Update Magazine reprinted with permission from FDLI

UPDATE

Food and Drug Law, Regulation and Education

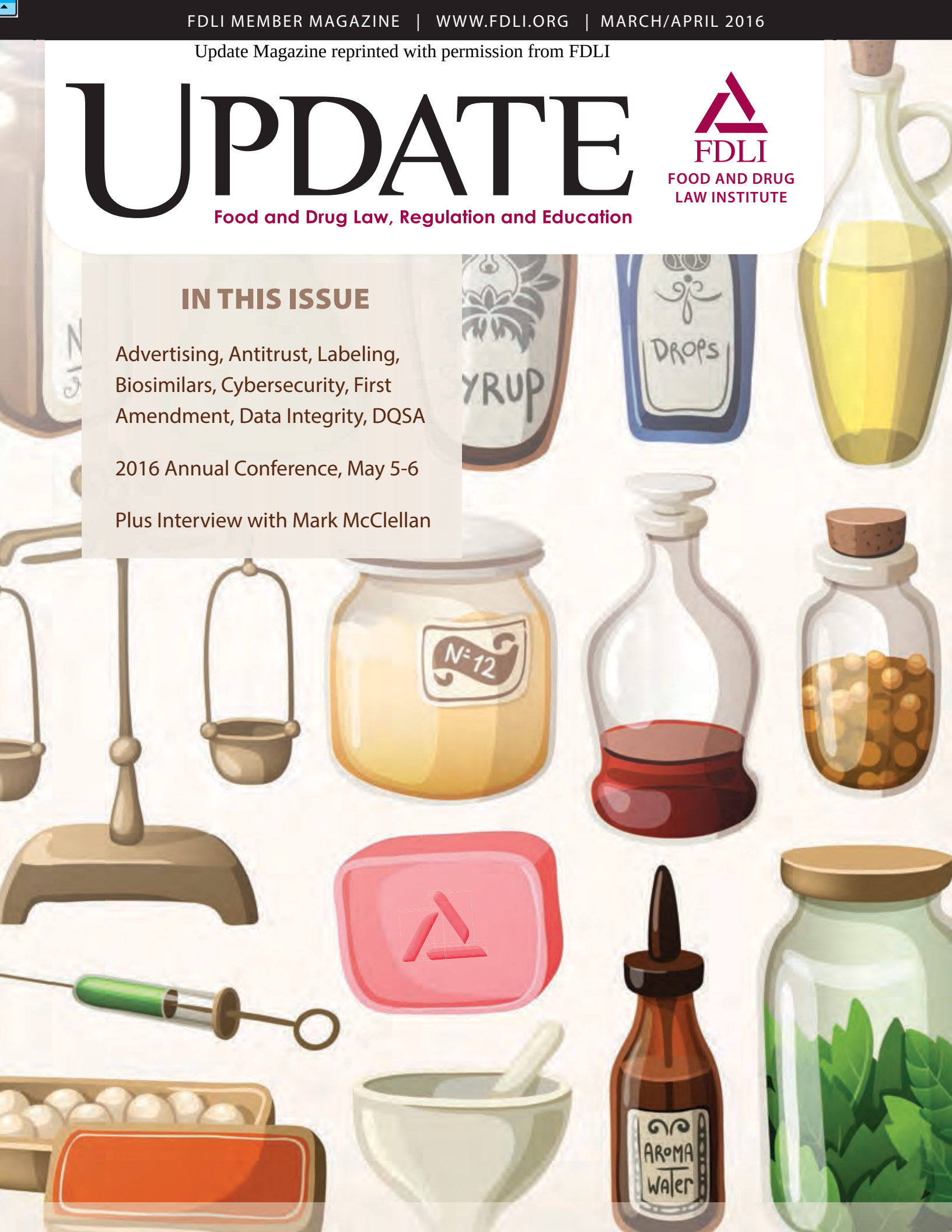
FDLI
FOOD AND DRUG LAW INSTITUTE

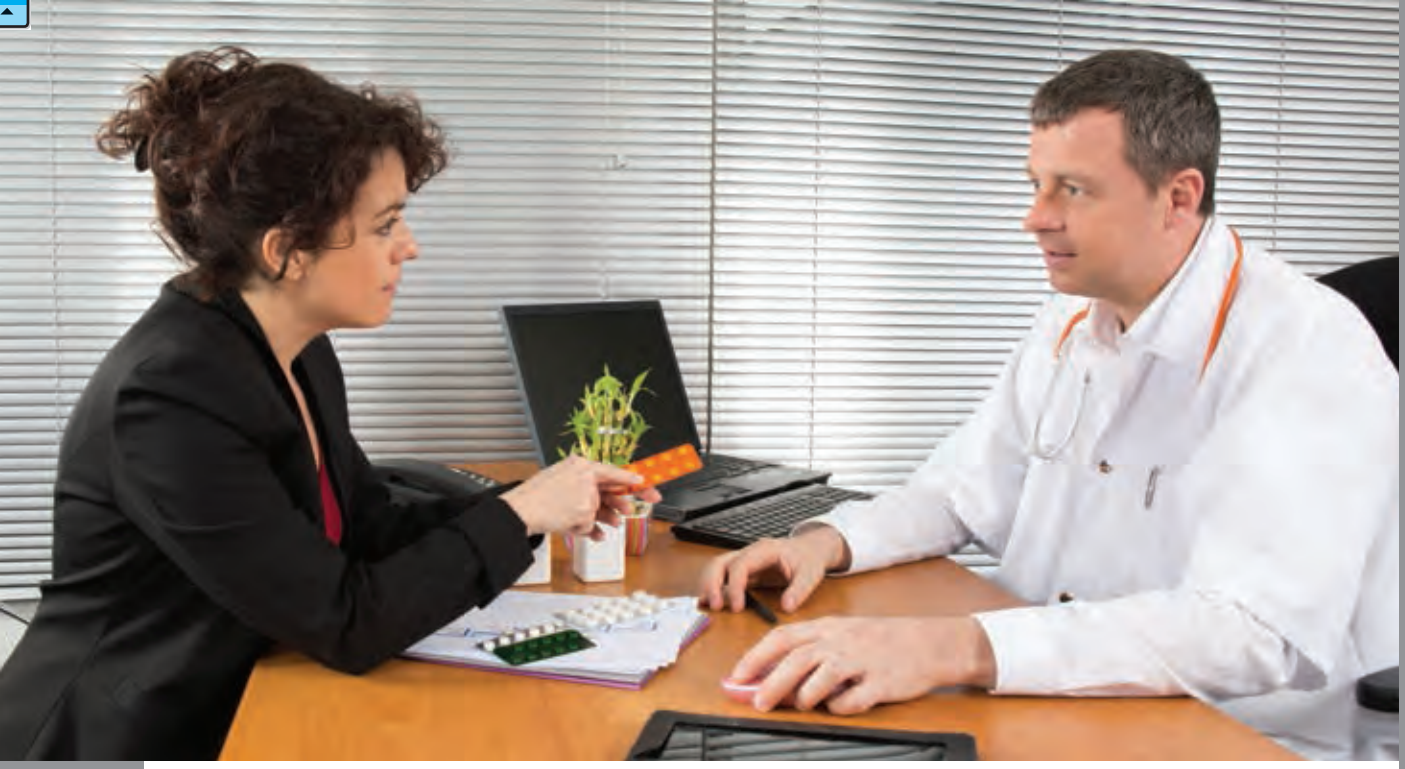
IN THIS ISSUE

Advertising, Antitrust, Labeling, Biosimilars, Cybersecurity, First Amendment, Data Integrity, DQSA

2016 Annual Conference, May 5-6

Plus Interview with Mark McClellan





Does FDA's Per Se Prohibition Against Off-Label Promotion Have a Future?

The Short Answer: No

By Jeffrey K. Shapiro

The Department of Justice's (DOJ) recent criminal prosecution of Vascular Solutions, Inc. (VSI) ended in a spectacular loss for the government. The defense rested without calling even a single witness, but the jury unanimously acquitted VSI and its chief executive officer of, among other things, misbranding products due to "off-label" promotion.

VSI's Vari-Lase products were 510(k)-cleared by FDA for the ablation of superficial veins, but VSI allegedly promoted them outside the scope of clearance for use in perforator veins, which connect the superficial vein system to the deep vein system. Although this off-label promotion allegedly misbranded the product, the trial judge instructed the jury that such promotion is not per se illegal:

> Doctors may use medical devices that have been approved or cleared for one use for a different use that has not been cleared or approved by the FDA. This is often referred to as unapproved use or off-label use. This is not illegal. It is . . . not a crime for a device company or its representative to give doctors wholly truthful and non-misleading information about the unapproved use of a device. If you find that VSI's promotional speech to doctors was solely truthful and not misleading, then you must find the Defendants not guilty of the misbranding offense.[1]

This jury instruction contradicts countless FDA Warning Letters sent to drug and device makers for at least 20 years. These Warning Letters are premised on the legal theory that if FDA clears or approves a device or drug for use X, it is unlawful to promote it for new use Y, even if such

Jeffrey K. Shapiro is a Director in the law firm of Hyman, Phelps & McNamara in Washington, DC (jshapiro@hpm.com). The views expressed herein are his own and are not necessarily shared by the firm or any of its clients.

promotion involves the dissemination of information that is entirely truthful and not misleading.

The jury instruction also contradicts numerous criminal and civil enforcement actions brought by the Department of Justice (DOJ). For example, in the GlaxoSmithKline case, DOJ announced a $1 billion criminal plea agreement with this description of the violation: "After the FDA approves the product as safe and effective for a specified use, a company's promotional activities must be limited to the intended uses that FDA approved. In fact, promotion by the manufacturer for other uses—known as 'off-label uses'—renders the product 'misbranded.'"[2] This statement of the law is flatly contradicted by the Vascular Solutions jury instruction.

Nor is the Vascular Solutions case an outlier. It is merely the latest courtroom defeat in FDA's long war on off-label promotion. FDA insists that it is unlawful to disseminate truthful and not misleading information about unapproved uses for promotional purposes. Yet, federal court decisions make it clear that the First Amendment affords significant protection to such speech.[3]

This controversy originates in FDA's longstanding response to a regulatory paradox. The paradox is that, once FDA approves a device or drug for marketing for any use, physicians lawfully may use it for all other possible uses.[4] Because many drugs and devices have more than one possible use, off-label use is often widespread. Indeed, all agree that off-label uses offer important benefits to patients and sometimes even become the standard of care.

FDA's position is that this legal regime has a negative consequence. It means that FDA's gatekeeper role against unsafe or ineffective devices and drugs is fully effective only for the first marketing approval. Until that point, the sponsoring firm has the burden of proving safety and efficacy (or substantial equivalence) to FDA's satisfaction, and FDA has significant leverage in dictating whether the product may be marketed and how it will be labeled.[5] However, the moment a device or drug lawfully enters commerce for any one use, FDA loses most of this leverage with respect to other uses.

Among other things, the burden is on FDA to prove that claims about the safety or efficacy of the off-label use are false or misleading.[6] The burden would shift back to the sponsor if it were to request a modification of the FDA-approved labeling to add the new use. But if sales are sufficiently robust, a sponsor may have little financial incentive to do so. In such cases, the new use permanently escapes the kind of control that FDA has over the use that it initially approved.

FDA has sought to reassert control by preventing sponsors from promoting off-label uses of their products. Because the Federal Food, Drug, and Cosmetic Act (FFDCA) does not expressly prohibit off-label promotion, FDA developed a legal theory (with supporting regulations) that such promotion creates a new "intended use" requiring separate approval under the FFDCA.[7] Until such approval is granted, according to FDA, the off-label promotion adulterates and/or misbrands the product.[8] The statutory details differ somewhat for devices and drugs, but the bottom line is the same: FDA's position has been that the manufacturer's ability to promote off-label is legally constricted. This restriction helps prevent manufacturers from driving sales based upon off-label use and may at least partially incentivize them to return to FDA to seek revised labeling for the new use.

The federal courts generally have understood that FDA has a substantial interest in premarket review of new uses for approved products. The problem they see with FDA's approach is that physicians may lawfully use drugs and devices off-label. Therefore, FDA is effectively suppressing the free flow of truthful and non-misleading speech to highly trained experts engaged in the lawful practice of medicine. And it does so by targeting a class of disfavored speakers while other speakers may provide exactly the same information without sanction. Under the First Amendment, such content and speaker-based restrictions can be accepted only if, among other things, they are narrowly drawn to directly advance FDA's interest in obtaining premarket review of all uses.

FDA has had little recent success persuading the courts that its enforcement approach satisfies this requirement. Perhaps the most important decision thus far is the Second Circuit's decision in *United States v. Caronia*,[9] in which the court overturned the conviction of a pharmaceutical sales representative who had promoted off-label uses of a drug. The court "decline[d] the government's invitation to construe the FFDCA's misbranding provisions to criminalize the simple promotion of a drug's off-label use by pharmaceutical manufacturers and their representatives because such a construction—and a conviction obtained under the government's application of the FFDCA—would

run afoul of the First Amendment."[10] Perhaps the Supreme Court would disagree. We will not find out in the *Caronia* case, because DOJ did not seek Supreme Court review. That tactical decision speaks volumes about DOJ's assessment of the probable outcome.

Even without Supreme Court review of *Caronia*, the courts have made it clear that truthful and non-misleading off-label promotion by device and drug companies is protected by the First Amendment. Accordingly, FDA very recently entered into a litigation settlement in *Amarin Pharma, Inc. v. FDA*[11] that expressly permits continued truthful and non-misleading off-label promotion without sanction. Likewise, DOJ in the *Vascular Solutions* case itself proposed the sentence instructing the jury that disseminating truthful and non-misleading information about an unapproved use is not a crime.[12]

At the same time, zombielike, FDA/DOJ continue to pursue truthful and non-misleading off-label promotion as if it were per se a crime. They continue to issue Warning Letters and bring prosecutions based upon this premise. Those like Vascular Solutions who vigorously challenge the government in court win or extract favorable settlements with increasing frequency, as has happened recently in *Pacira Pharms., Inc. v. FDA*[13] and *Amarin*. But not everyone has the resources or the will to fight the government to the bitter end. This two-tier system of law is unfair and unjust.

After *Caronia*, DOJ has taken to emphasizing that it is not prosecuting speech. Rather, DOJ says it is relying upon the speech as evidence of intent to create a new intended use. DOJ insists the unlawful act is not the speech but the conduct of distributing adulterated or misbranded product for a new intended use. This proposed distinction has no practical relevance and should be, and has been, rejected. If the distinction were accepted, device and drug companies could only comply by refraining from lawful speech about off-label use in order to avoid adulterating or misbranding product. The chilling effect would continue to violate their First Amendment rights and those of physicians who wish to receive information.

Absent an unlikely U-turn at the Supreme Court, the federal courts likely will continue to find that FDA's prohibition against truthful and non-misleading off-label promotion is inconsistent with the First Amendment. However, FDA's Warning Letters and DOJ enforcement actions could continue for years before enough case law accumulates to force real change, with some companies and individuals choosing to settle rather than risk overwhelming punishment.

There is no reason to believe that this slow motion face-off between FDA/DOJ and the courts will not continue to allow significant infringement of First Amendment rights. The Executive Branch has an independent obligation to obey the Constitution and not to seek to evade it on a case-by-case basis. One questions whether the right thing to do would be for FDA and DOJ to declare an immediate moratorium on this type of enforcement action while they develop an enforcement approach that does not infringe First Amendment rights.

There would still remain the requirement that device and drug manufacturers label and advertise their products in a manner that is not false or misleading.[14] The courts have expressly acknowledged that this type of enforcement does not infringe First Amendment rights. As the *Amarin* court emphasized in a ruling, this issue is nontrivial:

> The Court has held that Amarin's proposed communications, as modified herein, are presently truthful and non-misleading. But the dynamic nature of science and medicine is that knowledge is ever-advancing. A statement that is fair and balanced today may become incomplete or otherwise misleading in the future as new studies are done and new data is acquired. The Court's approval today of these communications is based on the present record. Amarin bears the responsibility, going forward, of assuring that its communications to doctors regarding off-label use of Vascepa remain truthful and non-misleading.[15]

As already noted, FDA's focus on off-label promotion may be intended to shift back to the manufacturer the burden of establishing whether claims of safety and effectiveness are truthful and not misleading. However, even in a postmarket context, there is sure to be low hanging enforcement fruit, e.g., intentionally false or misleading promotional statements. At the same time, FDA often poses more difficult and subtle challenges to the adequacy of data offered during premarket review. Should this same level of stringency be applied in a postmarket context? Or should the threshold be lower?

Another question is: how important is it to have FDA conduct premarket review of every single use for a device or drug? Should steps be taken to incentivize manufacturers to

undertake premarket review of new uses? Or is it sufficient to primarily rely, as is generally done now, upon physicians and researchers to ensure the safety and effectiveness of uses not reviewed by FDA? There is a lot of work to be done in sorting out these and other related issues, but it cannot fairly begin until FDA and the DOJ let go of the current system.

To sum up: The status quo has little to commend it. It does not respect the First Amendment rights of device and drug makers or physicians. It arbitrarily and capriciously exposes selected manufacturers and their executives to significant legal jeopardy for conduct that is not per se unlawful. And, most importantly, it does not provide real protection to patients, who indisputably benefit from many off-label uses. If healthcare providers cannot obtain truthful and timely information about these uses, these patients will suffer. It is long past the time to resolve this issue in a way that better meets the health care needs of the nation.

1. Final Jury Instructions at 12, United States v. Vascular Solutions, Inc., 5:14-CR-00926 (W.D. Tex. Feb. 25, 2016)
2. DOJ, Press Release, GlaxoSmithKline to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data (July 2, 2012). In addition to the $1 billion criminal plea agreement, the company settled civil liabilities under the False Claims Act and state claims for $2 billion.
3. E.g., Washington Legal Foundation v. Friedman, 13 F. Supp. 2d 51, 74–75 (D.D.C. 1998), order vacated as moot sub nom. Washington Legal Foundation v. Henney, 202 F. 3d 331, 336–37 (D.C. Cir. 2000); U.S. v. Caronia, 703 F. 3d 149 (2d Cir. 2012); Amarin Pharma, Inc. v. FDA, 119 F. Supp. 3d 196, 236 (S.D.N.Y. 2015). Cf. Thompson v. Western States Medical Center, 535 U.S. 357 (2002); Sorrell v. IMS Health, Inc., 131 S. Ct. 2653 (2011).
4. E.g., Federal Food, Drug, and Cosmetic Act § 1006.
5. E.g., id., §§ 505, 510(k), 514; 21 C.F.R. Parts 314, 807, 814.
6. FFDCA § 502(a).
7. Id. §§ 201(g), 201(h); 21 C.F.R. §§ 201.128, 801.4.
8. FFDCA §§ 501(f), 502(f), 502(o).
9. 703 F. 3d 149 (2d Cir. 2012).
10. Id. at 161.
11. Amarin Pharma, Inc. v. FDA, No. 15-3588 (S.D.N.Y. Mar. 8, 2016).
12. The government's proposed jury instructions were submitted on January 7, 2016.
13. Pacira Pharms., Inc. v. FDA, No. 15-7055 (S.D.N.Y. Dec. 14, 2015).
14. In the case of most devices, it would be the Federal Trade Commission that would need to pursue false or misleading advertising.
15. Amarin Pharma, Inc. v. FDA, 119 F. Supp. 3d 196, 236 (S.D.N.Y. 2015).