure that their statements regarding their products uphold this standard. The failure to maintain truthful and non-misleading status would immediately impact the ability of a manufacture to market a product off-label and return full enforcement powers to the FDA.

Conclusions

For now, any company considering expanded off-label marketing and promotion under the *Caronia* and *Amarin* rulings must carefully consider both the opportunities and risks, as well as the potential implementation of regulatory changes that change or solidify the current environment for off-label marketing, and this assessment will be unique for each company. Some, like Amarin and Pacira, will aggressively pursue this new opportunity, but many others will wait for further short term clarifications, such as an appeal of the *Amarin* decision or the issuance of new guidance by the FDA, before deciding their future strategies. Regardless, the introduction of First Amendment rights into the off-label marketing conversation is likely an inflection point that will be discussed for many years as a new baseline is established.

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