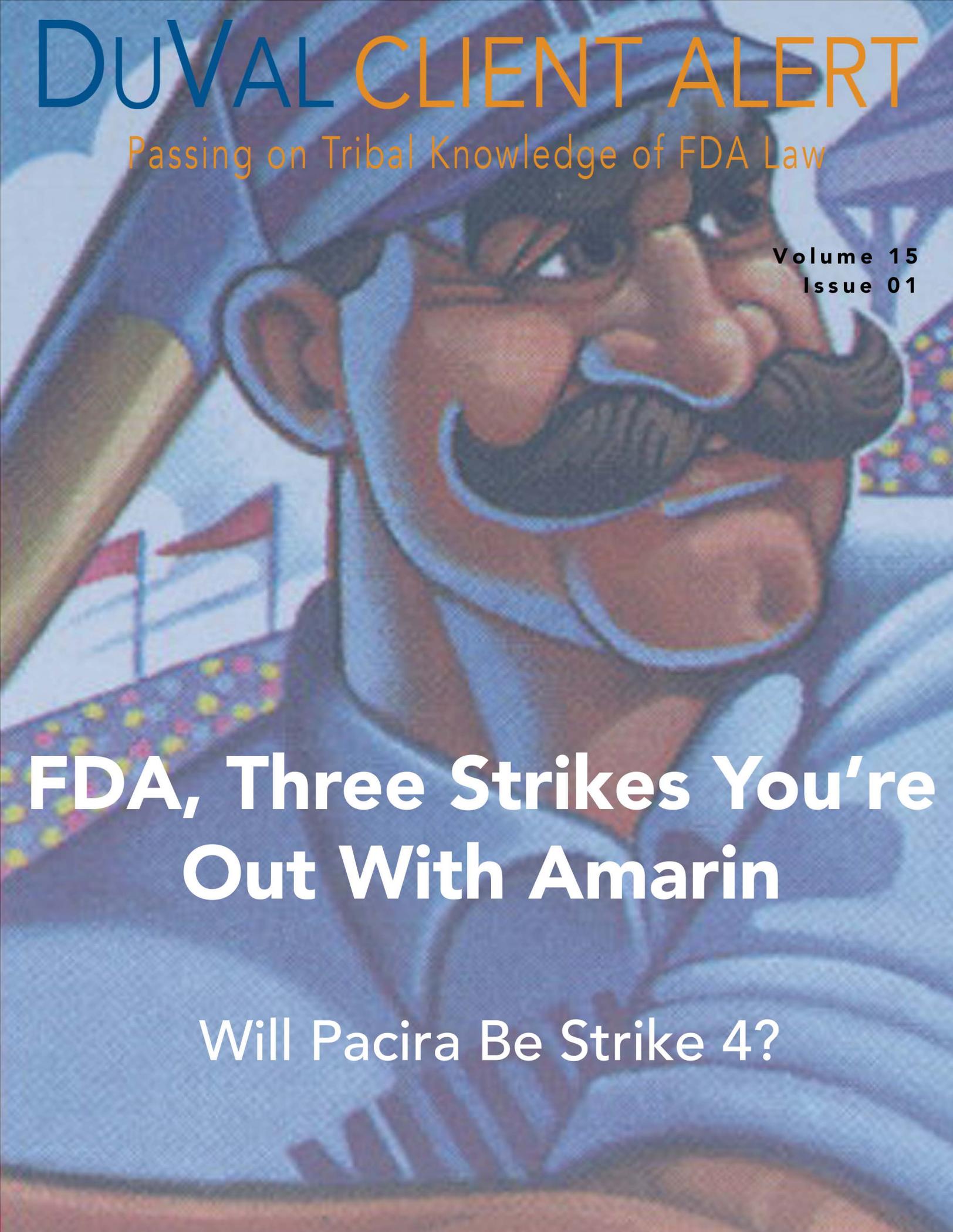


DUVAL CLIENT ALERT



Passing on Tribal Knowledge of FDA Law

Volume 15

Issue 01

FDA, Three Strikes You're Out With Amarin

Will Pacira Be Strike 4?

FDA Loses Another Off-Label Court Decision

Is *Amarin* Three Strikes and You're Out?

(Will Pacira be strike four?)

You remember the story of Mighty Casey (FDA) at bat, let us rewrite the story a bit to fit our story/analysis:

The outlook wasn't brilliant for Mudville (HHS) that day; the government team had never lost, always having it their way. Suppressing speech and pushing industry around; never mind the Constitution, their arrogance would abound. After his predecessors swung blindly at WLF and whiffed at Caronia, the Mighty Casey raised his hand to the government crowd, "Don't worry my friends, when I'm done, industry will be downed."

But the little guy *Amarin* stepped up to the mound, knowing the previous industry pitchers (WLF and Caronia) had kept the ball on the ground—for outs. This was the kind of day that made the Mighty Casey shout. Said Casey, "We are big and imposing and not used to losing because challenging us gets really quite confusing—intentionally so. We rely on calling the shots, even if they are far from apropos."

"We know all the rules and wrote many as well, we don't have to comply with the Constitution unless industry pushes back, don't tell—in court." And so industry found another pitcher, another man who could throw, and he pitched to Casey the great *Amarin* foe.

Casey swung three times with all of his might offering the umpire (court) his best arguments and fabricated fright. But the umpire could see through all of the bluster that Casey had just swung and missed with all the strength he could muster. And so the day belonged to Amarin when the Mighty Casey struck out; and after his three swings, industry got the third out. The First Amendment stands also for off-label promotion, but will Casey accept his inexorable demotion?

EXECUTIVE SUMMARY

Amarin and other cases like it challenge the conventional wisdom (is it acquiescence?) that FDA can regulate off-label speech to the extent it has. These judicial decisions require management to rethink how it wants to approach commercial discussions regarding off-label use/claims about approved/cleared drugs and medical devices. The Amarin case involved a pharmaceutical company that preemptively sued the FDA, arguing it had the right to promote a drug, Vascepa, for an off-label use using language that FDA admitted is truthful and not misleading and therefore protected commercial speech under the 1st Amendment. The judge in the case sided with Amarin, and the case stands for the general proposition that the government must have a compelling governmental interest before it can regulate, stop or interfere with truthful and non-misleading commercial speech regarding off-label uses of an approved product, and that the government must find the least restrictive means to serve a compelling government interest in regulating that speech.

The FDA is under siege and has a bad track record with 1st Amendment cases. We believe today that the holdings in the 1st Amendment cases of Washington Legal Foundation (WLF), Sorrell v. IMS Healthcare, Inc. (IMS), Caronia and Amarin cases trump the statute, regulations and guidance, but FDA has not conceded that fact. These cases have found the government has not used the least restrictive means to regulate protected commercial speech. The Amarin Court specifically rejected the idea that FDA can prosecute a manufacturer for speech that FDA admits is truthful and not

misleading, simply because that use is not approved/cleared by FDA. The Amarin decision reminds us of a famous quote made by Judge Royce Lamberth in one of his Washington Legal Foundation (off-label dissemination) decisions where he matter-of-factly stated the following:

In asserting that any and all scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs are presumptively untruthful or misleading until the FDA has had the opportunity to evaluate them, ***FDA exaggerates its overall place in the universe.*** [Emphasis added in bold and italics].

Notably, the most recent and prominent losses for FDA (*Caronia* and *Amarin*) have been limited to the federal 2nd Circuit Court of Appeals (New York, Connecticut and Vermont). Recently another case has been filed, *Pacira Pharmaceuticals*, which is also placed with a district court in the Second Circuit. We will see how that decision comes out. FDA holds out hope that other federal circuit courts around the country will decide these cases differently than the 2nd Circuit. We don't think they will because these courts are citing the U.S. Supreme Court case of *Sorrell vs. IMS Healthcare, Inc.* and the line of reasoning is similar. This is why many legal commentators think the FDA never appealed the *Caronia* case to the United States Supreme Court, i.e., because FDA likely would have lost in the highest court of the land.

What does this mean for industry? Industry must re-examine its promotional stance with respect to off-label uses (or extra-label claims) about its drug or device and decide whether it can lawfully promote for off-label uses by placing those uses in the proper context with disclosures/disclaimers about the information the manufacturer wishes to share with the medical community. ***Importantly, these decisions go beyond the Washington Legal Foundation (WLF) case which allowed for off-label dissemination under the 1st Amendment. Caronia, Amarin and***

Pacira involve off-label promotion under the 1st Amendment. There has been a real blurring of the lines between dissemination and promotion with these cases. The *IMS*, *Caronia*, *Amarin* and *Pacira* cases are discussed below.

FIRST SOME IMPORTANT BACKGROUND

Before we get to the *Amarin* case, let's briefly talk about the *IMS* and *Caronia* cases which preceded it and laid the foundation for the important 1st Amendment discussion taking place today.

A. The *Sorrell v. IMS case.* In the *Sorrell v. IMS Healthcare, Inc.* (2011) case the United States Supreme Court struck down a Vermont law prohibiting the sale, disclosure, and use of pharmacy records that reveal the prescribing practices of individual doctors for use in the marketing of drugs. This data is frequently used by pharmaceutical companies in targeting physicians for detailing and other marketing activities. Vermont argued that it had enacted the Prescription Confidentiality Law (Vt. Stat. Ann., Tit. 18, § 4631) to prohibit manufacturer use of such data in an attempt to (1) protect medical privacy by reducing the dissemination of physician prescribing information; (2) avoid harassment when detailers visit the physician's office by reducing the detailers' incentive to visit; (3) preserve the integrity of the doctor-patient relationship by assuaging patient fears that their physicians are being unduly influenced by the drug companies; and (4) lower healthcare costs by reducing the amount of brand name drugs prescribed.

The Supreme Court found that § 4631 was ineffective in addressing these goals and impermissibly infringed upon the 1st Amendment free speech rights of those seeking to use the IMS prescribing data for sales purposes. The Supreme Court stated that any regulatory scheme that seeks to infringe upon free commercial speech must be narrowly tailored to avoid burdening the speech.

B. The Caronia case. In December 2012, the United States Court of Appeals for the Second Circuit reversed the conviction of a sales representative for his alleged crime of off-label promotion of a drug. The *United States v. Caronia* case, involved a sales representative, Alfred Caronia, at Orphan Medical, Inc., now known as Jazz Pharmaceutical, who promoted a drug, Xyrem, for intended uses not approved by FDA. This is called “off-label” promotion, and it is a violation, called “misbranding,” under the FD&C Act. The government prosecuted the sales representatives’ conduct as a criminal conspiracy. The drug was approved for narcolepsy, but Mr. Caronia was caught on tape by the government, promoting the drug for fibromyalgia, chronic fatigue, chronic pain among other unapproved uses.

The Court ruled that Mr. Caronia is entitled to 1st Amendment rights which grant him the freedom to promote truthful “lawful” off-label uses of an approved product. The following language from the Court’s opinion illustrates its holding:

Accordingly, even if speech can be used as evidence of a drug's intended use, 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 government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug. [Emphasis added in bold and italics].

NOW THE AMARIN CASE

The preemptive suit. Amarin Pharmaceuticals preemptively filed a suit against FDA claiming FDA's threat of prosecution for allegedly promoting of Amarin's drug Vascepa for an off-label use rendered it misbranded under the Food, Drug & Cosmetic Act. Amarin argued this threat of prosecution had a chilling effect on Amarin's right to commercial speech protected by the 1st Amendment. They drew Judge Paul Engelmayer, U.S. District Court for the Southern District of New York. Amarin sought a declaration from the Court and injunction to prevent the Court from prosecuting the company for truthful, non-misleading speech. Amarin was attempting to disseminate three types of information relating to the use of Vascepa and did not want to communicate with consumers/patients but health care professionals only. First, they wanted to disseminate the results of the company's "ANCHOR" study which FDA and the Advisory Committee had rejected even though FDA agreed to the trial design and the endpoints were met.¹ Second, they wanted to make the statement that "supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease," a claim that EPA and DHA dietary supplements are allowed to make, under FDA's rules. Third, Amarin wanted to distribute reprints of "peer-reviewed scientific publications relevant to

¹ Interestingly the drug, Vascepa, is derivative of fish oil (EPA) and it was approved for a higher dose of the drug to reduce triglyceride levels in patients with severe hypertriglyceridemia. After approval Amarin obtained information that physicians were also using Vascepa to treat patients with "persistently high" triglycerides (lower doses than the approval for "severe") and the Company planned to seek approval for this population. They did a clinical trial (the ANCHOR study) in persistently high patients. FDA had agreed to the trial design and the endpoints were met. Amarin also agreed to conduct a trial (the REDUCE-IT trial) to determine whether Vascepa would be effective in reducing cardiovascular events. FDA agreed to accept Amarin's supplemental NDA (SNDNA) for the persistently high population once REDUCE-IT was 50% enrolled. Amarin met these enrollment obligations. FDA convened an Advisory Panel during which the Agency called into question the clinical validity of the Amarin's trial for the expanded indication. The Committee vote 9 to 2 against granting approval. FDA rescinded its Special Protocol Assessment (an agreement with FDA on a study design) and the new indication was dead in the water. FDA told Amarin that it was not allowed to promote for this indication or the product would be deemed "misbranded" and subject to enforcement.

the potential effect of EPA on the reduction of risk of coronary heart disease.”

In addition, Amarin proposed relevant disclosures contemporaneous with the dissemination to ensure the messages the company was communicating were in the proper context and thus not misleading. Here are the extensive disclosures Amarin proposed:

1. FDA has not approved Vascepa to reduce the risk of coronary heart disease;
2. FDA has not approved Vascepa for the treatment of statin-treated patients with mixed dyslipidemia and high (> 200 mg/dL and < 500 mg/dL) triglyceride levels;
3. The effect of Vascepa on the risk of cardiovascular mortality and morbidity has not been determined;
4. A cardiovascular outcomes study of Vascepa designed to evaluate the efficacy of Vascepa in reducing cardiovascular mortality and morbidity in a high risk patient population on statin therapy is currently underway; and
5. Vascepa may not be eligible for reimbursement under government healthcare programs, such as Medicare or Medicaid, to reduce the risk of coronary heart disease or for treatment of statin-treated patients with mixed dyslipidemia and high (> 200 mg/dL and < 500 mg/dL) triglyceride levels. We encourage you to check that for yourself.

An interesting twist—FDA’s letter to Amarin, an attempt to moot the case.

FDA, probably in an attempt to convince the judge that the case was moot, sent a letter to Amarin during the pendency of the case and filed a copy with the Court. FDA, after all, could not afford to lose yet another landmark 1st Amendment case so it sought to compromise with Amarin on terms acceptable to the Agency. FDA’s letter stated it did not intend to object to Amarin’s proposed communications if made in a truthful, non-misleading, and balanced manner. FDA agreed with Amarin that many of these proposed communications would be consistent with the Agency’s two guidance documents on the dissemination of reprints and responding to unsolicited requests for information. FDA liked the disclosures regarding the regulatory status of the drug and indication, approval limitations, and the status of the REDUCE-IT trial, as needed balancing information that would make these communications acceptable. FDA continued to object to Amarin’s use of the dietary supplement disclosure which it argued was appropriate for dietary supplements, but not prescription drugs due to the lower scientific threshold for dietary supplement claims and the difference in regulatory regimes between supplements and drugs. The judge in questioning at trial struggled with that position. A truthful, not misleading statement on a dietary supplement is still truthful and not misleading when used with a drug of the same or similar ingredient. FDA also asked for certain additional disclosures to which Amarin objected.

The Court found the case was ripe and not mooted by FDA’s letter and the Court went on to fashion a compromise. The Court agreed that Amarin had a right to be concerned with a threat of prosecution and the case was ripe and properly before the Court. Playing King Solomon, the Court split the proverbial baby by granting Amarin’s injunction, but agreeing with FDA to add a disclaimer more to FDA’s liking which referred to the reason why FDA did not approve the “persistently high” indication.

Amarin wanted the following disclaimer:

FDA has not approved Vascepa for the treatment of statin-treated patients with mixed dyslipidemia and high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels. [Emphasis is bold and underlining added].

FDA wanted this disclaimer:

FDA declined to approve this indication because the available evidence does not establish that reducing triglycerides with a drug reduces the risk of cardiovascular events among patients already treated with statins. [Emphasis is bold and underlining added].

The disclaimer the judge provided is as follows:

Vascepa is not FDA-approved for the treatment of statin-treated patients with mixed dyslipidemia and high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels due to current uncertainty regarding the benefit, if any, of drug-induced changes in lipid/lipoprotein parameters beyond statin lowered low-density lipoprotein cholesterol on cardiovascular risk among statin-treated patients with residually high triglycerides. No prospective study has been conducted to test and support what, if any, benefit exists.

The Court stated the disclaimer was, today, truthful and not misleading and the parties were free to “pursue further refinements” in the future.

FDA’s position was simple. Even if the information being shared is truthful and not misleading, any promotion for an unapproved use renders the drug “misbranded” under the Food, Drug & Cosmetic Act and subject to prosecution. FDA took that position to preserve the drug and device approval/clearance scheme in place. FDA feels any promotion of off-label uses undermines, and is an end-run around, their approval/clearance regime. The Court understood and sympathized with FDA’s concern, but disagreed concluding: “...in the end, however, if the speech at issue is found truthful and non-misleading, under *Caronia*, it may not serve as the

basis for a misbranding action.” The FDA continues to lose these 1st Amendment cases.

CONTINUED PRESSURE ON FDA WITH THE PACIRA CASE

Recently, on September 8, 2015, another pharmaceutical company, Pacira Pharmaceuticals, filed suit against the FDA on grounds similar to that in *Caronia* and *Amarin*. We will follow this case closely, but it suggests FDA continues to be under siege in the 1st Amendment arena. Pacira filed its case in the United States District Court for the Southern District of New York—still in the Second Circuit. In this case FDA issued Pacira a Warning Letter related to certain promotional materials alleging off-label promotion of the drug EXPAREL. At FDA’s insistence Pacira took steps to address FDA’s immediate concerns so it could minimize disruption to its business. But Pacira also presented FDA with arguments and evidence in its defense and repeatedly requested follow-up meetings with the Agency to discuss a settlement. FDA continued to deny requests for a meeting and did not provide any further rationale for its actions. The Agency then surprisingly issued a Close Out Letter indicating the topics outlined in the Warning Letter were closed. Pacira then brought suit alleging the following:

1. The unilateral attempt by the FDA to narrow the approved broad indication for EXPAREL without observing the procedure required by law for modifying a drug’s label violates the Administrative Procedure Act (APA);
2. The FDA regulations as applied to Pacira are vague, deprive the company of fair notice of what is prohibited, and operate as a retroactive, *ex post facto* penalty, all in violation of the Due Process Clause of the 5th Amendment; and
3. FDA’s actions attempting to forbid Pacira from sharing truthful and non-misleading information regarding both the efficacy and the administration of EXPAREL violate the Company’s 1st Amendment right to engage in truthful and non-misleading speech

Pacira is seeking declaratory relief as well as a preliminary and/or permanent injunction preventing the FDA and other defendants from taking any action to violate the Company's aforementioned rights. The Company stated in its motion for an injunction that it will be supported by several key declarants, notably including Larry Goldkind, M.D., a former Deputy Director of the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products in the FDA's Center for Drug Evaluation and Research (CDER), as well as Dr. Lee-Jen Wei, Professor of Biostatistics at the Harvard T.H. Chan School of Public Health.

CONCLUSION

FDA has consistently lost cases addressing 1st Amendment issues and the *Caronia* and *Amarin* cases suggest FDA cannot suppress off-label promotion that is truthful, not misleading and fairly balanced. There are at least four prominent 1st Amendment cases that apply to the promotion of claims or exchange of information that may be off-label (*Washington Legal Foundation*, *Sorrell vs IMS*, *Caronia* and *Amarin*), all of which stand for the general proposition that the government must have a compelling governmental interest before it can regulate, stop or interfere with truthful and non-misleading commercial speech and the government must find the least restrictive means to serve a compelling government interest in regulating that speech. These cases have found the government had not used the least restrictive means to regulate protected commercial speech. The *Amarin* Court specifically rejected the idea that FDA can engage in enforcement action against a manufacturer for speech that FDA admits is truthful and non-misleading, simply because that use is not approved/cleared by FDA.

DuVal & Associates
Drug, Device and Food Law

DuVal & Associates is a boutique law firm located in Minneapolis, Minnesota that specializes in FDA regulations for products at all stages of the product life

cycle. Our clientele includes companies that market and manufacture medical devices, pharmaceuticals, biologics, nutritional supplements and foods. Our clients range in size from Global Fortune 500 companies to small start-ups. As one of the only dedicated FDA regulatory law firms in the United States, our mission and absolute focus is providing our clients appropriately aggressive, yet compliant, guidance on any FDA related matter. We pride ourselves not only on our collective legal and business acumen, but also on being responsive to our client's needs and efficient with their resources. DuVal & Associates understands the corporate interaction between departments like regulatory affairs, marketing, sales, legal, quality, and clinical, etc. As former industry managers in the drug and device spaces, we have been in your shoes. Our firm has extensive experience with government bodies. We understand what it takes to develop and commercialize a product and bring it successfully to the market and manage its life cycle. Impractical or bad advice can result in delays or not allow for optimal results; while practical, timely advice can help companies succeed.

CALL ON US FOR ASSISTANCE WITH YOUR REGULATORY NEEDS

For more information, visit our website at www.duvalfdalaw.com or call Mark DuVal today for a consult at 612.338.7170 x102.

DISCLAIMER: Material provided in Client Alerts belongs to DuVal & Associates and is intended for informational purposes only and does not constitute legal advice.

© DuVal & Associates, P.A. 2021
