

Using Off-Label Communications to Responsibly Advance the Public Health

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Abstract

The debate over off-label communications doesn't begin or end with the *Caronia* or *Amarin* decisions. It's a continuing dialogue between manufacturers and the FDA, between doctors and patients, between doctors and academics, between lawyers and judges, and between advocates on all sides. And the red thread that ties these conversations together is responsible off-label communications. Not sales strategies. Not Direct-to-Consumer (DTC) advertising and marketing tactics. Not managed market negotiations—the responsible sharing of truthful and accurate information via nonregulated speech. Off-label communications, properly done, advances precision medicine, delivering speedier positive patient outcomes and reducing costs to our health care system. Off-label communications provides patients with more options for effective medicines.

Keywords

DTC, off-label communication, Amarin, Caronia, free speech

Introduction: Who Leads and Who Follows?

Off-label communications is about innovation. Innovation in the safe and effective use of medicines. Off-label communications is about getting the right medicine to the right patient in the right dose at the right time—even though the right medicine or the right dose may not correspond precisely to the US FDA label.

It's important to say early in the conversation that almost no one is against sharing valuable information about FDA-approved medicines. The discussion—the heated discussion—is over how (or if) that conversation should be regulated by the FDA, and if so, how.

Not Marketing for Sales but Communication for the Public Health

What is the role of the FDA in off-label communications? Well, first let's stipulate that the FDA doesn't regulate the practice of medicine. Initial licensing approval is not based on data for every possible indication. Initial approval is based on a "best foot forward" approach. But that doesn't mean there isn't robust scientific evidence to support broader therapeutic uses. In fact, initial approvals, based on a narrow, randomized population, only provide a window into future clinical possibilities.¹ In a draft guidance document, FDA has previously noted that "good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment."² Those who think that the argument over off-label is just about

marketing and sales are looking at this issue through very narrow blinders.

However good the agency's public health intentions, current practice isn't as benevolent. FDA has found that a drug is misbranded if the manufacturer makes a statement suggesting that the drug is safe and effective for a use that has not been approved by FDA. FDA frequently uses both the "adequate directions for use" and "intended use" regulations to reach this conclusion. The regulations require that labeling include adequate directions not only for approved uses of a product but also for intended uses of the product, and FDA broadly defines "intended use" to include the manufacturers' objective intent, which FDA believes can be "determined from its label, accompanying labeling, promotional claims, advertising and any other relevant source."³

Hence, if a manufacturer provides truthful and nonmisleading information about an alternative use of its approved drug, FDA's regulations require that the manufacturer provide "adequate directions" for that use in the "labeling" to protect against a misbranding charge. Short of compiling a new marketing application and waiting for FDA approval, the manufacturer is unable to make these labeling changes and comply with that requirement, however, because labeling can address only

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the approved uses of the drug. FDA's interpretation of the FDCA thus creates a Catch 22: If a manufacturer tries to avoid a misbranding charge by updating its labeling to include adequate directions for use, then the product is deemed by FDA to be a "new drug" that must be approved before being marketed to the public.³

Off-label communications is about recognizing that the speed of scientific discourse impacts clinical practice years before it drives official label changes. According to the House Energy & Commerce Committee's 21st Century Cures Initiative initial white paper,

Communication about how certain treatments are working in certain patients is happening through a multitude of media around the globe.

These conversations between and among doctors, patients, researchers, and scientists in academia and industry should be facilitated. This includes the free flow of data, research, and results related to what a therapy or combination of therapies does or does not do well and in what types of patients.⁴

How do physicians learn about off-label usage? Medical meeting presentations, professional journal articles, discussions with their peers, and through materials from manufacturers. This isn't about Direct-to-Consumer marketing or advertising. There are clear rules for this type of regulated speech (even for paid advertising on social media). There is a difference between off-label marketing and off-label communications—and it is a distinction with a difference.

Driving Change Through Clarity

So, what do academics and physicians, payers, and patients know about off-label communications that the FDA does not? Asked in a more progressive way, how can the FDA be an accelerator rather than a sea anchor when it comes to facilitating off-label communications? In a word, the answer is clarity.

It would be generous to call the FDA's views on the dissemination of off-label information ad hoc. With the important exception of the agency's guidance on Good Reprint Practices.⁵ According to the March 2014 revised guidance, reprints that discuss off-label use mustn't

- be false or otherwise misleading;
- recommend or suggest use of the product in such a way that the product is dangerous to health when used in the manner suggested; nor
- be marked, highlighted, summarized, or characterized by the manufacturer, in writing or orally, to emphasize or promote an unapproved use.

Those are pretty broad guideposts. More interesting and germane to current events are those related to Clinical Practice Guidelines.⁶

Any CPG that includes information on unapproved or uncleared uses must meet Institute of Medicine (IOM)

standards for whether it is a "trustworthy" guideline. According to IOM, a guideline is "trustworthy" if it

- is based on a systematic review of the existing evidence;
- is developed by experts in the subject area;
- considers important patient subgroups and patient preferences;
- is transparently developed and funded such that biases are minimized;
- provides logical relationships between treatment recommendations, health outcomes, and includes the quality and strength of the underlying evidence; and
- is reconsidered and revised as new information becomes available.

A 21st Century Off-Label Equation

Beyond this, what will the FDA do next? More importantly, will it lead or follow, or follow and then lead? And this brings us to the recent court decisions in the *Caronia* and *Amarin* cases.

The 2012 *Caronia*⁷ decision overturned the conviction of Alfred Caronia, a sales representative caught talking to physicians about various off-label uses of the narcolepsy drug Xyrem. The court said the First Amendment protected truthful and nonmisleading off-label speech. Key words, "truthful and non-misleading."

That's a good off-label equation: Truthful + Non-misleading = Trustworthy.

Things seemed to be moving ahead and the FDA seemed to be driving the conversation—and then came *Amarin*⁸ and its drug Vascepa—approved by the FDA for treatment of patients with "very high" triglycerides.

In April, the FDA rejected Amarin's claim for "persistently high" triglycerides and also decided Amarin couldn't include clinical trial data in Vascepa labeling about the extent to which the pill may effectively treat people with slightly lower levels of triglycerides.

Amarin filed a lawsuit in Federal Court claiming it "finds itself in a bind," since it "may not freely communicate truthful and non-misleading information about Vascepa to health-care professionals . . . without fear of criminal prosecution and civil liability." In its lawsuit, Amarin included a list of medical journal articles it would like to distribute to physicians.

At trial, the judge asked when the FDA would be issuing further guidance on off-label communication. The government's attorney said she had "no idea" when the agency would act or if more speech will be permitted when it does. Bad answer. The court agreed Amarin materials are truthful and took the government to task for essentially arguing that speech alone can be the basis for liability and that the agency's action is at odds with the *Caronia* holding and the First Amendment.

What do the *Caronia* and *Vascepa* cases have in common? Well, for one thing, all the plaintiffs are small companies, largely dependent on the sales of a single product for their

revenues. Suing the FDA used to be considered a high-stakes gamble, but recent rulings—and the lack of action on the part of the agency to put forward new draft guidance—seem to have changed the risk-benefit analysis. At least for small companies.

Whither Big Pharma? What About the FDA?

Industry isn't sitting on its hands. In a set of joint principles,⁹ BIO and PhRMA emphasized that companies should be able to communicate “truthful, non-misleading” information outside of an FDA-approved label to insurance providers, Pharmacy Benefit Managers (PBMs), and government healthcare programs as they consider reimbursement decisions.

To exercise sound medical judgment in treating patients, health care professionals must understand the full range of treatment options, including both established and emerging information about available medications. Biopharmaceutical companies are uniquely positioned to help health care professionals achieve the best outcomes for patients, because companies can provide timely, accurate, and comprehensive information about both approved and unapproved uses of the medications they research, develop, and bring to patients. PhRMA, BIO and their members believe that the availability of a wider range of truthful and non-misleading information can help health care professionals and payers make better informed medical decisions for their patients, which in turn will benefit patients.

The three key concepts of the PhRMA and BIO principles are as follows:

- **Commitment to science-based communication:**
There are many types of data and analyses that are scientifically and statistically sound, and which can help improve patient care. We must increase access to these types of communications.
- **Commitment to provide appropriate context about data:**
Communications should clearly disclose appropriate contextual information about data that are presented, including limitations on statistical methods and study design, to ensure that health care professionals and payers are clearly informed about emerging data on the safety, effectiveness, and value of medicines.
- **Commitment to tailoring communications to the intended audience:**

Communications should keep the sophistication of the intended audience in mind to ensure that new information is clearly communicated and incorporated into existing knowledge and expertise.

According to the principles, a company should be able to describe to payers its pipeline, the status of FDA applications, the anticipated uses of products, relevant clinical trial data, pharmacoeconomic information, and applicable treatment guidelines. Further, a company should be able to discuss

analyses of real-world data derived from “sound and well-described” research methods.

Communications should be tailored to the sophistication of the intended audience and should provide “scientific substantiation” for information not included in FDA-approved labeling, the document said. A company should provide details on the design and implementation of studies that generated data, including patient populations and statistical analysis plan.

What Happens Next?

Almost 7 years to the day of the FDA's November 2009 two-day part 15 hearing on social media, a new part 15 meeting on off-label communications, Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products. Public Hearing was announced via the Federal Register.

The 2009 affair was “The Super Bowl of Part 15 hearings.” Attended by hundreds of interested stakeholders, many of whom were skilled communications professionals. The FDA listened as speaker after speaker offered timely comments on the new frontier of social media. The FDA listened—and then waited until June 2014 to issue draft guidance.

The big difference between that meeting and the November 2016 version is that there are already a slew of lawsuits that have seriously undercut the agency's authority in regulating off-label speech. Another important difference is that industry already has released its own guidelines. It is also important to note the meeting will take place immediately after national elections. If the folks at White Oak think this will deter attention, they are mistaken.¹⁰

The agency is soliciting comments¹¹ as to the ways communications from drug-makers regarding off-label use information are distinct, and whether they provide unique benefits compared to other sources. The announcement lays out eight lengthy sets of questions. Some specific ones are as follows:

- What are the benefits for clinical decision making, research, coverage, reimbursement, or other purposes if firms communicate to health care professionals, payers, researchers, and patients information about off-label uses? Are there risks, and if so, ways to mitigate these risks?
- To what extent do changes occurring in the health care system that give payers and formulary committees more influence on prescribing decisions provide incentives for firms to generate the necessary high-quality data demonstrate safety and effectiveness for off-label uses?
- What processes do firms use to determine whether information is scientifically appropriate to communicate to health care professionals about a product?
- What information should firms communicate to make audiences aware that the medical product is not indicated for a certain use and to distinguish between the

approved uses of the medical product and the unapproved use?

The agency is asking a lot of excellent questions, but they've had a lot of time to ponder all of them already. The only thing that is clear is that no guidance on the topic will be forthcoming until well after a new president takes office—and that could have profound implications on the direction of both agency thinking and timing. It will surely be worthwhile, but can the sequel live up to the original?

Filling the Off-Label Void

Can the FDA recapture a leadership role in the off-label conversation? It can—and will, but will it require the agency to trade ambiguity for predictability because, when it comes to trustworthy off-label communications, predictability is power in pursuit of the public health. When it comes to off-label communications, priority number 1 is FDA leadership through bold action and clarity.¹²

This is urgent for many reasons: different federal agencies (FDA, FTC, DOJ) with differing views on pathways and jurisdiction, and the extreme danger of allowing federal judges dictate regulatory policy. If existing policy has evolved to protect the public from snake oil, the *Amarin* decision is precarious precedent for communications about fish oil—and beyond.

Nature abhors a vacuum and, absent strong and forward-looking FDA leadership, the off-label debate will result in public health chaos. And as many management gurus have written, one of the key tenets of successful leadership is the ability to *delegate* in order to get things done.

To that end, one policy alternative is for the FDA to pursue a strategy that embraces third-party sanctioned communication—a more intramural approach based on the FDA's partnering with an external entity charged with accrediting certain types of communication.¹³

This organization could focus its efforts on reviewing not an NDA, but an NDI, that is, New Drug/Device Information, consisting of a sponsor's evidence and associated communications about off-label use, and then potentially approve them for broader distribution.

An NDI review could be given within a rank, score, or grade system that confers greater weight to better evidence and could be given contingent upon continued evidence generation and resubmission to the clearing body.

For example, an off-label communication may be approved and given an initial grade or rating that sunsets within a specified number of years barring updated submission of relevant evidence. Continued off-label communication at the current evidentiary grade and after the specified date would then be subject to additional evidence development by the sponsor.

The proposed reviewing body would operate outside of FDA but with FDA participation. To avoid First Amendment issues and other legal concerns, the body's conclusions could not bind the FDA or otherwise hinder FDA's ability to pursue

enforcement action. While the reviewing body would not provide certainty to the regulated community, its recommendations could offer useful guidance to drug manufacturers.

The end goal would be a process that augments the FDA's capacity to review a diversity of communication types reflective of rapidly emerging evidence—but does not change FDA's ability to pursue enforcement action.

Such a third-party approach has precedents. In Canada, for example, the Pharmaceutical Advertising Advisory Board (PAAB, <http://www.paab.ca/>) serves as an independent pre-clearance review agency for assessing the accuracy and evidentiary basis for promotional information on prescription, nonprescription, biologic, and homeopathic products.

The PAAB process works within the Canadian regulatory framework with Health Canada as an ex-officio member of board leadership, conferring “approval” of advertising materials through a logo incorporated on cleared materials.

Broadening the Aperture

Current FDA draft guidance¹⁴ opens the door for companies to share truthful, scientifically accurate, and data-driven information with healthcare professionals to inform treatment decisions. For example:

- **Observational data and “real world evidence”**
Information on the safety and effectiveness of medicines taken from medical records based on actual use of approved medicines.
- **Subpopulation data**
Information on the safety and effectiveness of medicines in subpopulations including gender and race. Such information can help health care professionals tailor their treatment to meet the needs of individual patients.
- **Observational and comparative data**
Information from the use of a medicine outside of randomized clinical trials, especially comparisons between 2 or more therapies.
- **Pharmacoeconomic information**
Healthcare economic data and information on the economic value of medicines that can improve the efficiency of patient care.
- **Information on medically accepted alternative uses of medicines**
Information on new uses of approved medicines that are listed in major compendia and/or routinely reimbursed by the federal government and major payers.

After the recent court decisions, the FDA realizes that it must either lead the effort to disseminate off-label information that is truthful, accurate, and nonmisleading or lose its ability to direct the speed, direction, and quality of these communications. Things are moving fast and unless the FDA acts, we'll have federal judges making these decisions for us. That's not good for the FDA or the public health.

Conclusion: Why Delay?

As Congressman Fred Upton (the retiring chair of the House Energy & Commerce Committee) and Joe Pitts (the senior minority member) recently wrote to HHS Secretary Burwell, “It is our understanding that HHS has not allowed FDA to issue its completed draft guidance addressing the scope of permissible ‘scientific exchange,’” of useful information about drugs and devices.”

And according to a recent report,¹⁵

One source, who speaks regularly with both agencies, told us this: “HHS leadership doesn’t trust industry to do the right thing. . . . HHS leadership believes off-label speech will lead to more aggressive marketing of new products that will raise costs to [Medicare and Medicaid].

They are allowing both their prejudices [industry as the bad guy] and priorities [keeping spending down] to get in the way. . . . The White House shares these fears, and as a result the FDA’s desire to issue guidance is stymied.”

All this to say that off-label communication is now on the health policy front burner and the flame is on high and, as the late senator Everett Dirksen used to say, “When I feel the heat, I see the light.

We’ll see.

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