Off-Label DTC Advertising
Will FDA Be Forced to Allow It?

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In what has been described as a “surprise move” (see here: http://sco.lt/7M4dvN) the FDA recently published a Federal Register notice announcing that it will hold a 2-day public hearing November 9-10, 2016, to obtain input on issues related to off-label communications by manufacturers, packers, and distributors, including their representatives, regarding FDA-regulated drugs and medical devices. FDA says it is “engaged in a comprehensive review of its regulations and policies governing firms’ communications about unapproved uses of approved/cleared medical products, and the input from this meeting will inform FDA’s policy development in this area.”

What’s even more surprising is that FDA is asking questions about off-label direct-to-consumer (DTC) and direct-to-patient communications in addition to the typical questions about such promotions directed at physicians. More on that later.

A Brief History of Off-Label Promotion
FDA defines off label use of drugs as “use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labeling.”

Off-label drug promotion by pharma, which is unlawful, has been the subject of significant health care fraud enforcement efforts by the United States Department of Justice (DOJ) and the States’ attorneys general using the Federal False Claims Act and accounts for a large portion of the fines imposed (see Figure 1, below).

Historically (between 2004 and 2013), about 10% of violations cited in FDA “warning” letters was concerned with “Unsubstantiated Claims,” which includes off-label (“un-approved use”) promotion (see Figure 2, page 2).

First Amendment Challenges
FDA’s authority to prevent or even regulate off-label promotion by pharmaceutical companies is dwindling due to a recent series of First Amendment court cases brought against the agency by the industry and its advocates. There is no doubt that these cases were instrumental in forcing the FDA to call a public hearing.

STRIKE 1: In 2014, the FDA issued some “draft guidance” regarding the distribution of off-label reprints to physicians, but this did not mollify the Washington Legal Foundation (WLF)—a non-profit legal organization that promotes pro-business and free-market positions and is widely perceived as conservative—which argued that the guidance document is in “direct violation of a 1998 permanent injunction (WLF v. Friedman) it obtained against the agency to prevent it from trampling on industry’s purported First Amendment rights.” WLF said it “intends to enforce its injunction and will seek contempt of court citations against FDA officials who violate its terms” (for the details, read “WLF to FDA Regarding Distribution of Off-Label Reprints: See You in Court!”; http://bit.ly/WLFincourt).

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In the following cases, the plaintiffs argued that off-label marketing was protected free speech as long as the information was truthful and not mis-leading.

**STRIKE 2**: In a lawsuit against the FDA, Amarin argued it had the right to promote off-label uses of its drugs to physicians as long as the information it provided was truthful and not misleading. The judge agreed and the FDA reached a settlement with Amarin (read “FDA’s Deal with Amarin: Does It Mean More or Less Off-Label Promotion?”; [http://sco.lt/74fh0j](http://sco.lt/74fh0j)).

**STRIKE 3**: In September, 2015, the FDA sent a “warning” letter to Pacira telling it to stop the off-label marketing to physicians of its pain medication Exparel. Pacira followed Amarin’s lead and responded by filing a lawsuit that claimed the FDA’s off-label regulations violated its First Amendment right. Pfizer, Johnson & Johnson, GlaxoSmithKline, Novartis and others filed *amicus curiae* briefs for the case, which was an indication that the pharmaceutical industry was following these cases closely (read “FDA Avoids Another Off-Label Court Fight by Capitulating to Pacira’s Demands”; [http://sco.lt/74fh0j](http://sco.lt/74fh0j)).

**Is the Battle Lost?**

Despite three court strikes against it, the FDA is not out of the game. The Agency still insists it has the ultimate authority to decide what is and is not truthful and the settlement terms do not apply to the industry as a whole. In the Amarin case, for example, the company would have to submit proposed marketing materials to the FDA, which could then object if it felt the information was untrue or misleading. If the two parties could not agree, a federal judge would sort it out.

The WLF, however, will not be satisfied until the law changes and the industry wins the “First Amendment Battle” allowing drug companies to freely to communicate “truthful” and “non-misleading” drug information to physicians.

**A Slippery Slope**

Once the First Amendment battle is lost viz-a-viz physician off-label communications, what’s to prevent pharmaceutical marketers from promoting off-label to consumers and patient groups? In fact, as mentioned at the start of this article, the FDA hinted in the November, 2016, public hearing notice that it may have to allow pharma companies to engage in off-label communications directly to “patients and consumer audiences” and not just to physicians.

If you stay awake reading the Federal Register Notice (“Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products”; [http://sco.lt/7UY48X](http://sco.lt/7UY48X)) and get to the questions for which the FDA is seeking input, you’ll find this unusual set of questions:

- “To what extent is it appropriate for firms to communicate information about unapproved uses of their approved/cleared medical products to patient and consumer audiences [my emphasis]?"
- “What disclosures and additional information would be needed to help ensure that a communication to lay audiences is truthful and non-misleading, given consumers’ lack of medical training and expertise in critically evaluating this type of information?”

FDA may suggest legally-binding rule making changes (as requested by the drug industry), rather than issuing guidelines that have no legal standing viz-a-viz First Amendment rights. FDA asks:

- “What additional changes, if any, should FDA consider in its regulations related to firms’ communications about medical products, such as the regulations related to what is false or misleading, adequate directions for use, the definition of labeling, or other relevant provisions?”
- “With respect to proposed alternatives to the current regulations, as well as other proposed alternatives suggested in litigation briefs and journal articles, what are the advantages and disadvantages of these approaches as they relate to the public health objectives that the FDA Authorities are deemed to advance?”

*Continues…*
All this seems to be the beginning of a slow slide down a slippery slope to a new era of DTC drug advertising—an era where off-label uses are promoted to consumers via print and TV.

**Cancer Off-Label DTC May Be First Case?**
Desperate patients and their advocates, including politicians, will no doubt apply substantial pressure on payers to provide access to certain drugs that are prescribed off-label. This is especially true of cancer drugs, many of which are already prescribed off-label.

According to *Consumer Reports Health*, the "National Comprehensive Cancer Network—an entity made up of cancer treatment centers—estimates that 50 to 75 percent of all use of cancer drugs in the U.S. is off-label."

"Off-label use of cancer drugs has been widely accepted by doctors, insurers, and patients," notes Consumer Reports. "Medicare, for example, routinely covers off-label cancer drug use that has at least some evidence backing it up. It does not require a company to get FDA approval for that use. And many states require health insurers to pay for off-label use of cancer drugs."

So, if FDA approves off-label DTC and if the drug industry does venture to promote off-label uses to consumers, could it happen first with ads for treatments approved for life-threatening diseases such as cancer?

**Maybe Not!**
Even if the FDA is forced to allow off-label DTC advertising, it doesn’t mean the drug industry will engage in it for fear of a “tidal wave of payer backlash,” noted Rob Dhoble, CEO of Adherent Health, on LinkedIn. "Unless there's substantial RWE (Real World Efficacy) including PRO (Patient Reported Outcomes) data, and even then, prior authorization is the drawn out battlefield for Rx access ANYWAY!"

A legal/regulatory professional commenting in the *PMN Direct-to-Consumer Off-Label Drug Promotion Survey* (see page 4) said this:

“There’s enough confusion with and panning of current legal DTC. There is just too much information being shared with each TV ad. There appears to be a strong, growing movement from medical professionals to ban DTC [see here: http://bit.ly/BanDTC]. Adding an off-label element is 100% unnecessary. If anything, laws should change that only allow the brand name, generic, and indication to be shared with consumers and direct to the product website.

If consumers are doing their own (online) homework and relying on their research to help understand their or their loved ones condition, then FDA should foster that by creating better DTC and less information sharing on TV. Force consumers to go to the product website and learn more. Let the consumer absorb the info at their own pace.”

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**Duke Chimes in on Off-Label Drug Promotion.**
(Curated from Pharma Marketing Blog; http://sco.lt/5m2aL3)

Drug "wonks" at the Duke-Margolis Center for Health Policy released a report on "Policy Options for Off-Label Communication." The authors want to end the off-label drug promotion "chaos" creating an FDA-sanctioned clearing house or third-party organization that would accredit (rank, score, or grade) off-label drug communications.

This group and authors of the report have ties to the FDA.

Mark B. McClellan, the Center's head, is a former FDA commissioner appointed by president George Bush. McClellan resigned after a very short term involving a controversy over Plan B. The FDA deleted or threw out all of McClellan's e-mail and written correspondence on the subject (read "Plan B FDAgate"; http://bit.ly/PlanBgate).

Peter Pitts is a former FDA Associate Commissioner for External Relations.

Dr. Robert Califf, a former Duke cardiologist, is the current FDA commissioner. Although Califf is not directly associated with this report, he has been critical of FDA in the past, something he has tried to put behind him (re: "Califf Removes His Name as Author of Scientific Paper Critical of FDA"; http://sco.lt/8dwRer).

An FDA Commissioner with strong ties to the Duke health policy community may be likely to approve the recommendations of the Duke-Margolis Center for Health Policy.

You can read more details regarding this proposal here: http://sco.lt/8u88u1

**Has It Already Happened?**
Public Citizen, a consumer advocacy group with more than 350,000 members and supporters nationwide, sent FDA's OPDP Director Tom Abrams a letter on March 31, 2015, urging him "to stop the apparently violative off-label promotional statements in the direct-to-consumer (DTC) advertisements of five prescription drugs approved for the treatment of Type 2 diabetes. The drugs are Farxiga (dapa-
gliflozin), Jardiance (empagliflozin), Invokana (canagliflozin), Victoza (liraglutide) and Bydureon (extended-release eventide)."

Public Citizen referred to a Farxiga ad that "touts" weight loss and blood pressure reduction as potential benefits although the drug has not been approved for those indications (see the ad in Figure 3, below).

"These five drugs have been approved solely to lower hemoglobin A1C levels in patients with Type 2 diabetes," says Public Citizen, "but the advertisements presented in this letter clearly convey the false perception to patients and doctors that the drugs have been deemed safe and effective for weight loss and/or reducing blood pressure."

Public Citizen wonders if the FDA approved the ads and asks a couple of interesting questions:

1. Has the Food and Drug Administration (FDA) reviewed and approved the advertisements presented in Appendix 1 prior to, or since, their release? If not, what is the agency's position on the weight-loss claims, as well as the blood-pressure-reduction claims for Farxiga and Invokana, made in the advertisements? If the agency did review and approve the advertisements, what was its rationale for allowing the inclusion of the weight-loss and blood-pressure-reduction claims?

2. Has the FDA approved similar off-label efficacy claims in other DTC advertisements? If so, did these approvals result from a formal policy allowing such off-label efficacy claims in pharmaceutical DTC advertisements?

Do the Right Thing
Regardless of FDA regulations and/or guidelines, pharmaceutical marketers have an ethical obligation to be cautious in they communicate directly to consumers about off-label uses of drugs and medical devices, both for the sake of patient safety, but also for healthcare economic reasons. The drug industry, which deals with situations where lives are hanging in the balance, would do well to always pause and ask itself if what it does is ethical.