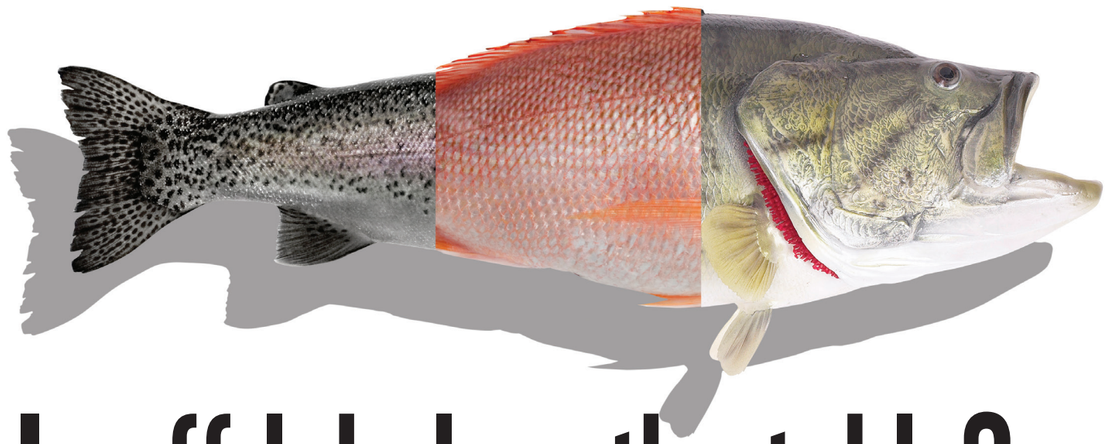

Is off-label on the table?

In years past pharma marketers had to check themselves before conveying off-label product claims, even though those off-label uses had long since become standards of care. But in recent months the FDA has signaled a willingness to open the off-label information floodgates. Former FDA Associate Commissioner **Peter Pitts** explains exactly why this matters

FOR YEARS THE PHARMACEUTICAL INDUSTRY AGONIZED OVER communicating "non-compliant" off-label claims that, in many instances, were already standards of care. And yet the Food and Drug Administration, always concerned about protecting the free and fair dissemination of scientific information, remained mostly silent. That silence of the regulatory lambs has ended. And the winner is the public health.

To that end, interested readers might have noticed a querulous headline in their March 11 copies of the *Washington Post:* "FDA proposes to let drug companies undermine official safety warnings." Unfortunately, it was interesting for the wrong reasons, because the headline was misleading at best and downright wrong at worst. And it wasn't a case of an off-target headline written by an uninterested editor. Here's how the article began: "The Food and Drug Administration is proposing to allow pharmaceutical companies to undermine official safety warnings in sales presentations to customers."

That's not true. What the draft guidance addresses is the ability of pharmaceutical companies to present research published in peer-reviewed journals that goes beyond the information provided in the FDA label. That undermines nothing. In fact, it leads to the conveyance of scientifically acceptable, often cutting-edge information.

Under the proposal, the FDA would not "object to the distribution of new risk information that rebuts, mitigates or refines risk information in the approved labeling." The studies must be "well designed" and "at least as informative as the data sources" that the FDA used in generating the official warning. In sum, it's the FDA recognizing that knowledge is power in pursuit of the public health.

Furthermore, this language makes it clear that the FDA retains the right to object when such information does not meet this standard. And since there is no definite "standard," the FDA's actions will be carefully watched. The Center for Drug Evaluation and Research's office of medical policy currently lacks a permanent director. When that slot is filled, this is a key issue that person will need to prioritize.

Public Citizen offered the expected broadside that the proposal "seriously undermines FDA authority." Balderdash. What it does is affirm that the FDA does not regulate the practice of medicine and that there are finite limits to the agency's powers relative to regulated speech.

It also raises an important issue: There's a difference between off-label communications and off-label marketing. It's an issue we've been pussyfooting around for too long. Now, at long last and with the FDA leading the charge, it's time for a serious conversation.

THINKSTOCK

Circa 2015 Communication

The first thing to point out is that this agency action preempts attempts to legislate similar outcomes. According to the House Energy and Commerce Committee's "21st Century Cures" initiative 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."

As PhRMA has pointed out in the past, some of the FDA regulations and guidance have a more direct impact on patient care than others. The FDA's restrictions on biopharmaceutical companies' ability to share authoritative, regulated data about prescription medicines limits healthcare professionals' access to information that can help them make informed decisions based on the healthcare needs and preferences of their patients.

The new FDA draft guidance opens the door for companies to share truthful, scientifically accurate and data-driven information with healthcare professionals to inform treatment decisions. Some examples of this kind of information include:

- 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, which can help HCPs tailor treatment regimens.
- Observational and comparative data: information from the use of a medicine outside of randomized clinical trials, especially comparisons between two or more therapies.
- Economic information: healthcare economic data and information on the economic value of medicines can improve the efficiency of patient care.
- Information on medically accepted alternative uses of medicines: Patients being prescribed medicines off-label deserve to know that their HCPs have the latest information.

There is a distinction between "off-label communications" and "off-label marketing," and it is a distinction with a difference. "Off-label marketing" means sharing information with the intent to impact sales. "Off-label communications" means sharing information to improve and advance the public health. One well-known moniker for off-label communications is "the free and fair dissemination of scientific data." The new FDA action clearly is directed at off-label communications. Another way to look at it is that "communications = education" and "marketing = sales."

Patients Join the Fray

Patient groups have had their say as well. The National Organization for Rare Disorders noted that "Congress should seek new policies that permit drug companies to share appropriate information without fear of enforcement action," while the Ovarian Cancer National Alliance expressed its worries that proposed changes might "chill off-label use of drugs and the dissemination of scientific information about non-approved uses."

There's much food for thought here, but two things in particular should be mentioned: This is not an out-of-the-blue action by the FDA and it's not just about communications with physicians—payer formulary committees are another audience. Let's look at the record.

To address concerns that FDA regulations were limiting the dissemination of outcomes research, Congress added Section 114 (in 1997) to set a new, less stringent standard applicable to promotional dissemination of healthcare economic information to MCO formulary committees: "competent and reliable scientific evidence." Still, as deputy center director for clinical science and acting deputy director of the Office of Drug Evaluation, Bob Temple, noted, FDAMA 114 is "an interesting section, and it's not entirely simple to figure out what's included and what's not included." No kidding.

One of the phrases in Section 114 that defies easy interpretation is that promotion must involve a claim that "directly relates to an indication approved" by the FDA. In the draft guidance, PhRMA proposed that extrapolation from data included on labeling would be appropriate at least under the following circumstances: from duration of use in labeling to actual duration of use found in pharmacy databases, from dosages included in labeling to actual dosages found in pharmacy databases and from controlled trial settings to actual practice settings.

PhRMA recommended that FDA allow the competent and reliable standard to be satisfied with data obtained through a number of different methods, including observational study designs, database reviews and other economic modeling techniques. "There should be no pre-specified number or type of study required to substantiate a claim," the organization wrote in a 2012 white paper. "A claim that a drug is more cost-effective than a competing drug may be made where the cost savings are due to reduced resource utilization resulting from improved efficacy outcomes, decreased administration or monitoring costs, or where the difference in cost is due to the drug causing fewer adverse events, as long as these differences are supported by competent and reliable evidence."

Risks/Benefits

For industry, the new FDA guidance opens up tremendous potential for enhanced (but restrained and responsible) sharing of important scientific data. The key question is this: Do the opportunities outweigh the risks? There are a few ways to answer this.

There's the First Amendment angle. Did the *Caronia Philharmonia* decision—which, in December 2012, held that the federal government could not prosecute a sales representative for speech promoting the legal off-label use of an FDA-approved drug—impact the way the FDA views off-label promotion within the context of the free-and-fair dissemination of scientific data?

An extreme way to look at it is that, in a post-*Caronia* world, some pharmaceutical companies may no longer feel obligated to seek FDA approval for new indications, since they can openly "promote" them without fear of prosecution. This is a flawed argument. Indications of the on-label variety have many benefits, not least among which is reimbursement. But such unintended consequences are important. Any company that chooses this route would be acting in a highly irresponsible manner, putting promotion before the public health. The recent FDA action makes this a relatively implausible option.

In other words, the FDA's action advances the public health by accelerating the free and fair dissemination of scientific data while maintaining appropriate regulatory oversight of communications behavior. That's the FDA doing its job both protecting and advancing the public health. Bravo!

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