

Recent Settlements Suggest Off-Label Cases Aren't Extinct

By **John Bentivoglio, Jennifer Bragg, Avia Dunn and Elizabeth Berry**

Law360, New York (August 30, 2017, 12:30 PM EDT) -- The courts in recent years have handed the U.S. Department of Justice and the U.S. Food and Drug Administration a string of defeats in cases involving government efforts to prosecute companies and individuals for so-called off-label promotion. While many hoped that these rulings would usher in an era where companies could safely engage in truthful and nonmisleading discussions without fear of enforcement, a review of recent government activity suggests that the government remains committed to aggressively pursuing off-label cases, even if limited to using civil remedies.



John Bentivoglio

The takeaway from recent settlements is that promotional activities continue to be a significant compliance risk for life sciences companies. Companies should be particularly mindful of promotional messages targeted toward vulnerable populations and of characterizing risk and adverse event data.

Courts Restrict Government Enforcement Theories Premised on "Off-Label" Promotion

Several key judicial rulings since 2012 have restricted government attempts to criminalize or prohibit the off-label promotion of drugs and devices. In *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012), the Second Circuit held that the Federal Food, Drug and Cosmetic Act (FDCA) neither prohibits nor criminalizes truthful, nonmisleading speech that may constitute off-label promotion of prescription drugs approved by the FDA. The DOJ and FDA declined to seek further judicial review through either an en banc hearing or writ of certiorari to the U.S. Supreme Court.



Jennifer Bragg

Notwithstanding the government's efforts to minimize the precedential impact of its loss in *Caronia*, the U.S. District Court for the Southern District of New York granted a preliminary injunction in favor of Amarin Pharma Inc. and several physician plaintiffs. The injunction permitted affirmative off-label promotional activities in connection with the company's already approved drug. See *Amarin Pharma Inc. v. FDA*, 119 F. Supp. 3d 196, 226 (S.D.N.Y. 2015). The court in *Amarin* rejected the FDA's contention that *Caronia* was limited to the facts of the case, stating that the FDA may not bring an action based on "truthful promotional speech alone." *Id.* at 224. Although the "First Amendment does not protect false or misleading commercial speech," when the "speech at issue consists of truthful and non-misleading speech promoting the off-label use of an FDA-approved drug, such speech ... *cannot* be the act upon which an action for misbranding is based." *Id.* at

226, 228 (emphasis in original).

The government's defeats continued in 2016, when a federal district court in Texas reaffirmed the constitutional protection afforded to truthful and nonmisleading, off-label speech. In *United States v. Vascular Solutions Inc.*, the company and its CEO, Howard Root, were charged with selling a medical device without FDA approval and conspiring to defraud the United States by concealing this allegedly illegal activity. No. 5:14-CR-00926-RCL (W.D. Tex. Feb. 26, 2016), ECF No. 1. At trial, the court gave a jury instruction stating: "It is ... not a crime for a ... company or its representatives to give doctors wholly truthful and non-misleading information about the unapproved use of [its FDA-regulated product]." Final Jury Instructions at 12, *Vascular Solutions*, No. 5:14-CR-00926-RCL, ECF 282. The jury acquitted both defendants.

Skepticism by the courts of the government's off-label promotion theories has also extended beyond the FDCA's criminal misbranding framework to civil False Claims Act claims. In a recent opinion, the Second Circuit, in dicta, questioned whether off-label allegations could even support an implied certification theory of FCA liability, given the presumed naivety of the patient and the independent, intervening actions of the physician. [1] *United States ex rel. Polansky v. Pfizer*, 822 F.3d 613, 619-20 (2d Cir. 2016). While the Polansky opinion leaves readers with an obtuse warning that an off-label FCA case might survive dismissal where "it would be obvious to anyone that the use promoted is one that is not approved," the opinion also notes the "important distinction between marketing a drug for a purpose obviously not contemplated by the label (such as, with Lipitor, 'to promote hair growth or cure cancer') and marketing a drug for its FDA-approved purpose to a patient population that is neither specified nor excluded in the label." *Id.* at 620.

DOJ Has Resorted to FCA Cases Supported by Generalized Allegations of False and Misleading Conduct

In the wake of these legal setbacks, it would be easy to believe that the government would simply move on and focus its efforts on building cases premised on other legal theories. This has not been the case. Although the government has shifted its focus to cases involving allegations of false and misleading promotional claims or incorporating off-label promotion allegations into a larger scheme of promotional misconduct (e.g., kickbacks), [2] it has continued to aggressively pursue so-called off-label cases. In the past 19 months, the DOJ and state attorneys general have recovered more than \$716.5 million in four settlements based, at least in part, on improper promotional claims.

A former Genentech employee filed a qui tam lawsuit against the company alleging that, between January 2006 and December 2011, Genentech made misleading representations to health care providers about the effectiveness of the drug Tarceva to treat non-small cell lung cancer (NSCL) across multiple patient populations. The company allegedly knew there was "little evidence" showing the drug could treat NSCL unless the patient had never smoked or had a mutation in their epidermal growth factor reception, and yet represented otherwise. [3] As with most civil settlements, the underlying complaint contained a host of additional allegations not directly reflected in the covered conduct, including allegations that Genentech misrepresented trial data, used visual aids that promoted Tarceva to treat the entire NSCL population and discouraged physicians from testing for the mutation for which Tarceva was demonstrated effective to treat. [4] In June 2016, Genentech and co-defendant OSI Pharmaceuticals LLC (both without admitting liability) reached a civil FCA settlement with the federal and state governments for \$67 million.

Various Shire subsidiaries recently settled allegations that the companies "market[ed] Dermagraft® for uses outside the FDA-approved indication (i.e., 'off-label' uses)." [5] The settlement papers, however, focus primarily on alleged kickbacks the companies paid to physicians, with only passing reference to off-label promotion. In at least one of the underlying complaints, the relators asserted that Shire promoted Dermagraft® — a skin

substitute for diabetic ulcers — off-label to treat venous leg ulcers. The company denied liability, and entered into a global resolution under the civil FCA with federal and state governments in January 2017 for \$350 million.

In December 2016, Bristol-Myers Squibb (BMS) resolved a multistate consumer protection investigation involving claims that the company improperly marketed the antipsychotic drug Abilify. State prosecutors alleged that the company promoted the drug for use in unapproved pediatric and geriatric patient populations by focusing its promotional messages on specific symptoms, instead of FDA-approved indications. Additionally, BMS allegedly misrepresented the findings of scientific studies on the drug and the risks associated with certain side effects.[6] Although BMS denied all allegations, the New York consent decree not only prohibits BMS from making false or misleading claims, it prohibits BMS from promoting atypical antipsychotics for any off-label purpose.[7] The consent decree further requires BMS to disseminate medical information pursuant to multiple controls, including in accordance with FDA guidances, and monitor incentive compensation, call plans and sample distribution to ensure its atypical antipsychotic drugs are promoted only for FDA-approved uses.[8] BMS also is required to comply with certain restrictions and disclosure requirements for medical education grants, speaker payments and clinical trial data.[9] Several state attorneys general released statements criticizing BMS's actions, claiming that BMS manipulated "advertising to promote ... products at the expense of patients." [10] BMS paid \$19.5 million to 42 states and Washington, D.C.[11]

The most recent settlement involving off-label claims resolved allegations brought by a former Celgene sales manager who alleged that the company marketed two cancer drugs — Thalomid and Revlimid — for unapproved uses. According to the settlement agreement, Celgene promoted Thalomid to treat multiple forms of cancer prior to the drug receiving its first FDA-approved cancer indication, and promoted both Thalomid and Revlimid for a broader range of cancers than approved by the FDA.[12] While the settlement agreement lists off-label promotion under the covered conduct, the section separately covers alleged "false and misleading" statements Celgene made about the drugs, including by concealing or minimizing adverse events.[13] The underlying complaint, likewise, describes various off-label promotion schemes, such as use of visual aids on unapproved uses and dissemination of flawed studies. Celgene also faced allegations that the company made or caused false and misleading statements by improperly influencing the content of published medical literature, provided kickbacks to physicians, and manipulated diagnosis codes.[14] The company denied any wrongdoing, and settled with its former employee for \$280 million in July 2017.[15]

The DOJ and state attorneys general appear particularly focused on promotional claims that they believe minimize or ignore risk information or adversely impact vulnerable patient populations. Companies may face scrutiny for allegations that they misrepresented scientific studies (see BMS and Genentech), minimized risk (see BMS and Celgene), or failed to warn patients of harm (see BMS and Celgene). In addition, three of the four settlements involved particularly vulnerable patient populations: children (BMS), the elderly (BMS) and cancer patients (Celgene and Genentech). Government officials have also heavily criticized actions that they believe compromised patient health. For example, in Celgene — a case in which the government declined to intervene — federal officials released a statement remarking that the aggressive marketing of drugs affects doctors' ability to prescribe drugs for "effective treatment." [16] Notably, there are no specific references to any of the alleged aggressive conduct in the press release, and the DOJ offered no explanation for how it missed such aggressive practices when it declined to intervene in the underlying case.

The Shifting Legal Landscape Has Significant Consequences for DOJ and Life Sciences Companies Alike

It is important to note that none of these recent settlements involved a criminal

component, and none involved a violation of the FDCA. This seems to allow the DOJ to continue to leverage settlements for promotional activities, without risking another legal setback based on a First Amendment challenge to its criminal off-label promotion theories. Such a prosecution strategy also provides the DOJ with the advantage of a lower burden of proof and the ability to rebuild a post-Caronia arsenal of settlements based on flimsy allegations. Further, as seen in the two resolutions that yielded the highest settlement dollars, incorporating off-label promotion claims into a larger scheme of promotional misconduct (e.g., kickbacks), provides the DOJ significant negotiating leverage.

The recent judicial setbacks, however, appear to have tempered the DOJ's approach, which we believe signals an impression within the DOJ that the bar for criminal prosecutions under the FDCA is — and should be — relatively high, particularly considering that it is not at all clear that the current Supreme Court would uphold a straight Park doctrine prosecution, even for a misdemeanor. However, the cases challenging DOJ and FDA actions are still relatively new, and it remains to be determined whether the DOJ will be emboldened by recent FDA guidances that attempt to reaffirm the FDA's ability to regulate off-label communications.[17] In any event, the judicial setbacks should signal to the DOJ that it should go back to basic principles of criminal law and reserve prosecutions under the FDCA for knowing and willful violations of reasonably clear laws or regulations, and reserve its scarce resources to those cases involving an established (not just theoretical) risk of patient harm.

Implications for Pharmaceutical and Device Makers

The takeaway from these settlements is that federal and state enforcement efforts directed at false and misleading promotional practices are here to stay, even if they end up with a civil rather than criminal resolution. Thus, promotional activities continue to present a significant compliance risk for pharmaceutical and device makers. While companies can more comfortably provide truthful information about off-label uses of their products in well-controlled contexts (e.g., distribution of peer-reviewed reprints directly to physicians with appropriate warnings and risk information), companies should continue to invest resources in compliance controls at headquarters and in the field to ensure promotional messaging is truthful and to identify promptly and address instances of improper promotional activity. Recent corporate integrity agreements provide useful guideposts for controls around areas such as promotional review, interactions with organizations involved in payment or coverage decisions, and headquarter and field-based monitoring,

John T. Bentivoglio and Jennifer L. Bragg are partners, Avia M. Dunn is counsel, and Elizabeth L. Berry is an associate at Skadden Arps Slate Meagher & Flom LLP in Washington, D.C. Bentivoglio previously served as associate deputy attorney general and special counsel for health care fraud at the DOJ. Bragg previously served in the FDA's Office of Chief Counsel as associate chief counsel for enforcement.

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[1] Although the Second Circuit noted, also in dicta, that Caronia left open the possibility that promotional speech could be used as evidence of off-label intended use, it did not address whether truthful, non-misleading promotional speech may constitutionally form the sole basis for a criminal misbranding charge.

[2] See Memorandum from Skadden Arps Slate Meagher & Flom LLP, *The Future of Government Regulation, Enforcement of Off-Label Promotion* (Sept. 28, 2015),

https://files.skadden.com/sites%2Fdefault%2Ffiles%2Fpublications%2FThe_Future_of_Government_Regulation_Enforcement_of_Off_Label_Promotion.pdf.

[3] Genentech Settlement, ¶ E.

[4] See, e.g. Second Am. False Claims Act Compl. ¶¶ 66, 70, 81, 83, 84.

[5] Shire Settlement, ¶ C.

[6] Complaint ¶¶ 14, 15, New York v. Bristol-Myers Squibb Co., No. 452407 (N.Y. Sup. Ct. 2016), ECF No. 1.

[7] Consent Order and Judgment ¶ I.E, Bristol-Myers Squibb, No. 452407, ECF No. 10.

[8] Id. §§ I.J, II, V.

[9] Id. §§ III, IV, IV.

[10] See Press Release, N.Y. State Office of the Attorney Gen., A.G. Schneiderman Announces \$19.5 Million Multi-State Agreement With Bristol-Myers Squibb To End Deceptive Advertising Practices and Off-Label Promotion of Drug Used to Treat Schizophrenia (Dec. 8, 2016), <https://ag.ny.gov/press-release/ag-schneiderman-announces-195-million-multi-state-agreement-bristol-myers-squibb-end>. The Texas and Massachusetts Attorneys General also released statements condemning BMS's actions, taken at the expense of patients' health.

[11] In September 2007, BMS entered into a \$515 million FCA settlement with DOJ to resolve similar allegations related to the company's promotion of Abilify.

[12] Celgene Settlement ¶ F(2).

[13] Compare Celgene Settlement ¶ F(1) with ¶ F(2).

[14] See generally Celgene Settlement ¶ F.

[15] See Press Release 17-141, U.S. Department. of Justice, USAO-C.D. Cal., Celgene Agrees to Pay \$280 Million to Resolve Fraud Allegations Related to Promotion of Cancer Drugs for Uses Not Approved by FDA (July 24, 2017), <https://www.justice.gov/usao-cdca/pr/celgene-agrees-pay-280-million-resolve-fraud-allegations-related-promotion-cancer-drugs>.

[16] See id. ("Patients deserve to know their doctors are prescribing drugs that are likely to provide effective treatment, rather than drugs marketed aggressively by pharmaceutical companies."); see also Press Release 16-653, U.S. Department. of Justice, Office of Pub. Affairs, Pharmaceutical Companies to Pay \$67 Million to Resolve False Claims Act Allegations Relating to Tarceva (June 6, 2016) ("Drug manufacturers that make misleading claims about their product's effectiveness can jeopardize the health of patients – in this case, cancer patients .."), <https://www.justice.gov/opa/pr/pharmaceutical-companies-pay-67-million-resolve-false-claims-act-allegations-relating-tarceva>.

[17] See Memorandum from Skadden Arps Slate Meagher & Flom LLP, FDA Publications Double Down on Agency's Ability to Prohibit Off-Label Communications, but Narrow Scope of Debate (Feb. 1, 2017), <https://www.skadden.com/insights/publications/2017/02/fda-publications-double-down-on-agencys-ability-to>.
